

# Reciprocal Interaction of Human Immunodeficiency Virus and Hepatitis C Virus Infections

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Many individuals with hepatitis C virus (HCV) infection are coinfecting with the human immunodeficiency virus (HIV). Since HCV and HIV are transmitted by parenteral exposure and both viruses have long clinical latent periods, persons with a history of illicit injection drug use and receipt of blood or blood products, such as factor VIII or IX, are commonly infected with both viruses. It has been estimated that 100,000 to 240,000 of the estimated 900,000 HIV-infected persons in the United States also are infected with HCV, and a similar proportion are coinfecting in Europe (T. Benfield, 12th World AIDS Conf., abstr. 22261, 1998). Therefore, it is important to understand how these two viruses modify one another's disease course and affect efforts to treat and prevent these common infections.

## HCV RNA LEVELS

For both HIV and HCV, the amount of viral RNA in the blood (viral load) is believed to represent the steady state of viral replication and clearance. HCV RNA levels tend to be higher in persons with chronic HCV infection than in adults with HIV infection, and the HCV half-life is probably shorter than for HIV (18). However, the HCV RNA level does not predict the progression of liver disease as strongly as the HIV viral load correlates with development of AIDS (16, 29).

As shown in the study by Mathews-Greer et al. (28), the HCV viral load is higher in individuals who are coinfecting with HIV than in those without HIV coinfection. This relationship has been demonstrated both in cross-sectional and in longitudinal studies (15, 19, 28, 42, 44). In addition, in some but not all studies there is an inverse relationship between the CD4<sup>+</sup> cell count and the HCV RNA level. Persons coinfecting with HIV have been reported to be less likely to clear HCV spontaneously than those without HIV infection (44). Other factors associated with an increased HCV RNA level are older age and other forms of immune suppression (35, 41, 43). Persons who are hepatitis B surface antigen positive appear to have lower levels of HCV RNA (40, 42). Despite these factors known to be associated with HCV viral load, most of the variation in HCV viral load between infected individuals remains unexplained (40, 42).

## HIV INFECTION AND THE COURSE OF HEPATITIS C

Several investigators have documented higher rates of liver-related morbidity and mortality in persons infected with HIV

and HCV (1, 3, 4, 8, 14, 25, 26, 35, 37, 40). Eyster et al. reported that liver failure and liver-related death occurred exclusively in HCV-infected hemophiliacs who were coinfecting with HIV (11). Likewise, Darby and colleagues reported a fivefold increase in liver-associated mortality in HIV-infected hemophiliacs (who almost certainly had HCV infection) compared to those without HIV infection (8). Another study reported that HIV coinfection was an independent risk factor for the development of cirrhosis in a study population of HCV-infected drug users (33). It is not yet clear what the effect of highly active antiretroviral therapy will be on HCV morbidity and mortality.

Since the incubation period after infection to the development of cirrhosis, liver failure, or liver cancer usually is many years or decades, prolonged survival could increase HCV-related morbidity and mortality. Studies of the immunopathogenesis of liver disease and the immunologic control of HCV replication in infected individuals are ongoing. Data published recently suggest that cellular immune responses, particularly those mediated by CD8<sup>+</sup> T lymphocytes in liver tissue, may be associated with lower levels of HCV RNA but more active liver disease (30). Nevertheless, the studies to date suggest that the immunopathology and immunocompromise associated with HIV infection has an adverse effect on the natural history of the progression of HCV infection.

The natural history of HCV and HIV may also be modified among injection drug users or other high-risk populations by frequent reexposures to these viruses. The frequency of reinfection with HCV needs further evaluation. Farci et al. showed that chimpanzees could be reinfected with the same strain of HCV after they had cleared an initial infection (17).

## HCV INFECTION AND THE COURSE OF HIV

The data on the impact of HCV infection on HIV progression are conflicting. Piroth et al. found a more rapid progression of HIV in 119 HCV-coinfecting patients compared to controls who were infected only with HIV (32). Also, that study demonstrated more rapid CD4<sup>+</sup> lymphocyte decline as well as clinical progression of HIV in HCV-coinfecting patients. A study was reported recently of the rate of HIV progression in 207 HCV-HIV-coinfecting hemophiliacs who were monitored prospectively for 7 years after enrollment with annual measurement of CD4<sup>+</sup> lymphocyte cell counts and HCV and HIV viral loads (9). After controlling for CD4<sup>+</sup> counts and HIV-1 RNA level, every 10-fold increase in baseline HCV RNA was associated with a relative risk for clinical progression to AIDS of 1.66 (95% confidence interval, 1.03 to 2.30). In another recent study of members of the large Swiss HIV cohort who started highly active antiretroviral therapy, those with

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HCV and HIV coinfection had more rapid progression to adverse outcomes (21). In addition, among those whose HIV viral load was reduced below 400 copies/ml, HCV-positive subjects had smaller increases in CD4<sup>+</sup> lymphocyte counts.

