Perspective

Strategies for Managing Hepatitis C Virus Infection in HIV-Infected Patients

Liver disease associated with hepatitis C virus (HCV) is a significant and increasing cause of death for HIV-infected patients, but limited data exist to guide treatment of coinfection. Increased knowledge of HCV disease and its treatment among HIV care practitioners and adoption of routine care procedures can improve management of coinfected patients. This article discusses HCV screening and diagnosis, counseling and health care maintenance, and evaluation for and supervision of treatment in HIV-seropositive patients who are coinfected with HCV. The experiences of the Oakland, California-based Alameda County Medical Center, which treats more than 200 coinfected patients, are detailed and serve as the basis for suggested management strategies. This article summarizes a presentation given by Kathleen A. Clanon, MD, at the November 2002 International AIDS Society–USA course in San Diego.

Challenges in the Management of HIV/HCV Coinfection

Hepatitis C virus (HCV) infection is a common comorbidity in HIV-infected individuals in the United States, with current estimates indicating that one-fourth to one-third of HIV-seropositive patients are coinfected with HCV. Liver disease associated with HCV, as well as with hepatitis B virus (HBV) and other causes, is a significant and increasing cause of death in the HIV-infected patient population. Current treatment for HCV infection, consisting of an interferon alfa-based therapy (currently pegylated interferon alfa/ribavirin), is of limited effectiveness, difficult to tolerate, expensive, and dangerous in some subsets of patients. Currently, HIV clinicians are struggling with how extensively they can and should treat HCV in coinfected patients.

Some idea of the inadequacy of care extended to HCV-coinfected patients is demonstrated by a chart review performed in 2000 among patients from a consortium of community clinics in Alameda County, Calif (S. O'Brien, MD, unpublished data). This review showed that the majority of the 1021 HIV-infected patients attending these clinics had been screened for HCV and HBV infection and that 271 (27%) had HCV coinfection. In the HIV/HCV-coinfected group, however, counseling about coinfection status was rarely documented clearly, less than half the group had received recommended vaccinations for HBV and hepatitis A virus (HAV), and only 5 patients (1.8%) had received interferon alfa-based treatment for HCV infection. Since the time of this review, however, the clinics have made efforts to improve the routine management of HCV-coinfected patients, as discussed below.

There are a number of barriers to providing optimal treatment for HIV/HCV-coinfected patients. HIV care providers are inexperienced with and skeptical of interferon alfa-based treatment of HCV infection. HCV experts are pessimistic about the outcomes of HCV treatment in HIV-infected patients and reluctant to provide such care. Relevant work-ups, especially liver biopsy, and treatment are expensive and often not funded for the medically indigent. In many cases, mental health care and substance abuse treatment are crucial to optimal HCV treatment but are frequently difficult to access.

Inadequate overall knowledge of HCV infection and treatment among HIV care practitioners also appears to hinder provision of optimal care. A recent survey tested HCV knowledge among 109 HIV care practitioners rating themselves as experts in HIV care (Smith et al, 39th IDSA, 2001). Of the respondents, 64% were physicians and the remainder were nurse practitioners or physician assistants; most had practices with more than 100 HIV-infected patients. Overall, only 23% of the respondents received a passing score of 65% or better.

On the other hand, optimal care for HCV infection appears to be elusive even when physician expertise is not at issue. In a chart review study in an urban gastroenterology specialty clinic, only 83 (28%) of 293 patients evaluated for HCV infection received treatment; the most frequent reason for not providing treatment was patient nonadherence to scheduled visits (37%), followed by medical contraindication (34%), active substance abuse (13%), and patient preference (11%) (Falck-Ytter et al, *Ann Intern Med*, 2002). The authors of this report concluded that most HCV-infected patients will not be able to derive benefit from interferon alfa-based therapy. However, the above findings also suggest opportunities for improving care. In particular, appropriate support in the HCV care clinical setting guided by improved knowledge of HCV disease and treatment might improve management and treatment of coinfected patients.

