To the editor:

Hepatitis C virus RNA dynamics during antiretroviral therapy

In a recent issue, Yokozaki et al published a report in which they demonstrated that highly active antiretroviral therapy (HAART) induces a decline in hepatitis C virus (HCV) viremia in hemophiliac patients with HIV-HCV coinfection. They concluded that coinfected patients should be treated with HAART before starting the treatment with interferon and ribavirin.[1] HIV-HCV coinfection is common and affects more than one third of all HIV-infected persons worldwide. HIV-coinfected patients have higher HCV RNA levels and a higher risk of rapid progression of HCV liver disease, with increasing risk of cirrhosis. Chronic HIV infection mimics an opportunistic disease because the natural history of HCV infection is accelerated in HIV patients.[2] Because the prognosis of HIV disease has been modified by HAART, the need to treat HCV coinfection is now a significant issue. In contrast to the findings of Yokozaki et al, several reports failed to demonstrate any activity of HAART on HCV viral load.[3] Improvement in immune status during effective antiretroviral therapy is generally not sufficient to reduce HCV viral titers, although a paper reported that HAART therapy has a beneficial effect on fibrosis in patients with HIV.[4] In fact, treatment with HAART may result in increased HCV replication, higher alanine aminotransferase (ALT) levels and aspartate aminotransferase (AST) levels, and greater liver damage. This may mean that treatment of hepatitis should precede HAART. Other studies showed that HAART had no effect on HCV RNA levels or on ASTs and ALTs.[5] Moreover, a study of antiretroviral therapy in coinfected patients showed higher aminotransferase levels in coinfected patients and more hepatotoxicity overall (54% of HIV/HCV versus 39% HIV), although 88% of coinfected patients did not experience severe hepatotoxicity during antiretroviral therapy. Ritonavir accounted for more than 50% of cases of severe aminotransferase toxicity, and indinavir accounted for more than 50% of cases of hyperbilirubinemia.[6]

Recently, we published a preliminary report on the outcome of an aggressive therapeutic schedule of daily alpha interferon (IFN) in coinfected patients.[7] In our previous study performed in immunocompetent patients,[8] we demonstrated that daily IFN administration is more effective than three times a week administration. The need for a more aggressive therapy in HIV-HCV patients is justified by the worse clinical course. We demonstrated that, even in patients with undetectable HIV RNA, HAART therapy did not modify the HCV RNA levels, which responded poorly to an aggressive IFN therapy. Our results indicate the difficulty to treat with IFN HIV-HCV coinfected patients, because side effects restrict the compliance to IFN therapy and could affect the adherence to HAART. Hence, interferon therapy influenced the tolerability of HAART and could affect long-term antiretroviral response. Further problems may originate from the use of combination therapy with IFN plus ribavirin because of the drug interaction (in vitro studies have demonstrated that ribavirin could affect intracellular phosphorylation of deoxynucleoside, mainly AZT,[9,10] leading to a reduced therapeutic effect) and the increase of pill burden, which reduces the adherence to HAART. In conclusion, we do not agree with Yokozaki et al and suggest that therapy for hepatitis should precede HAART, at least in patients without severe immunodeficiency, because the interferences between the 2 treatments limit the adherence and the response to both therapies.

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Response:

Highly active antiretroviral therapy and interferon therapy for HIV-HCV–coinfected patients: which should precede?

We thank Drs Bruno, Sacchi, and Filice for their comments regarding our paper on immunologic dynamics during antiretroviral therapy in HIV-HCV–coinfected hemophiliac patients. In the paper, we suggested that treatment for HIV-HCV patients should begin with highly active antiretroviral therapy (HAART) for HIV prior to interferon (IFN) therapy for HCV because HAART improves the host immune function in the host by increasing the $CD4^+$ cell count and often results in decreasing HCV viral load, which is thought to be advantageous for patients starting IFN therapy. Bruno et al raise the following issues regarding starting HAART before starting IFN: *(a)* HAART is not necessarily associated with HCV viral load, *(b)* anti-HIV drugs are more often

toxic for hepatocytes in HCV-coinfected individuals, *(c)* severe side effects of IFN treatment may affect the patients' adherence to HAART, and *(d)* IFN therapy combined with ribavirin could affect the response to HAART because of a drug interaction.

