

Perspective

New Insights in HIV and Hepatitis C Virus Coinfection

At the International AIDS Society–USA course in Los Angeles in March 2002, Margaret J. Koziel, MD, discussed recent studies of HIV and hepatitis C virus coinfection and its effect on the course and management of both diseases.

Characteristics of HCV Infection

Initial infection with hepatitis C virus (HCV) is characterized by rapid viral replication. Alanine aminotransferase (ALT) levels increase dramatically over the course of the initial 1 to 3 months but may be highly variable thereafter. Following the initial period of viremia, humoral and cellular immune responses develop, but in most cases are insufficient to clear the infection (Liang et al, *Ann Intern Med*, 2000). HCV has 6 major subtypes; in the United States, approximately 70% of HCV isolates from infected patients are genotype 1. Multiple strains of HCV are present in an individual patient; hence, the virus exists as a quasi species.

HCV infection rates based on antibody-positive status in individuals at risk for HIV infection include rates of 70% to 80% in injection drug users and 8% to 10% in men who have sex with men. A recent study in an AIDS Clinical Trials Group population, which was representative of all patients with HIV in the United States, showed an overall HCV seroprevalence rate of 37% (Sherman et al, *Clin Infect Dis*, 2002). In contrast, studies in volunteer blood donors in the United States indicate a seroprevalence rate of 0.4%.

Approximately 80% to 85% of individuals with acute HCV infection develop chronic infection (defined as continuing viral replication). The mechanisms that permit apparent clearance in the 15% to

20% in whom chronic infection is not established remain unclear, although infection with a narrow range of viral quasi species and more vigorous humoral and cellular immune responses may be major factors (Farci and Purcell, *Semin Liver Dis*, 2000).

Over the course of about 20 years, approximately 20% of individuals with chronic infection develop cirrhosis and some patients may progress to death from liver failure or hepatocellular cancer. However, progression appears to be highly variable. In studies of progression to cirrhosis after known exposure, rates have varied from 2.4% over 17 years (in a study of women in Ireland who were infected via contaminated anti-D[RH1] immune globulin) to 32.3% over 7.5 years (in patients in Italy infected via transfusion). Factors associated with poor prognosis for chronic HCV infection include male sex, age at HCV acquisition of more than 40 years, alcohol consumption, iron overload, and immunosuppression (Thomas et al, *JAMA*, 2000).

The incidence of HCV infection dropped dramatically after the mid-1980s; the reasons for this decrease remain unclear, although it likely reflects

changes in practice in injection drug use. However, the prevalence of chronic infection is increasing and is expected to triple from current rates by about 2015 (Armstrong et al, *Hepatology*, 2000). This projected increase is of great concern, since the health care system is already stressed at current levels of liver transplantation and expenditures for chronic liver disease.

Rational use of HCV diagnostic tests in patient management includes serologic testing and qualitative HCV RNA testing for diagnosis, and liver biopsy for prognosis. ALT level can be quite variable and is not a reliable indicator of severity of disease. Studies in asymptomatic individuals positive for HCV RNA indicate that ALT levels are normal in 31%, increased by less than 2 times the upper limit of normal (ULN) in 42%, and increased by greater than 2 and 3 times the ULN in 15% and 12%, respectively. Similarly, neither the genotypic nor the viral load is an accurate indicator of the degree of histologic injury (Goedert et al, *J Infect Dis*, 2001). The degree of fibrosis on initial liver biopsy provides important prognostic information; as shown in Figure 1 (Yano et al, *Hepatology*, 1996), the rate of progression