Indeed, HCV infection should be considered a primary care issue in the HIV-infected population, given the high frequency of coinfection. HIV care practitioners should become knowledgeable about HCV disease and treatment issues and design or adopt protocols for managing coinfected patients and providing direct care or referrals consistent with available resources. The Alameda County Medical Center, for example, has organized management of HIV/HCV coinfection by phases of care, consisting of screening and diagnosis, counseling and health care maintenance, evaluation for

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treatment, and supervision of such treatment. Alameda County Medical Center practitioners also use the treatment decision tree for HIV/HCV coinfection depicted in Figure 1. Published resources that may be of assistance in devising management protocols include Veterans Administration guidelines for HCV testing and prevention counseling (available at www.va.gov/hepatitisc/pdf/ce203_testncoun slguides.pdf) and for providing and monitoring HCV therapy (available at www.va.gov/hepatitisc/pved/trtgdlns00.htm). The National Institutes of Health has also recently released updated consensus guidelines for managing HCV (available at http://consensus.nih.gov/cons/116/116cdc_intro.htm).

Screening and Diagnosis

Screening for and diagnosis of HCV infection are relatively straightforward. All HIV-infected patients should be assessed by enzyme immunosorbent assay for HCV antibody and by standard HCV serology. A small proportion of patients, particularly those with low CD4+ cell counts, may be HCV antibody-negative but exhibit HCV viral load. For example, 3.4% of 474 patients in one series had false-negative antibody results (Boyle and Vaamonde, Dig Dis Week, 2002), and 7 of the more than 200 HIV/HCV-coinfected patients in the Alameda County Medical Center's clinic population have remained HCV antibody-negative. Thus, assessment of HCV viral load should be considered in antibody-negative patients who have risk factors for HCV infection or unexplained persistently elevated alanine aminotransferase or aspartate aminotranferase levels.

Counseling and Health Care Maintenance

Counseling should include discussion of prognosis of coinfection, importance of avoiding alcohol consumption and potentially hepatotoxic medications, avoidance of transmission of HCV, and basic treatment approaches for HCV infection. With regard to prognosis, a number of studies have indicated that coinfection results in increased risk of progression of liver disease, though it remains unclear whether progression of HIV disease is accelerated. For example, one study in a cohort of 134 hemophilia patients (Lesens et al, *J Infect Dis,* 1999) found an odds ratio of 7.4 for progressive liver disease among 81 coinfected patients compared with risk in 53 patients with HCV infection alone. The median survival after diagnosis of progressive liver disease in coinfected patients was 3.2 years.

Needle sharing is the primary mode of HCV transmission. According to the Centers for Disease Control and Prevention, risk also appears to be associated with shared household items, such as toothbrushes and razors (www.cdc.gov/ncidod/diseases/hepatitis/c/faq.htm). Some guidelines recommend against sharing such items. Sex does not appear to be a major route of HCV transmission, but barrier methods are clearly indicated in the coinfected population. Health care maintenance steps include referrals to alcohol and drug treatment programs, needle-exchange programs, and peer support groups and resources; provision of HAV and HBV vaccines to patients without immunity; and intensified monitoring of liver enzymes in patients receiving potent antiretroviral therapy.

> Liver disease associated with HCV, as well as with HBV and other causes, is an increasing cause of death in HIV-infected persons

Evaluation for Treatment

Evaluation for potential interferon alfa-based treatment includes assessment of treatment readiness, ensuring that the patient:

- Understands the difficulty and uncertain benefits of treatment and wishes to go forward with it
- Abstains from alcohol and drugs for more than 6 months or is engaged in a drug treatment program
- Has support resources in place
- Has or can obtain insurance coverage for treatment (in some states, AIDS Drug Assistance Program funding covers HCV treatment in HIV-infected persons)

