ABSTRACT

Abnormal liver function is common among patients with HIV infection. Hepatic disease, including death from hepatic failure, is among the most frequently encountered severe complications in this population. Hepatitis C virus (HCV) coinfection is also common. HIV infection accelerates the fibrosis caused by HCV, resulting in the rapid loss of liver function and increased risk of mortality. Highly active antiretroviral therapy (HAART) regimens improve survival in coinfected patients. The treatment of hepatitis C in HIV-coinfected patients has been difficult because of generally poor responses to traditional therapies. More recently, interferon (IFN) formulations have been developed in which IFNs are conjugated with polyethylene glycol, resulting in increased half-life of IFN and greater IFN exposure to HCV. These pegylated IFNs have been shown to improve clinical outcomes among patients coinfected with HIV/HCV in several large, randomized clinical trials. Treatment of HIV and HCV infections is more challenging in coinfected patients. For example, the risk of HAART-related toxicity is greater among patients with HCV, and patients with HIV infection are often considered poor candidates for HCV therapy. Clinician experience with treatment regimens is an important predictor of long-term outcomes in patients coinfected with HIV/HCV.

samples were collected from the AIDS Clinical Trials Group (ACTG) among 54,000 adults in the United States with HIV infection found an overall rate of coinfection of approximately 16%. Based on this finding, it has been estimated that approximately 250,000 people in the United States with HIV also have HCV infection. Alternatively, for the total US population of HCV-infected individuals, approximately 10% have concurrent HIV infection. However, HCV and HIV do not occur together in every population. Studies in east Africa have found that rates of HCV infection were relatively low.

**IMPACT OF HIV ON HCV-RELATED LIVER DISEASE**

Hepatitis C virus infection results in the gradual development of scar tissue and alteration of hepatic blood flow that set the stage for the subsequent liver cirrhosis and ESLD (ie, encephalopathy, coagulopathy, development of ascites, and portal hypertension with bleeding varices). Several studies have shown that HIV infection significantly accelerates this progression. The impact of HIV infection on the fibrotic progression of HCV was examined in a study of 122 patients with HIV infection, 122 matched control patients, and 122 simulated control patients in a study conducted in France. Over a follow-up period of up to 40 years, this analysis demonstrated an acceleration of the rate of liver fibrosis among patients with HIV infection. A more recent prospective study by Sulkowski et al demonstrated that progression of liver disease among patients with HIV infection can be quite rapid. These investigators performed liver biopsies on a cohort of patients who had mild fibrosis at baseline. The patients were not treated but were followed up with repeat biopsies after approximately 3 years. A worsening of at least 2 stages on a liver fibrosis score was noted for more than 25% of the patients during this relatively short period. This is a considerable change for a 3-year period of time and is much more extensive than progression of liver disease in studies of patients with HCV infection alone. In HCV infection, current practice is to perform a repeat biopsy not more often than once every 5 years. However, these data suggest that in coinfected patients, it may be necessary to perform repeat biopsies more often.

Several studies also have demonstrated lower rates of patient survival or other adverse clinical outcomes among patients coinfected with HIV/HCV. Bonacini et al examined the causes of death among a cohort of 472 patients with HIV infection who were followed for a total of more than 8000 patient-months. The incidence of liver-related mortality increased markedly among patients who also had hepatitis. Liver-related mortality was noted for 6% of patients with HIV alone, 15% of patients with HBV coinfection, 13% of patients with HCV coinfection, and 28% of patients with HBV and HCV. Graham et al performed a meta-analysis of studies that examined the effects of HIV and HCV on decompensated liver disease and biopsy-proven cirrhosis. The relative risk of histological cirrhosis for coinfected patients was 2.07 (95% confidence interval, 1.40–3.07) compared to HCV infection alone; the relative risk for decompensated liver failure associated with coinfection was 6.14 (95% confidence interval, 2.86–13.20). It also has been shown that HAART reduces mortality in patients coinfected with HIV/HCV. In a retrospective study conducted in Bonn, Germany, the investigators examined survival times of 285 patients who were treated with HAART (based on a protease inhibitor or non-nucleoside reverse transcriptase inhibitor), less effective 1-drug or 2-drug antiretroviral therapy (ART) regimens (only nucleoside analogues), or no therapy. Mortality was significantly reduced among patients who received HAART, compared to no treatment or with single agents or 2-drug ART combinations (Figure 1). The incidence of liver-related mortality was significantly lower among patients who received HAART (0.45 per 100 patient-years) than patients who received ART (0.69 per 100 patient-years) or no treatment (1.70 per 100 patient-years; \( P = .018 \) for the comparison of HAART vs the other 2 groups).

