Liver disease has emerged as a major cause of morbidity and mortality in patients infected with the human immunodeficiency virus (HIV). The introduction of pegylated interferon α (PEG-IFN α) and ribavirin (RBV) combination therapy has greatly improved treatment options for patients coinfected with HIV/hepatitis C virus (HCV). However, management of HCV in HIV-coinfected patients is complicated by the myelosuppressive effects of anti-HCV therapy, potential hepatotoxicity of antiretroviral therapy, and accelerated progression of liver fibrosis. Patient selection, timing of anti-HCV therapy, and evaluation of the potential drug interactions between HCV and antiretroviral therapy are important factors in the management of HCV infection in this patient population. Current evidence from large randomized studies of PEG-IFN α plus RBV indicates that coinfected patients should be treated earlier in the course of HCV infection, and the duration of therapy should potentially be longer to maximize the likelihood of sustained virologic response. Several questions remain regarding optimal timing of treatment, length of treatment, and the role of HIV/HCV virus-specific interactions on prognosis and response to treatment. (Adv Stud Med. 2005;5(4C):S356-S360)
HCV in HIV-infected patients, interactions between anti-HIV and anti-HCV drugs, suppression of immune response, and lack of experience with current anti-HCV therapies in this patient population. Over the past few years, several consensus reports have addressed the management of patients with HIV/HCV coinfection. This review discusses the management of chronic HCV infection in the patient infected with HIV, highlighting diagnosis, timing and duration of HCV therapy, and potential toxicity associated with HCV therapy in patients infected with HIV-1.

**Screening and Diagnosis**

The high prevalence of HIV/HCV coinfection and increased risk for progression to advanced liver disease prompted the US Public Health Service (USPHS), in collaboration with the Infectious Diseases Society of America, to recommend that all HIV-infected patients be tested for HCV infection. Despite these recommendations, many patients with HIV are not appropriately screened for HCV. Proper diagnosis and treatment of HCV infection may reduce the progression of HCV-related liver disease and the risk for severe hepatotoxicity in patients receiving highly active antiretroviral therapy (HAART).

**SEROLOGIC AND VIROLOGIC TESTS**

Hepatitis C virus is usually diagnosed first with a test for anti-HCV antibodies in the blood or serum, and positive results are confirmed with an HCV-RNA test to document viremia. Third-generation enzyme immunoassay (EIA-3) tests, with a sensitivity of greater than 99%, can serologically confirm the presence of HCV by detecting antibodies to the virus. Additional or supplemental testing using recombinant immunoblot assay (RIBA; Ortho Diagnostics, Raritan, NJ) is often used to confirm the results of EIA tests. However, patients coinfected with HIV/HCV often have indeterminate or negative RIBA reactivity compared with monoinfected patients. In one study, HIV-positive patients who were HCV-RNA positive were found to react to fewer HCV antigen bands and to have weaker reactivity to HCV antigens than HIV-negative patients.

Despite the high specificity and sensitivity of EIA-3 tests, false positives do occur. Consequently, all positive EIA tests for anti-HCV antibodies should be confirmed by measuring HCV RNA. The importance of confirmatory HCV-RNA testing is highlighted in a study that evaluated the diagnostic accuracy of serologic tests (enzyme-linked immunosorbent assay [ELISA]-2, ELISA-3, and RIBA) for antibodies to HCV in 369 patients with and without HIV-1 infection. In this study, HCV RNA was detected in the serum of 6 of 110 patients who had negative results on anti-HCV ELISA-2. Furthermore, the results of ELISA-3 were negative in 2 of 6 patients, and the results of RIBA were negative in 3 of 6 patients.

In addition, false-negative EIAAs have been reported in patients with HIV, particularly in those patients with low CD4 counts. False-negative HCV antibody may be associated with very low CD4 cell counts in patients coinfected with HIV/HCV. The failure to detect early HCV antibodies, particularly in patients with acute infection or with advanced immunodeficiency (CD4 cell count <0.1×10^9 cells/L), may result in a negative EIA. In a recent study, HCV viremia was found by polymerase chain reaction for HCV RNA in 6% of patients with HIV with a negative EIA. In the setting of unexplained liver enzyme abnormality or suspected acute HCV infection, it may be useful to test HCV RNA even when HCV EIA is negative.

Although quantitative HCV-RNA assays detect and measure HCV, the clinical significance of quantitative HCV-RNA testing in HIV-infected patients remains unclear. Unlike the relationship between HIV viremia and rate of disease progression, no correlation has been demonstrated between HCV RNA and severity of hepatic inflammation or fibrosis on liver biopsy. Therefore, quantification of HCV load in HIV-infected patients should be interpreted as a need for anti-HCV treatment rather than an indication of disease severity.