Medical assessments include HCV genotype, which determines the length of therapy and influences the likelihood of a successful outcome. Liver enzymes, prothrombin time/partial prothrombin time, bilirubin, albumin, and complete blood count should be measured as part of an assessment for preexisting cirrhosis, which does not serve as a contraindication to treatment but increases associated risk of cytopenia. Thyroid-stimulating hormone and antinuclear antibody levels should be measured to detect preexisting thyroid abnormalities and autoimmune hepatitis, since each can occur with interferon alfa-based therapy. Ferritin and alpha-fetoprotein should be assessed to check for concomitant liver disease associated with HCV or other causes. Pregnancy tests should be performed in women with child-bearing potential, since ribavirin is teratogenic. Liver biopsy should be obtained if possible to assess fibrosis and inflammation, with these findings being the primary determinant of whether a patient should begin treatment.

The potential benefits of treatment include delaying progression of liver disease and death in patients with fibrosis stage 3 or 4. It should be noted that although there is evidence of such benefit in patients with HCV infection alone, data are not yet available on outcomes in coinfected patients. Additional benefits may include the potential for eradicating HCV (if HIV disease is stable and CD4+ cell count is >200/µL), making potent antiretroviral therapy safer and more tolerable by reducing liver toxicity, and reducing pain, offering hope, and

