ABSTRACT

Approximately 33% of human immunodeficiency virus (HIV)-infected patients are coinfected with hepatitis C virus (HCV). Because antiretroviral therapy has become more effective and has prolonged life expectancy in HIV-infected patients, liver disease has emerged as a major cause of morbidity and mortality in those patients dually infected with HCV. HIV adversely affects all stages in the natural course of HCV infection, leading to increased viral persistence after acute infection, higher levels of viremia, and accelerated progression of cirrhosis and end-stage liver disease. The effect of HCV on the course of HIV infection is unclear, aside from the increased risk of hepatotoxicity in HIV/HCV-coinfected persons taking antiretroviral therapy. This article reviews current knowledge on the epidemiology and clinical course of HCV in HIV-infected patients.

INTERACTION BETWEEN HIV AND HCV INFECTIONS

NATURAL COURSE OF HCV IN HIV-INFECTED PERSONS

In most studies, HIV adversely affects the natural history of HCV infection. HIV infection has been associated with higher rates of HCV persistence, higher HCV viral loads and, in most studies, an increased risk for end-stage liver disease (ESLD).6,10 HCV-RNA levels are higher after HIV infection than before.6,10 In some studies, HCV-RNA levels are higher in HIV-infected persons with CD4+ lymphocyte counts lower than 200/mm³, as compared to HIV-infected persons with higher counts. The biologic explanation for the effect of HIV infection on HCV-RNA level is unknown.

Hepatitis C virus-related liver disease also generally progresses faster in HIV-positive patients than in HIV-negative controls. In a Spanish study, the time from initial HCV infection to cirrhosis was much shorter in patients coinfected with HIV/HCV (7 years) than in patients with HCV monoinfection (23 years; P < .001; Figure 1).4 The incidence of cirrhosis within the first 10 years of HCV infection was also sig-
nificantly higher in HIV-infected patients than in non-HIV-infected patients (15%–25% HIV-positive vs 2%–6% HIV-negative; \( P < .01 \)). Similarly, an increased risk of HCV-related ESLD was found among HIV-positive coinfected patients in a cohort of 1816 HCV-infected patients with hemophilia who were followed for up to 16 years. In this study, the estimated 16-year cumulative incidence of ESLD was 14% for HIV-positive patients compared to 2.6% for HIV-negative patients. In another study of more than 4000 patients in the United Kingdom with hemophilia, a 5-fold higher risk of death caused by chronic liver disease was found in HIV-positive hemophiliac patients than in those patients who were HIV negative (6.5% in HIV-positive patients vs 1.5% in HIV-negative patients). A meta-analysis of 8 studies showed a 6-fold greater relative risk of progression to ESLD in patients coinfected with HIV/HCV than in those patients infected with HCV alone. Taken together, these results suggest that HIV, through unknown mechanisms, accelerates the course of HCV-related liver fibrosis.

Consequently, in some centers, liver disease has become an important cause of death. Bica et al documented one dramatic example at the New England Medical Center. In this study, 50% of deaths in 1999 were caused by ESLD compared to only 11.5% and 13.9% in 1991 and 1996, respectively (\( P = .003; \)

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**Figure 1. HIV/HCV Coinfection Accelerates the Progression of HCV Disease**

![Graph showing the average time to develop cirrhosis among HCV+ patients and the incidence of cirrhosis in the first 10 years among HCV+ patients.](image)

HCV = hepatitis C virus; HIV = human immunodeficiency virus. Data from Soto et al.

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**Figure 2. Mortality Rate from ESLD in Patients Coinfected with HIV/HCV**

![Graph showing the percentage of ESLD-related deaths from 1991 to 1998.](image)

ESLD = end-stage liver disease; HCV = hepatitis C virus; HIV = human immunodeficiency virus. Data from Bica et al.

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**Effect of HCV Infection on HIV Progression**

There are conflicting reports regarding the effect of HCV infection on the natural history of HIV disease. Among the 1955 patients in the Johns Hopkins HIV cohort, no difference was detected in the progression to AIDS (hazard ratio [HR], 1.03; 95% confidence interval [CI], 0.86–1.23) or death (HR, 1.05; 95% CI, 0.85–1.30) after adjustment for exposure to highly active antiretroviral therapy (HAART) and HIV. The study also found no difference between HCV-positive and HCV-negative patients in CD4+ cell recovery after initiation of HAART. These findings are in agreement with recent analysis of the EuroSIDA cohort, which revealed no difference in HIV-RNA viral copies and CD4+ cell recovery between HCV-positive and HCV-negative patients who were coinfected with HIV and treated.
with HAART. Conversely, in the Swiss HIV cohort study, Greub et al found that HCV was independently associated with a modest increased risk of progression to a new AIDS-defining event or death, even among the subgroup with continuous suppression of HIV replication. HCV infection was associated with an increased risk of progression to AIDS or death (HR, 1.55; 95% CI, 1.00–2.41; P = .05) and slower CD4+ cell recovery in a cohort of 600 patients coinfected with HIV/HCV. More recently, in the HIV Atlanta VA Cohort Study, survival from the time of AIDS diagnosis was significantly shortened for patients coinfected with HIV/HCV (HR, 1.84; 95% CI, 1.09–3.10), as was time from HIV diagnosis to death (HR, 2.47; 95% CI, 1.26–4.82).

**IMPACT OF ANTIRETROVIRAL THERAPY**

The net effect of antiretroviral therapy on the liver is unknown. Approximately 10% of persons taking a new antiretroviral regimen develop a more than 5-fold elevation in liver enzymes. Some drugs (nevirapine and ritonavir, at full dose) cause hepatotoxicity more frequently than other drugs. Starting a new antiretroviral regimen is also associated with a transient increase in HCV viral load, particularly in patients with low CD4+ counts.

Mechanisms of liver enzyme elevations are not fully understood. Hypersensitivity reactions occur and are particularly associated with nevirapine and abacavir use by women with high CD4+ lymphocyte counts. Hepatic steatosis has been clearly linked to use of nucleoside analogue reverse transcriptase inhibitors, such as stavudine and zidovudine, presumably as a result of mitochondrial damage. Because of the increased risk for severe hepatotoxicity, coinfected patients should be carefully monitored for symptoms of severe liver disease, mitochondrial toxicity, and acute hypersensitivity reactions after initiation of antiretroviral therapy.

However, there also are data suggesting that HAART may actually have a beneficial effect on liver disease in patients coinfected with HIV/HCV. In one study, protease inhibitor-based HAART was associated with less liver fibrosis in patients coinfected with HIV/HCV, after adjusting for other factors. Duration of antiretroviral therapy has been independently associated with the absence of fibrosis on liver biopsy. These results agree with findings of a recent study that showed prolonged survival and lower liver disease-related mortality in patients coinfected with HIV/HCV in the era of HAART (Figure 3).

**CONCLUSIONS**

Since the introduction of successful antiretroviral therapy, the life expectancy of HIV-infected patients has increased dramatically, but HCV-related liver disease has...
emerged as a leading cause of morbidity and mortality. HIV infection adversely affects all stages in the natural history of hepatitis C, but the effect of HCV infection on the course of HIV remains controversial. Likewise, additional research is needed to clarify the effect of antiretroviral therapy on liver disease progression.

REFERENCES