**Liver Biopsy**

Liver biopsy is the key to staging liver disease. Occasionally, a liver biopsy may reveal other occult diseases, such as steatohepatitis or hemochromatosis, in addition to other opportunistic infections. The new USPHS guidelines recommend liver biopsy in the evaluation of all patients coinfected with HIV/HCV, including patients with hemophilia. Some experts would choose not to biopsy patients with genotype 2 or 3 disease, based on the high initial treatment response rates.

Recent data from the AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT) com-
pared treatment with PEG-IFN α-2a plus RBV/placebo with IFN α-2a plus RBV in a total of 859 patients and underscored the value of liver biopsy in patients coinfected with HIV/HCV. In this study, 10% (14 of 859) of patients experienced hepatic decompensation during the study. All 14 patients had cirrhosis and Child-Pugh scores of 5 or higher at baseline; 6 of 14 patients died. These results demonstrate that patients with advanced cirrhosis, despite the absence of a history of hepatic decompensation, should be monitored closely during IFN-α–based therapy because they are at risk of hepatic decompensation. Treatment with antiretroviral agents, such as didanosine (ddl), may increase the risk further.

The use of noninvasive biochemical serum markers to predict the extent of fibrosis in patients infected with HCV may provide an alternative for patients who are reluctant to undergo liver biopsy or for whom biopsy is contraindicated. Although several of these approaches effectively distinguish patients at the extremes (ie, with little or no fibrosis and those patients with advanced disease), they are less reliable at identifying patients with intermediate stages of disease. Although a recent review of the diagnostic value of biochemical markers of liver fibrosis (FibroTest) and necrosis (ActiT est) concluded that these tests can be used as alternatives to liver biopsy to assess liver injury in patients with chronic HCV, many experts disagree with this assessment. Pending validation of noninvasive staging surrogates in patients coinfected with HIV/HCV, liver biopsy provides the most accurate information for grading and staging liver disease.

**Timing and Duration of Hepatitis C Virus Therapy**

The appropriate timing of HCV treatment in HIV-coinfected patients is a complicated issue for which there is no empiric answer. In addition to the stage of liver disease, CD4 levels and viral load should be considered when deciding to initiate HCV therapy in HIV-coinfected patients. In trials using standard IFN/RBV, SVR rates were higher when CD4+ count was higher than 500 cells/µL and lower when CD4 count was 200 to 500 cells/µL. These results have not been confirmed in large PEG-IFN/RBV trials, although detailed analyses at levels below 500 cells/µL have not been reported. Typically, patients with CD4 counts higher than 500 cells/µL are optimal candidates for treatment, exhibiting response rates that mirror HCV-monoinfected patients. Patients with CD4+ counts of 200 to 500 cells/µL may also benefit from anti-HCV therapy before starting antiretroviral therapy if plasma HIV-RNA levels are low (<5000 copies/mL). Patients with CD4+ counts lower than 200 cells/µL should generally not receive anti-HCV therapy because of low SVR rates to anti-HCV therapy and potential for IFN-α therapy to further reduce CD4 levels in this patient population. These patients may benefit from aggressive antiretroviral therapy.

Failure to achieve early virologic response during anti-HCV therapy is predictive of failure to reach SVR in HIV-coinfected patients and can be used to determine the duration of therapy. Recent randomized studies of PEG-IFN α plus RBV in patients coinfected with HIV/HCV have found that early virologic response after 12 weeks of therapy is a negative predictor of SVR rates. In these studies, patients who failed to achieve an early virologic response (defined as an undetectable HCV-RNA level or a decrease of ≥2 logs in the HCV-RNA level by week 12) were very unlikely to achieve an SVR. Therefore, the duration of PEG-IFN α plus RBV therapy may be tailored according to the virologic response achieved after 12 weeks of treatment. To prevent unnecessary toxicity, early discontinuation of antiviral therapy should be considered for patients with minimal or no fibrosis and those patients who do not have a 2-log reduction in HCV-RNA levels at 12 weeks of therapy.