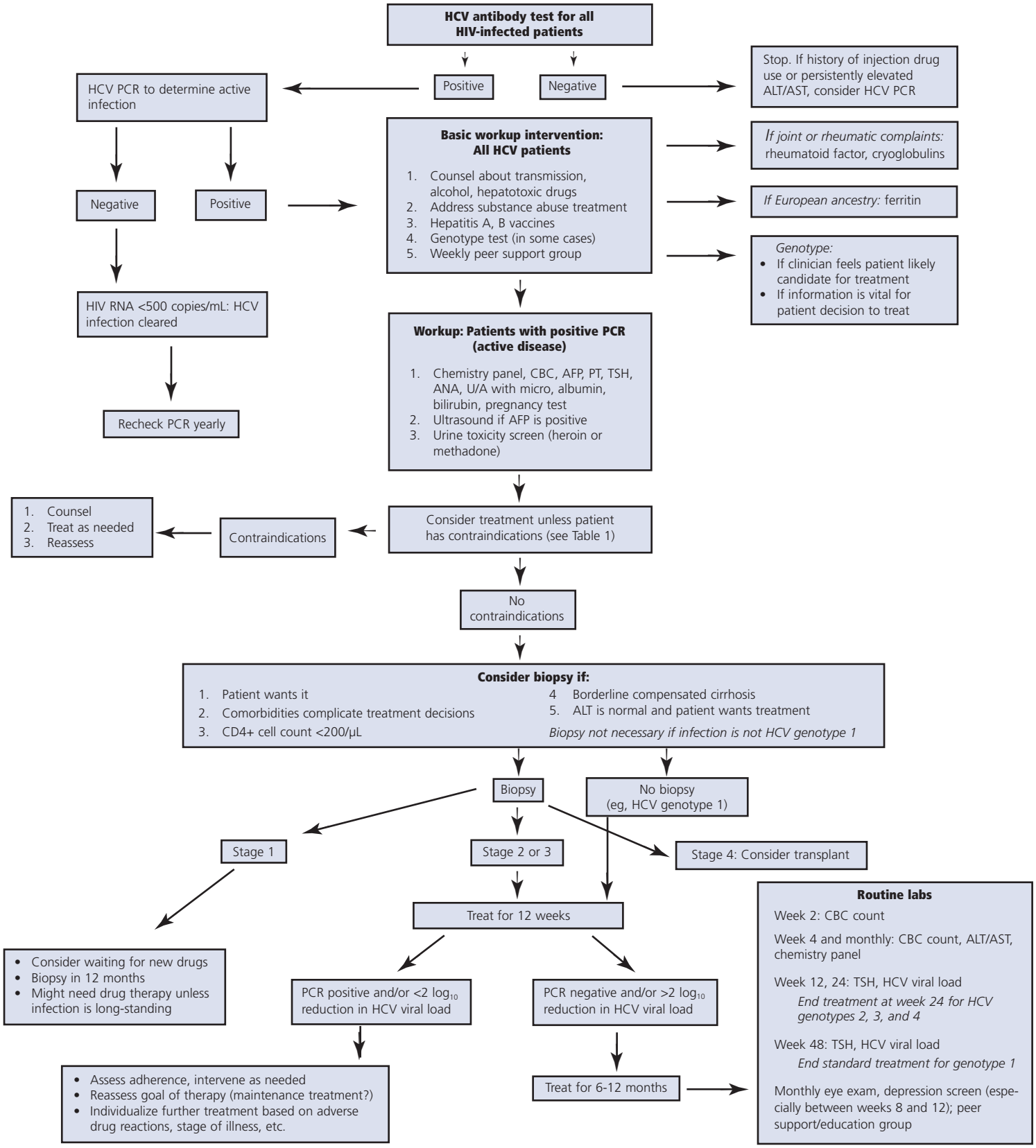

Figure **1.** Alameda County Medical Center treatment decision tree for coinfection with HIV and hepatits C virus (HCV). This decision tree contains expert opinion but is not clinically validated. AFP indicates alpha-fetoprotein; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CBC, complete blood cell; PCR, polymerase chain reaction; PT, prothrombin time; TSH, thyroid-stimulating hormone; U/A, urine analysis.

staving off liver transplantation. None of the studies of interferon alfa/ribavirin therapy performed thus far, however, provides information on whether treatment is successful in inducing regression of liver disease, even in the absence of control of HCV replication.

An idea of the results achieved with interferon alfa/ribavirin therapy in coinfection is provided by the recent RIBAVIC study (Perronne et al, 42nd ICAAC, 2002). In that study, 416 coinfected patients with a mean CD4+ cell count of 515/μL were randomized to pegylated interferon alfa/ribavirin or standard interferon alfa/ribavirin for 48 weeks. Eighty percent of patients were receiving potent antiretroviral therapy and 66% were infected with HCV genotype 1 or 4, the most common HCV genotypes in the United States. End-of-treatment response rates (proportion of patients with HCV viral load below assay detection limits at the end of treatment) at 48 weeks in an intent-to-treat analysis were 38% (59 of 157) in the pegylated interferon alfa/ribavirin group and 24% (39 of 162) in the standard interferon alfa group ($P = .01$). On as-treated analysis, end-of-treatment response rates were 50% (50 of 100) in the pegylated interferon alfa/ribavirin group versus 31% (32 of 105) in the standard interferon alfa/ribavirin group ($P < .01$), including rates of 27% for pegylated interferon alfa/ribavirin and 9% for standard interferon alfa/ribavirin in the group of patients with genotype 1 or 4 HCV.

Sustained virologic response is defined as viral load below limits of assay detection at 6 months after the end of therapy; in patients with HCV monoinfection, such response is predictive of absence of detectable virus at 5 years. Sustained virologic response rates in coinfected patients have been reported in smaller studies of standard interferon alfa-based therapies of 17.9% (Bochet et al, 8th CROI, 2001), 21% (Landau et al, *AIDS,* 2001), 40% (Sauleda et al, *Hepatology,* 2001), and 22% (Perez-Olmeda et al, 9th CROI, 2002). The RIBAVIC study discussed above will also examine post-treatment liver biopsies, which are expected to provide important information on the effects of treatment on liver disease regression and progression. Another ongoing large-scale study in coinfected patients, undertaken by the AIDS Clinical Trials Group, will provide additional data on treatment response in the coinfected population.

On the basis of currently available data, medical factors that provide strong indications and contraindications for initiating interferon alfa-based therapy are listed in Table 1.