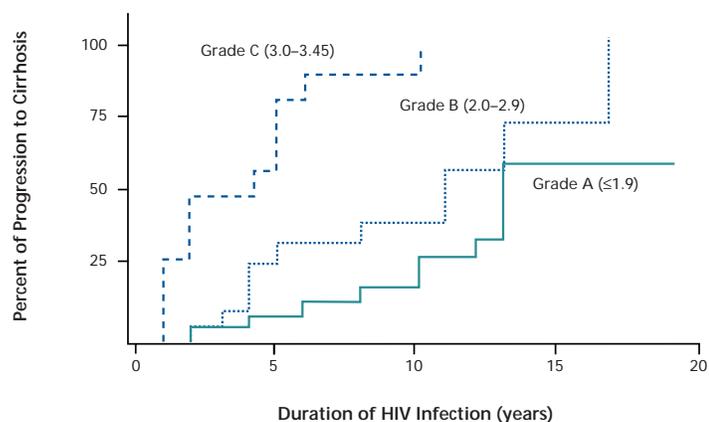


Figure 1. Rate of progression to cirrhosis in chronic hepatitis C virus (HCV) infection according to degree of fibrosis on initial liver biopsy (grades A to C in the METAVIR scoring system for fibrosis indicate progressively higher fibrosis score and worsening fibrosis on a 0-4 scale). Adapted with permission from Yano et al, *Hepatology*, 1996.

Dr Koziel is Assistant Professor of Medicine at Beth Israel Deaconess Medical Center, Harvard Medical School, in Boston, Mass.

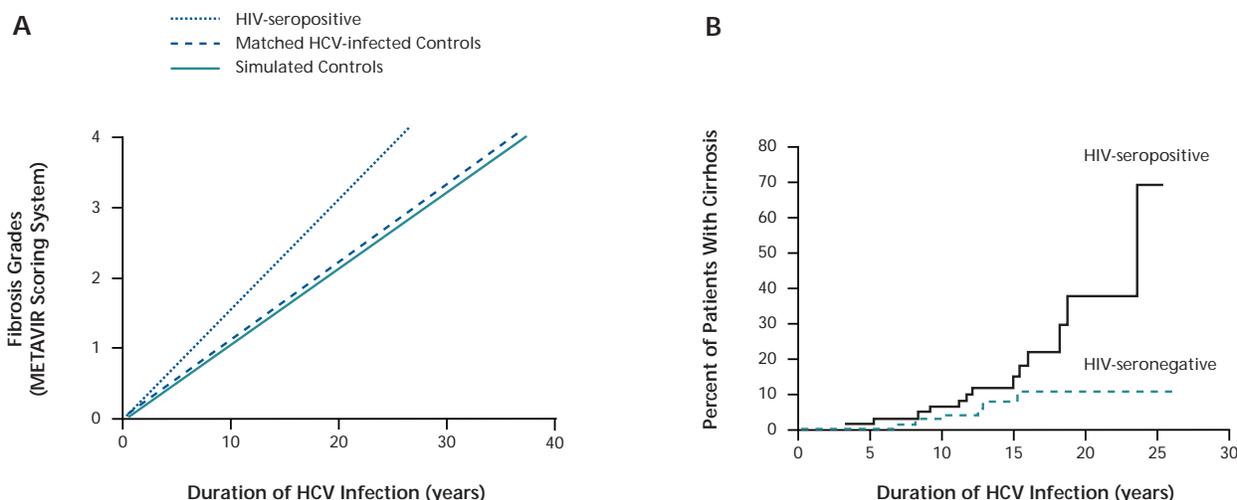


Figure 2A. Rates of progression of liver fibrosis in chronic hepatitis C virus (HCV) infection in patients with HIV infection (n=122), matched HCV-infected controls without HIV infection (n=122), and simulated controls (for which fibrosis progression was predicted using a mathematical model that corrects for age at infection, sex, and alcohol consumption [grams/day]) (n=122). Adapted with permission from Benhamou et al, *Hepatology*, 1999. **B.** Rates of progression to cirrhosis in HCV-infected patients with and without HIV disease. Adapted with permission from Di Martino et al, *Hepatology*, 2001.

to cirrhosis is markedly increased in those with more severe fibrosis.

Genotyping and assessment of HCV viral load are useful for determining duration of anti-HCV treatment; however, response to treatment can be assessed by quantitative HCV RNA assay. Management of patients with HCV infection must include counseling regarding avoidance of alcohol consumption and any drug that might damage the liver (including limiting the use of acetaminophen). It is also important that patients receive vaccination against hepatitis A virus, especially those at increased risk of acquiring infection (eg, men who have sex with men and injection drug users), since the relative risk of hepatic failure is increased 8-fold in patients with HCV infection who acquire hepatitis A infection.