Current evidence from large randomized trials of PEG-IFN α-2a plus RBV also suggests that longer treatment duration has a beneficial effect on SVR by decreasing relapse rates in patients coinfected with HIV/HCV. In the AIDS Clinical Trial Group A5071 and APRICOT studies, virologic response rates at the end of treatment (48 weeks) were sustained at the end of follow-up (72 weeks) in patients with HCV genotype 2 and 3. In contrast, high relapse rates (30%) were observed in earlier studies of patients treated for only 24 weeks. These findings highlight the importance of viral clearance in achieving SVR. In fact, findings from a viral kinetic study comparing viral clearance in patients coinfected with HIV/HCV to that in HCV-monoinfected patients showed that viral clearance is prolonged by approximately 62 days in coinfected patients. Therefore, although patients infected only with HCV genotype 2 or 3 require only 24 weeks of treatment, 48 weeks of combination ther-
apy appears to be appropriate for patients coinfected with HIV and HCV genotype 2 or 3. Maintenance therapy may be an option for virologic nonresponders who exhibit histologic improvement with therapy, particularly patients with advanced liver disease.

**Management of Toxicity**

High discontinuation rates observed in early clinical studies of anti-HCV therapy in patients coinfected with HIV/HCV may have occurred, in part, because of lack of experience with management of HCV treatment-related side effects by HIV specialists. Close collaboration among physicians with expertise in HIV disease, liver disease, and mental health is required for optimal treatment of HCV infection. Clinicians should be aware of the most frequent side effects and potential drug interactions of anti-HCV therapy in coinfected patients receiving HAART. IFN-α is associated with many adverse effects. The most common are influenza-like symptoms with the first several doses; fatigue, malaise, anorexia, weight loss, skin rash, thyroid dysfunction, and reversible alopecia can also occur months into therapy. Hematologic disorders also occur in patients receiving anti-HCV therapy. Early recognition and management of HCV-related side effects can improve adherence to therapy. Hematologic abnormalities can be treated with subcutaneous injections of erythropoietin α or granulocyte colony-stimulating factor.

The potential for serious drug interactions between RBV and zidovudine or ddi-containing antiretroviral regimens is an additional concern in patients coinfected with HIV/HCV. A recent evaluation of the US Food and Drug Administration’s Adverse Event Reporting System found that patients who were coinfected with HIV/HCV and were treated with a regimen of RBV and ddi, with or without stavudine, were at increased risk for events associated with mitochondrial toxicity, including fatal hepatic failure, peripheral neuropathy, pancreatitis, and symptomatic hyperfctatemia/lactic acidosis.

Clinicians are advised to be cautious when considering HCV therapy for patients being treated with antiretroviral therapy. Based on data from large clinical studies, RBV should not be prescribed for patients coinfected with HIV/HCV who are receiving ddi-containing antiretroviral regimens. Furthermore, patients should be closely monitored for manifestations of decompensated disease, including coagulopathy, encephalopathy, ascites, and bleeding varices.

Patients with any of these manifestations should be referred to 1 of 16 regional centers who are participating in the National Institutes of Health HIV Liver Transplantation protocol for appropriate care (http://spitfire.emmes.com/study/htr/).

**Nonresponders and Novel Agents**

Despite improvement in treatment options, the number of nonresponders and patients who relapse remains high. Therefore, new agents with activity against HCV are needed. Several new and promising agents for treating HCV are in early stages of clinical investigation, including HCV protease inhibitors (BILN already on clinical hold because of toxicity), a fusion protein (albuferon), a monoclonal antibody (HCV-AB68), an HCV antisense inhibitor (ISIS 14803), and an immunomodulating agent (thymalfasin). Future treatment strategies will probably include combinations of these different agents with IFN-α-based therapy. Until these agents become available, several strategies can be used to improve responses by minimizing the risks that contribute to progressive liver disease. Abstaining from alcohol, limiting exposure to hepatotoxic drugs, and receiving vaccination against hepatitis A and B can help minimize these risks.

**Conclusions**

The introduction of PEG-IFN-α plus RBV therapy has greatly improved treatment options for patients coinfected with HIV/HCV. However, treatment of patients coinfected with HIV/HCV is more complex than the treatment of patients monoinfected with HCV because of the myelosuppressive effects of anti-HCV therapy, potential hepatotoxicity of antiretroviral therapy, and accelerated progression of liver fibrosis that may prevent the use of IFN-α-based therapy. Patient selection, timing of anti-HCV therapy, and evaluation of antiretroviral therapy are important factors in the management of HCV infection in this patient population. Current data from large randomized studies of PEG-IFN-α plus RBV indicate that coinfected patients should be treated earlier in the course of HCV infection, and the duration of therapy should be longer to maximize the likelihood of SVR. Several questions remain regarding timing and length of treatment and the role of HIV/HCV coinfection on prognosis and response to treatment. Ongoing trials...
are now addressing these questions and exploring the use of IFN-based maintenance regimens in nonresponders and treatment options for relapsing patients. The data from these trials will help clarify treatment issues in patients coinfected with HIV/HCV.

REFERENCES