Supervising Treatment

Supervising HCV therapy is an intensive process and should be undertaken only if sufficient resources can be devoted to patient monitoring. Pegylated interferon alfa/ribavirin has better efficacy than standard interferon alfa/ribavirin (Fried et al, *N Engl J Med,* 2002). It is administered by once-weekly injection for 48 weeks in the case of HCV genotype 1 infection and for 24 weeks in the case of infection with other genotypes. Treatment efficacy is indicated by normalization of aspartate aminotransferase levels (which generally occurs at 6 weeks to 2 months after the start of successful treatment) and by HCV viral load below limits of assay detection at 24 weeks, end of treatment, and 6 months after treatment. Treatment discontinuation should be considered if there is no virologic response at 24 weeks. Coinfected patients are more likely than patients infected with HCV alone to develop hemolytic anemia and leukopenia within the first few weeks of interferon alfa/ribavirin therapy. Complete blood cell count with differential should be obtained for coinfected patients after the second week of treatment and then every month thereafter. A low threshold for use of epoetin alfa (ie, hemoglobin < 10 g/dL) and granulocyte colony-stimulating factor (ie, neutrophil count < 1000/mL) should be maintained; in fact, all coinfected patients receiving HCV treatment at the Alameda County Medical Center begin epoetin alfa therapy immediately since anemia has been a predictable complication of treatment (Dieterich et al, 53rd Am Assoc Stud Liver Dis, 2002). The ribavirin dose should be decreased by 200 mg if hemoglobin decreases to less than 10 g/dL.

Depression is a very common complication of treatment, and pretreatment with selective serotonin reuptake inhibitor antidepressants should be considered (Schaefer et al, *Hepatology,* 2003); such pretreatment is routinely performed at Alameda County Medical Center. Thyroid-stimulating hormone should be assessed every 6 months. Pregnancy tests should be performed every month during treatment and for 6 months after treatment. Although routine screening of lactate levels is not recommended yet, it is prudent to remain alert for signs of lactic acidosis. A recent report of 265 coinfected patients on potent antiretroviral therapy (mean CD4+ cell count, 505/μL) who received either pegylated or standard interferon alfa/ribavirin for 48 weeks found 10 cases of hyperlactatemia and 4 cases of

Table **1.** Indications and Contraindications for Interferon Alfa-Based Treatment of HCV Infection

Indications

- Portal or bridging fibrosis and moderate inflammation or necrosis on liver biopsy
- Clinical signs of compensated cirrhosis and persistently elevated alanine aminotransferase and detectable HCV RNA levels
- In HIV/HCV-coinfected patients, high CD4+ cell count and not currently on antiretroviral therapy (these patients are better candidates for HCV therapy)

Contraindications

- Signs of decompensated cirrhosis (eg, varices, encephalopathy, ascites)
- Severe anemia or platelets <75,000/mL or white blood cell count <1500/mL
- Current severe or uncontrolled depression
- Pregnancy, breastfeeding, or likelihood of getting another person pregnant
- In HIV/HCV-coinfected patients, unstable HIV disease (eg, recent opportunistic disease)

HCV indicates hepatitis C virus.

pancreatitis in 13 patients. Twelve of these patients were receiving stavudine or didanosine for HIV therapy and 9 were receiving both (Hor et al, 42nd ICAAC, 2002). Suspicion of lactic acidosis or pancreatitis should be heightened in patients receiving either of these nucleoside reverse transcriptase inhibitors, and switching to other antiretroviral drugs should be considered if HCV therapy is to be started.

Treatment Protocols at Alameda County Medical Center

At Alameda County Medical Center, 22 coinfected patients had begun receiving pegylated interferon alfa/ribavirin therapy as of November 2002. For training purposes, clinicians shadow a gastroenterology specialist for 3 days to learn management strategies. Weekly patient peer support groups are important for symptom management, with patients providing invaluable advice to each other on how to handle adverse effects of treatment. Patients are contacted by telephone at a minimum of once daily during the first week of treatment and once weekly thereafter, as daily contact during the first week has been found to be a significant predictor of continuation of treatment into the second week. As the number of coinfected patients being monitored on HCV therapy grew to more than 10, one registered nurse was assigned to work exclusively with these patients, with the time expenditure equaling approximately one-half that of a full-time employee.