Effect of HIV Infection on HCV Disease

A variety of data indicate that coinfection with HIV and HCV results in increased HCV viral load as immune deficiency progresses, increased risk of HCV perinatal and sexual transmission, and possible alteration of HCV-specific immune responses and accelerated pro-

gression of HCV disease. However, the most important clinical issue is whether HIV coinfection results in more rapid progression of liver disease. Figure 2A shows the more rapid advance in fibrosis grade occurring in coinfecting patients versus HCV-infected matched controls in a study using paired liver biopsies (Benhamou et al, *Hepatology*, 1999). Figure 2B shows the more rapid progression to cirrhosis among coinfecting patients in another study using paired liver biopsies, with risk of cirrhosis at 20 years being about 40% in coinfecting patients compared with about 10% in those with HCV disease alone (Di Martino et al, *Hepatology*, 2001).

A recent meta-analysis of 6 studies used liver biopsy data, documented cirrhosis, or data on hospitalized patients dying from liver failure or hepatocellular carcinoma to assess outcome (Graham et al, *Clin Infect Dis*, 2001). The results indicate that risk of progression to cirrhosis in HCV disease is increased 3.6-fold in HIV-infected patients. A recent study by Bica and colleagues (*Clin Infect Dis*, 2001) shows a marked increase in mortality from end-stage liver disease (ESLD) among cohorts of HIV-infected patients, with the proportion of deaths attributable to ESLD-related deaths increasing from 11% in 1991 and 14% in

1996 to 50% in 1998. One third of patients in the 1998 cohort had a recent history of discontinuing potent antiretroviral therapy due to hepatic toxicity. More than half who died with ESLD had either plasma HIV RNA levels below assay detection limits or CD4+ cell counts greater than 200/ μ L 6 months prior to death. However, many important questions remain, such as whether these rates will change in the era of potent antiretroviral therapy.

Effect of HCV Infection on HIV Disease

Coinfection with HCV appears to be associated with diminished immune reconstitution with antiretroviral therapy in HIV-infected patients. In a cohort study of 3111 HIV-infected patients, HCV infection was associated with a significantly reduced likelihood of achieving a CD4+ cell increase of greater than or equal to 50/ μ L (Greub et al, *Lancet*, 2000). This significant association was maintained when analysis was restricted to the 1596 patients with plasma HIV RNA levels persistently less than 400 copies/mL. Although diminished capacity for immune reconstitution has been observed in other studies as well, not all

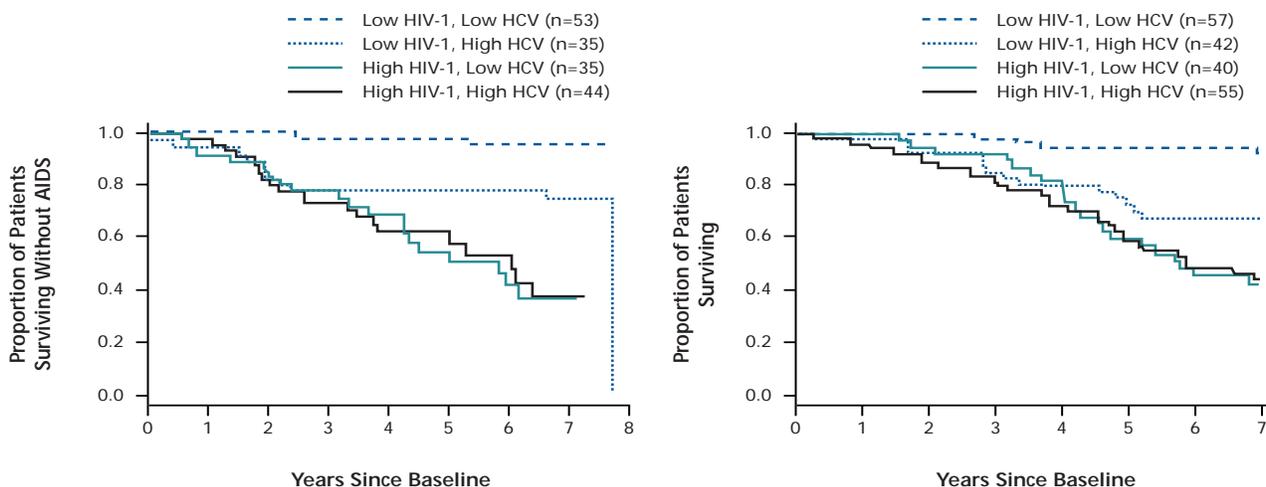


Figure 3. Proportion of patients coinfecting with HIV and hepatitis C virus (HCV) surviving without AIDS (left) and proportion surviving (right) according to low or high HCV and HIV viral load values at the time of study enrollment (baseline). Adapted with permission from Daar et al, *J Infect Dis*, 2001.