Whether HAART reduces HCV load in HIV-HCV patients is still controversial. Although Samaniego et al initially reported no association between HAART and HCV load,[1] after a longer observation period they did find such an association.[2] The influence of HAART on HCV load may be delayed in relation to $CD4^+$ cell count recovery. It also may be that the response varies between patient races[3] or between patient populations (hemophilia patients have no repeated transmission mode, such is seen in drug abusers or homosexual men). The duration of infection and pretreatment $CD4^+$ cell count of patients may also be involved. Our hemophiliac patients had been infected with HIV before the establishment of screening for clotting factors and, thus, may have been infected longer and had a lower $CD4^+$ cell count than HIV-HCV patients described in other studies.

Anti-HIV-drug–induced hepatotoxicity is considered more common among HCV-coinfected patients, but this may be due to underlying HCV-related liver disease. Even among those patients experiencing toxic effects, the elevated transaminase level was transient and no irreversible outcomes were observed.[4] HAART can be administered safely to HIV-HCV–infected patients, though the patients' transaminase levels should be monitored.

Our hemophiliac patients who are suffering from both diseases are earnest in seeking treatment. They gave informed consent for the IFN therapy and were prepared for the side effects. To date, none of our patients treated by HAART and IFN therapy have ceased treatment due to side effects. Careful attention to the patient's outlook and careful serum monitoring by the physician is very important, however.

Once a patient starts HAART, it is continued even after the start of IFN therapy. In vitro study has suggested that ribavirin inhibits action of anti-HIV drugs.[5] Certainly cotreatment with ribavirin may strengthen the IFN effect but may weaken the underlying effect of HAART. A recent report, however, demonstrated the safety and effectiveness of this combination during HAART: as many as 50% of the study patients were sustained responders to treatment with IFN plus ribavirin.[6]

HCV-related disease has become a more significant issue than HIV disease that is well controlled by the establishment of HAART. Due to the fact that HIV accelerates the progression of HCV disease, a successful outcome with IFN therapy is critical. IFN therapy for HCV infection aims at complete elimination of the virus and is short-term, whereas the aim and duration of HAART for HIV infection are quite different. Because the outcome of IFN therapy, alternatively successful viral elimination or not, depends greatly on the initial host and virus conditions,[7] the starting point for IFN therapy must be optimally advantageous for the host.

Approximately 85% of acutely HCV-infected persons develop chronic, persistent viremia, suggesting the difficulty of viral clearance even under normal immune conditions. The remaining persons who fortunately recover from hepatitis with eradication of HCV show a dominant Th1-response among $CD4^+$ cells,[8] inducing specific CTL activity.[9] Thus $CD4^+$ cells are central to the cytotoxic immune system, playing an important role in the eradication of viruses. Actually, in HIV-HCV–infected patients, a sustained IFN response has been associated with a pretreatment $CD4^+$ cell count.[10] Thus IFN therapy should be performed under as near-normal immune conditions as possible.

Finally, a standard therapy for HIV-HCV–coinfected patients has not been established. Which therapy should precede: HAART or IFN? The answer may depend on the pretreatment host and viral factors such as the $CD4^+$ cell count and the HCV viral load. More information or a large study addressing this question is urgently needed.

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To the editor:

WA monoclonal rheumatoid factors and non-Hodgkin lymphoma

De Re et al describe the sequences obtained from B-cell monoclonal expansion analysis of patients with non-Hodgkin lymphoma (NHL).[1] The characterization by the authors of 17 patients with NHL makes comparisons of the antibodies found to rheumatoid factor genes and hepatitis C virus (HCV) anti-E2 antibodies. The study did not include serologic or sequence determinations demonstrating identity between the serum monoclonal rheumatoid factors (mRFs) and the immunoglobulins (Igs) antigen receptors of the lymphoma cells in the patients. Sequence data can be useful in attempting to understand the origin of NHL in patients with chronic HCV infection, but there are pitfalls in drawing conclusions on specificities of antibodies based on sequence homologies to only