In contrast to these reports, other studies have failed to detect a more rapid progression of HIV in HCV coinfecting patients (10, 34, 39, 50). In one study of 416 HIV seroconverters who were monitored for an average of 3 years, similar rates of progression were found in the 51.4% who were HCV coinfecting compared to those with only HIV infection (10). Sulkowski et al. found that HCV infection was not independently associated with progression to AIDS or death after adjusting for exposure to HAART and CD4<sup>+</sup> count among 1,742 HIV-positive patients (M. S. Sulkowski, D. L. Moore, S. Mehta, S. L. Laughton, and D. L. Thomas, 8th Conf. Retrovir. Opportunistic Infect., abstr. 34, 2001). Aside from the HCV infection, there are a number of differences between persons with both HCV and HIV compared to those with HIV infection alone. These factors may explain differences in the results of published studies. Clearly, additional studies to evaluate the role of HCV in HIV progression are needed in order to clarify this interaction.

#### HIV INFECTION AND TREATMENT OF HEPATITIS C

Treatment of hepatitis C may be different in an HIV-infected person for several reasons. Overall rates of sustained clearance of HCV appear to be reduced in HIV-HCV-coinfecting persons, especially those with advanced HIV infection (38). In addition, it may be difficult to use ribavirin in persons whose antiretroviral regimen relies on the activity of either zidovudine or d4T, since phosphorylation to the active compounds may be reduced (49). Conversely, ribavirin may increase the activity (and toxicity) of dideoxyinosine, and alpha interferon itself has antiretroviral activities, reducing the HIV viral load approximately one-half log.

These considerations notwithstanding, there is an emerging international experience with treatment of HCV infection in HIV-HCV-coinfecting persons. Soriano and coworkers have made the important observation that HCV infection can be cured with alpha interferon therapy in HIV-HCV-coinfecting persons (38). While large studies are under way to assess the safety and efficacy of interferon (including pegylated interferon) and ribavirin in the treatment of HCV in the HIV-HCV-coinfecting person, there already are a few reports suggesting their safety and efficacy (24).

#### HCV INFECTION AND TREATMENT OF HIV

Chronic HCV infection can affect the response to antiretroviral therapy. Since the liver is the primary site of HCV replication, the pharmacokinetics of drugs that are metabolized in the liver may differ in HCV-HIV-coinfecting patients. Although all antiretroviral drugs have been reported to have hepatotoxicity in some patients, hepatotoxicity for these and other drugs may be worse in HCV-infected patients (2, 5, 11, 47). Other investigators have reported enhancement of HCV replication and liver damage in HCV-HIV-coinfecting patients treated with antiretroviral combination therapy (23, 27, 36, 39a, 40, 48, 52). Some authors have postulated that the enhanced liver

toxicity in HCV-infected patients receiving antiretroviral therapy could be due to immune restoration (23). However, other factors clearly are involved since hepatotoxicity also occurs in persons without apparent CD4<sup>+</sup> lymphocyte increases and in those without viral hepatitis.

#### EFFECT OF HIV ON HCV TRANSMISSION

HCV is transmitted from an infected mother to her infant after 2 to 5% of deliveries (51). However, HIV-coinfecting mothers transmit HCV to their infants more often (22, 45).

The frequency of transmission of HCV by heterosexual or male homosexual intercourse is controversial (6, 12, 20, 31). Studies of HCV-infected blood donors have identified multiple sex partners as a risk factor for HCV prevalence, independent of parenteral exposures (7). Another study of patients attending a sexually transmitted disease (STD) clinic found HCV prevalence to be elevated among clients with an STD who had had unprotected sex with multiple partners and who denied drug use or other parenteral exposures (46). The overall evidence to date, however, suggests that sexual transmission of HCV occurs but that it is substantially less efficient than the sexual transmission of HBV and HIV. Coinfection with HIV appears to increase the rate of sexual transmission of HCV. In one study, 3% of the female partners of HIV-HCV-coinfecting male hemophiliacs were HCV infected, while none of the female partners of HCV-infected persons without HIV were infected (13).

The reason for the apparent increased sexual transmission from HIV-HCV-coinfecting persons is unknown. Although HCV RNA has been identified in genital secretions (i.e., vaginal washes and semen), there appears to be quantitatively less than in blood. HCV RNA levels are higher in HIV-infected persons, but it is probably too simplistic to presume that greater circulating levels themselves explain the enhanced transmission. The relationship between HCV RNA level and sexual transmission has not been evaluated, as it has with HIV infection. However, despite the fact that HCV RNA levels in the plasma often exceed those seen in persons with HIV or HBV infection, sexual or other nonparenteral transmission is uncommon. Little is known at present about how HCV crosses mucosal barriers when and if it does.

In summary, there are many interactions between HCV and HIV. It is important that research efforts be increased in order to better understand HIV-HCV coinfection and the optimal means of treating the large number of coinfecting persons.

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