studies support this finding. The impact of HCV infection on HIV disease progression to AIDS remains unclear. As shown in Figure 3, however, there are data indicating a more rapid progression to AIDS and to death among coinfecting patients with low HIV viral load who have high HCV viral load than among those with low HCV viral load (Daar et al, *J Infect Dis*, 2001).

HCV infection may also complicate management of HIV disease by increasing the risk of liver toxicity of protease inhibitors and toxicity of antituberculosis medications. One study has indicated increased risk of nephrolithiasis associated with indinavir in coinfecting patients (Brodie et al, *AIDS*, 1998). In addition, there have been case reports of liver failure during immune reconstitution; it has been suggested that such failure may occur in some patients as a result of the increased recognition and destruction of HCV-infected hepatocytes during immune reconstitution under potent antiretroviral therapy (Price et al, *J Clin Virol*, 2001; John et al, *AIDS*, 1998).

Effect of HCV Infection on Antiretroviral Therapy

A number of studies indicate that HCV-infected patients are at increased risk of hepatotoxicity associated with potent antiretroviral regimens. In one recent

study in HIV-infected patients receiving potent therapy, grade 3 or 4 hepatotoxicity was more common in patients with HCV or hepatitis B virus infection than in patients without such coinfection. It was noted, however, that 88% of the coinfecting patients tolerated non-ritonavir regimens without grade 3 or 4 toxicity (Sulkowski et al, *JAMA*, 2000). Risk factors for hepatotoxicity included ritonavir use and CD4+ cell count increase to greater than 500/ μ L.

In a subsequent study, hepatotoxicity, defined as any increase in liver enzymes, occurred in 14.9% of HCV-infected patients versus 5.6% of patients

without HCV coinfection (Aceti et al, *J Acquir Immune Defic Syndr*, 2002). Severe toxicity, defined as a greater than 5-fold increase in enzymes, occurred in 4.8% versus 1.1% of patients. Risk of increased ALT was associated with all protease inhibitors, but only ritonavir use was associated with severe hepatotoxicity. In another study (Monforte et al, *J Acquir Immune Defic Syndr*, 2001), the hazard ratio for aspartate aminotransferase elevation to greater than 200 U/L was 4.01 for HCV-infected patients compared with those without HCV infection. This study found no association of liver enzyme increases with any particular

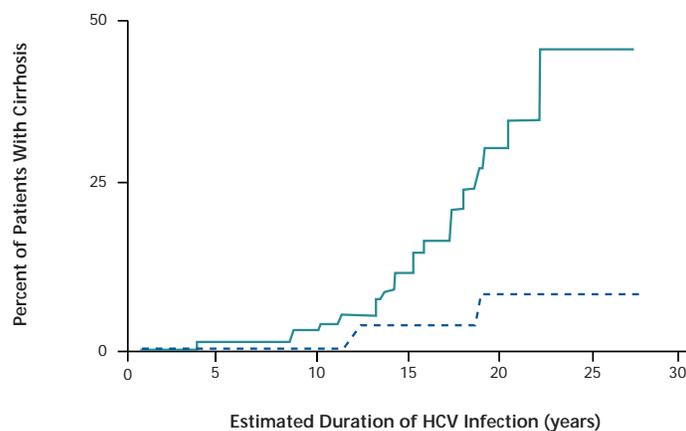


Figure 4. Proportion of patients coinfecting with HIV and hepatitis C virus (HCV) with cirrhosis according to treatment (blue) or no treatment (green) with protease inhibitor-containing regimens. Adapted with permission from Benhamou et al, *Hepatology*, 2001.

antiretroviral regimen. It is important to note that trials of new agents often specifically exclude patients with evidence of chronic liver disease due to HCV infection, so that understanding the true degree of risk from a particular regimen may be difficult until there is extensive phase 4 experience.