In addition to learning that routine early use of epoetin alfa and pretreatment with antidepressant therapy are advisable, Alameda County Medical Center has found that drinking water is the best way for patients to reduce the symptoms of adverse drug effects and recommends intake of 10 to 15 8-oz glasses a day. Patients are also warned that T-cell counts will fall, with CD4+ cell percentage remaining unchanged, during the white blood cell count decrease accompanying interferon alfa/ribavirin therapy. These measures have likely increased adherence to treatment and improved quality of care; however, the treatment dropout rate remains high at about 30%, consistent with what has been reported in the clinical trial literature.

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Suggested Reading

Bochet M, De Torres M, Valantin MA, et al. Efficacy and tolerance of IFNa 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.

Boyle B, Vaamonde C. Prevalence of and risk factors for HCV RNA detection in HIV/HCV coinfected patients who are HCV antibody negative. [Abstract 106665.] Digestive Disease Week. May 19-22, 2002; San Francisco, Calif.

Centers for Disease Control and Prevention National Center for Infectious Diseases. Viral Hepatitis C: Frequently Asked Questions. Available at: http://www.cdc.gov/ncidod/diseases/hepatitis/c/faq.htm. Accessed February 5, 2003.

Dieterich D, Pockros P, Schiff E, et al. Epoetin alfa once weekly maintains ribavirin dose in HCV-infected patients treated with combination therapy: interim results of a randomized, double-blind, placebo-controlled study. 53rd Annual Meeting of the American Association for the Study of Liver Diseases. November 1-5, 2002; Boston, Mass.

Falck-Ytter Y, Kale H, Mullen KD, Sarbah SA, Sorescu L, McCullough AJ. Surprisingly small effect of antiviral treatment in patients with hepatitis C. *Ann Intern Med.* 2002;136:288-292.

Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med.* 2002;347:975-982.

Hor T, Deshayes J, Banisadr F, et al. Concomitant ddI/d4T and IFN (standard or pegylated)/ribavirin treatments may induce a high risk of mitochondrial toxicity in HIV/HCV infected patients (ANRS HC02-RIBAVIC Study). [Abstract H-1735.] 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy. September 27-30, 2002; San Diego, Calif.

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.

Lesens O, Deschenes M, Steben M, Belanger G, Tsoukas CM. Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus-positive hemophiliacs and should be treated as an opportunistic infection. *J Infect Dis.* 1999;179:1254-1258.

National Institutes of Health Consensus Development Program. Management of hepatitis C: 2002. 2002;19(1). Available at: http://consensus.nih.gov/cons/116/116cdc_intro.htm. Accessed December 17, 2002.

Perez-Olmeda M, Asensi V, Romero M, et al. Treatment of chronic hepatitis C: SHIRT (Spanish HIV Interferon Ribavirin Trial). [Abstract 653.] 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002; Seattle, Wash.

Perronne C, Carrat F, Banisadr P, et al. A randomized controlled trial of pegylated-interferon alfa-2b plus ribavirin vs interferon alfa-2b plus ribavirin for the initial treatment of chronic hepatitis C in HIV co-infected patients. [Abstract H-1083.] 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy. September 27-30, 2002; San Diego, Calif.

Sauleda S, Juarez A, Esteban JI, 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.

Schaefer M, Schmidt F, Folwaczny C, et al. Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. *Hepatology*. 2003;37:443-451.

Smith CA, Johnson M, Brown LS. Hepatitis C knowledge base of providers caring for HIV positive communities of color. [Abstract 902.] 39th Annual Meeting of the Infectious Diseases Society of America. October 25-28, 2001; San Francisco, Calif.

Veterans Administration National Hepatitis C Program. Hepatitis C testing and prevention: counseling guidelines for VA health care practitioners. Available at: http://www.va.gov/hepatitisc/pdf/ce203_testncounslguides.pdf. Accessed February 3, 2003.

Veterans Administration National Hepatitis C Program. Treatment recommendations for patients with chronic hepatitis C: 2002 version 3.0. Available at: http://www.va.gov/hepatitisc/pved/trtgdlns00.htm. Accessed January 31, 2003.

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