Effect of Antiretroviral Therapy on HCV Disease

One study has shown a large reduction in progression to cirrhosis in HIV/HCV-coinfected patients in association with the use of protease inhibitor-containing regimens versus no protease inhibitor treatment (Figure 4; Benhamou et al, *Hepatology*, 2001). However, other recent data do not support this finding. It is possible that studies comparing the effects of protease inhibitor therapy versus non-protease inhibitor treatment are open to selection bias, since patients with more severe HCV-associated liver disease may be precluded from receiving protease inhibitor treatment owing to increased risk of hepatotoxicity. This is obviously an important area for future research.

Treatment of HCV Infection in Patients With HIV Disease

The current recommended drug treatment for HCV infection is pegylated interferon alfa plus ribavirin. Pegylated interferon alfa-2b/ribavirin treatment was associated with sustained virologic response (absence of detectable virus for 6 months after treatment) in 54% of 511 patients, compared with a 47% response rate with the formerly used regimen of thrice weekly standard interferon alfa-2b/ribavirin (Manns et al, *Lancet*, 2001). Among patients with genotype 1 HCV infection, who are the majority of patients in the United States, sustained response rates with the combination interferon alfa/ribavirin regimens have been reported at 42% with pegylated interferon alfa-2b at 1.5 µg/kg (significantly greater than standard interferon alfa/ribavirin treatment), 34% with pegylated interferon alfa-2b at 0.5 µg/kg, and 33% with standard interferon alfa at 3 million units. Response rates with these regimens in patients infected with HCV genotypes 2 or 3 were reported at 82%, 80%, and 79%, respectively.

A number of small studies have examined the effects of interferon

alfa/ribavirin treatment in patients with HIV disease (Table 1), with most having been reported only in abstract form. The 3 fully reported studies showed sustained response rates of 35%, 14%, and 40% in small groups of patients (Landau et al, *AIDS*, 2000; Zylberberg et al, *Gut*, 2000; Sauleda et al, *Hepatology*, 2001). Only 1 study has reported the effect of pegylated interferon alfa/ribavirin in coinfecting patients, with a 33% sustained response rate (Pérez-Olmeda et al, 9th CROI, 2002). However, this European study included a much greater proportion of patients with genotype 3 HCV infection than is characteristic of HCV-infected populations in the United States, which would tend to increase the proportion of sustained responders. Although the virologic response rates at least appear to be lower in coinfecting patients than in those without HIV infection based on the extant literature, there are data suggesting that histologic outcome of treatment does not differ between coinfecting patients and those without HIV infection. As shown in Figure 5, a recent study showed no significant differences in changes in inflammation grade and changes in fibrosis grade with treatment for HCV liver dis-

Table 1. Reported Studies of Interferon Alfa/Ribavirin Treatment for HCV Disease in Patients with HIV Infection

Study	N	Overall Response		Sustained Response		Comments
		Number	Percent	Number	Percent	
Landau et al, <i>AIDS</i> , 2000	20	10/20	50%	7/20	35%	Median CD4+ cell count of 350/µL. No change in plasma HIV RNA levels.
Zylberberg et al, <i>Gut</i> , 2000	21	6/21	29%	3/21	14%	2/10 subjects with plasma HIV RNA levels below detection limit at baseline had HIV RNA increase to detectable levels.
Bochet et al (abstract)	56	-	-	10/56	18%	26% dropout rate.
Sauleda et al, <i>Hepatology</i> , 2001	20	-	-	-	40%	2/10 subjects with plasma HIV RNA levels below detection limit at baseline had HIV RNA increase to detectable levels.
Kostman et al (abstract)	53	-	26%	-	-	54% dropout rate.
Bini et al (abstract)	32	-	-	-	22%	25% dropout rate.
Pérez-Olmeda et al (abstract)*	65	-	50%	-	33%	14% dropout rate.

HCV indicates hepatitis C virus.

*Treatment was pegylated interferon alfa/ribavirin.

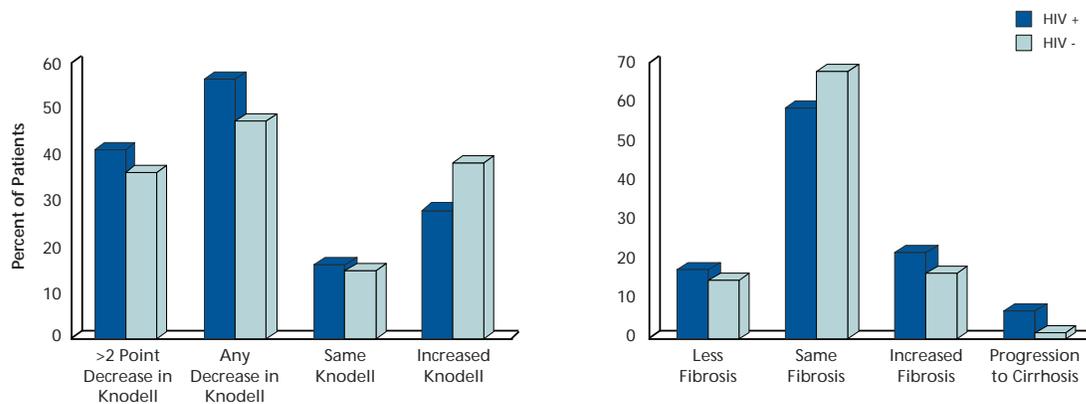


Figure 5. Histologic outcome after treatment of hepatitis C virus (HCV) disease in patients with (dark blue) or without (light green) HIV disease. Change in inflammation on Knodell scale (decrease = less inflammation) is shown on left; change in fibrosis is shown on right. Adapted from Di Martino, *AIDS*, 2002.

ease according to HIV infection status (Di Martino et al, *AIDS*, 2002).

Adverse effects of interferon alfa treatment include a characteristic flu-like syndrome, anemia (myelosuppression) gastrointestinal symptoms, alopecia, somnolence, depression (including suicidal ideation), thrombocytopenia, and neutropenia, including a reduction in CD4+ cell count but not percentage of CD4+ cells. Ribavirin, which is a nucleoside analogue, causes a hemolytic anemia in 8% to 10% of nonimmunocompromised patients. In addition, there are theoretical concerns that ribavirin may interact with nucleoside reverse transcriptase inhibitors (nRTIs) to decrease efficacy of the nRTIs by decreasing intracellular phosphorylation and increase the risk of mitochondrial toxicity and metabolic adverse effects. Ribavirin treatment has been associated with lactic acidosis in patients receiving potent antiretroviral therapy, and zidovudine and ribavirin may be antagonistic in terms of their antiretroviral effects.

Summary

Available data suggest that patients coinfecting with HCV and HIV have an accelerated HCV disease course. HCV infection may impact HIV disease course by inhibiting immune reconstitution and impairing ability to use potent antiretroviral therapy and other HIV-related medications. There is a potential role for drug treatment for HCV infection when histologic disease is present in patients with HIV disease, although

additional data on the effectiveness of treatment in this population are needed. If interferon alfa/ribavirin therapy is used in HIV-infected patients, it is important to monitor for hepatotoxicity, HIV RNA level, CD4+ cell percentage, anemia, and immune reconstitution-related hepatic destruction during HCV therapy.

Presented in March 2002; reviewed and updated by Dr Koziel in May 2002.

Financial Disclosure: Dr Koziel has no affiliations with commercial organizations that may have interests related to the content of this article.

Suggested Reading

Aceti A, Pasquazzi C, Zechini B, De Bac C, The LIVERHAART Group. Hepatotoxicity development during antiretroviral therapy containing protease inhibitors in patients with HIV: the role of hepatitis B and C virus infection. *J Acquir Immune Defic Syndr*. 2002;29:41-48.

Armstrong GL, Alter MJ, McQuillan GM, Margolis HS. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. *Hepatology*. 2000;31:777-782.

Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfecting patients. The Multivirc Group. *Hepatology*. 1999;30:1054-1058.

Benhamou Y, Di Martino V, Bochet M, et al. Factors affecting liver fibrosis in human immunodeficiency virus- and hepatitis C virus-coinfecting patients: impact of protease inhibitor therapy. *Hepatology*. 2001;34:283-287.

Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis*. 2001;32:492-497.

Bini EJ, Reid M, Mannix RA. Safety and efficacy of interferon alpha-2B and ribavirin combination therapy for the treatment of hepatitis C in patients co-infected with HIV. *Hepatology*. 2001;34:335A.

Bochet M, De Torres M, Valantin MA, et al. Efficacy and tolerance of IFN α plus ribavirin for chronic hepatitis C in HIV-infected patients. [Abstract 574.] 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001; Chicago, Ill.

Brodie SB, Keller MJ, Ewenstein BM, Sax PE. Variation in incidence of indinavir-associated nephrolithiasis among HIV-positive patients. *AIDS*. 1998;12:2433-2437.

Daar ES, Lynn H, Donfield S, et al. Hepatitis C virus load is associated with human immunodeficiency virus type 1 disease progression in hemophiliacs. *J Infect Dis*. 2001;183:589-595.

Di Martino V, Rufat P, Boyer N, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. *Hepatology*. 2001;34:1193-1199.

Di Martino V, Thevenot T, Boyer N, et al. HIV coinfection does not compromise liver histological response to interferon therapy in patients with chronic hepatitis C. *AIDS*. 2002;16:441-445.

Farci P, Purcell RH. Clinical significance of hepatitis C virus genotypes and quasi species. *Semin Liver Dis*. 2000;20:103-126.

Goedert JJ, Hatzakis A, Sherman KE, Eyster ME, Multicenter Hemophilia Cohort Study. Lack of association of hepatitis C virus load and genotype with risk of end-stage liver disease in

patients with human immunodeficiency virus coinfection. *J Infect Dis.* 2001;184:1202-1205.

Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis.* 2001;33:562-569.

Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet.* 2000;356:1800-1805.

John M, Flexman J, French MA. Hepatitis C virus-associated hepatitis following treatment of HIV-infected patients with HIV protease inhibitors: an immune restoration disease? *AIDS.* 1998;12:2289-2293.

Kostman J, Rodriguez-Torres M, Prokupek D, et al. Results of a multicenter randomized, double-blind, controlled trial of interferon alfa-2b/ribavirin combination therapy in HCV/HIV coinfecting persons. [Abstract 555.] 1st International AIDS Society Conference on HIV Pathogenesis and Treatment. June 8-11, 2001; Buenos Aires, Argentina.

Landau A, Batisse D, Van Huyen JP, et al. Efficacy and safety of combination therapy with interferon-alpha2b and ribavirin for chronic hepatitis C in HIV-infected patients. *AIDS.* 2000;14:839-844.

Landau A, Batisse D, Piketty C, et al. Long-term efficacy of combination therapy with interferon-alpha 2b and ribavirin for severe chronic hepatitis C in HIV-infected patients. *AIDS.* 2001;15:2149-2155.

Liang TJ, Rehermann B, Seeff LB, Hoofnagle JH. Pathogenesis, natural history, treatment, and prevention of hepatitis C. *Ann Intern Med.* 2000;132:296-305.

Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet.* 2001;358:958-965.

Monforte A, Bugari R, Pezzotti P, et al. Low frequency of severe hepatotoxicity and association with HCV coinfection in HIV-positive patients treated with HAART. *J Acquir Immune Defic Syndr.* 2001;28:114-123.

Pérez-Olmeda M, Núñez M, Romero M, et al. Pegylated interferon plus ribavirin as therapy for chronic hepatitis C in HIV-infected patients. [Abstract 652-M.] 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002; Seattle, Wash.

Price P, Mathiot N, Krueger R, Stone S, Keane NM, French MA. Immune dysfunction and immune restoration disease in HIV patients given highly active antiretroviral therapy. *J Clin Virol.* 2001;22:279-287.

Sauleda S, Juarez A, Esteban JJ, et al. Interferon and ribavirin combination therapy for chronic hepatitis C in human immunodeficiency virus-infected patients with congenital coagulation disorders. *Hepatology.* 2001;34:1035-1040.

Sherman KE, Rouster SD, Chung RT, Rajcic N. Hepatitis C virus prevalence among patients infected with human immunodeficiency virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. *Clin Infect Dis.* 2002;34:831-837.

Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA.* 2000;283:74-80.

Thomas DL, Asemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA.* 2000;284:450-456.

Yano M, Kumada H, Kage M, et al. The long-term pathological evolution of chronic hepatitis C. *Hepatology.* 1996;23:1334-1340.

Zylberberg H, Benhamou Y, Lagneaux JL, et al. Safety and efficacy of interferon-ribavirin combination therapy in HCV-HIV coinfecting subjects: an early report. *Gut.* 2000;47:694-697.