**TREATMENT OF HCV INFECTION IN HIV-COINFECTED PATIENTS**

For many years, clinicians often were discouraged about the poor response rates obtained during treatment of hepatitis C with standard interferon (IFN)-based regimens, such as IFN monotherapy or the combination of IFN with ribavirin. In the late 1990s, the first new agents began to emerge—the pegylated interferons (PEG-IFN). These agents are composed of IFN molecules that have been conjugated with a polyethylene glycol moiety, which decreases the rate of IFN clearance and increases the half-life. PEG-IFNs may be administered once weekly, and they are more effec-
Pegylated interferons were evaluated for patients coinfected with HIV/HCV in 3 large, randomized clinical trials. The ACTG 5071 study was conducted at 21 sites in the United States. The patients were randomized to receive standard doses of PEG-IFN-2a, combined with 1 of several different doses of the nucleoside analog ribavirin. After 24 weeks of treatment, nonresponders underwent liver biopsy, and patients who exhibited histologic response to treatment were offered the opportunity to continue. A viral kinetic substudy also was performed. The AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT) was a multicenter, multinational phase III registration trial that included 3 treatment arms. The patients received PEG-IFN-2a with ribavirin, PEG-IFN-2a without ribavirin, or standard IFN-2a with ribavirin. Finally, the RIBAVIC trial, which was conducted in France, compared treatment with PEG-IFN-2b and standard IFN in combination with ribavirin. The effects on virologic response rates were similar in the 3 trials. For comparison purposes, patients with HCV alone in pivotal trials of PEG-IFN exhibited sustained virologic response (SVR; defined as the absence of detectable virus using a sensitive polymerase chain reaction-based technique 24 weeks after completion of therapy) rates greater than 50%. SVR is thought to represent the cure of HCV infection in nearly all cases in which it occurs. These 3 large, randomized trials produced SVR rates of approximately 25% to 30% in the ACTG and RIBAVIC trials and 45% in APRICOT. Thus, treatment effectiveness is lower than would be expected for patients with only HCV infection, but was superior in all 3 studies to administration of standard IFN. These findings represent a significant advance for the treatment of this population, who are at high risk of rapid progression to ESLD.

During the past few years, it has been hypothesized that early virologic response is a strong predictor of eventual SVR; if a patient does not achieve a decrease in viral load of at least 2 log units within 2 weeks of treatment, it is unlikely that SVR will ever be achieved. The relationship between early response and SVR was evaluated for 106 patients after 12 weeks of treatment in the ACTG trial previously described. A decrease in HCV RNA of at least 2 log units was noted for 43
(41%) of the patients. Of these patients, 21 (49%) achieved SVR and 22 patients (51%) did not. However, for the group of 63 patients who did not exhibit a 2-log decrease in HCV RNA after 12 weeks, none achieved SVR. Similar findings were observed in the other 2 large studies. The role of CD4 cell count on treatment outcome in coinfected individuals remains controversial, even after the completion of these 3 major clinical trials.

Previous studies suggested that treatment is less effective when CD4 cell counts are below 500 cell per mm$^3$. SVR is unlikely in individuals with CD4 cell counts below 350 cells per mm$^3$, and virtually never occurs when CD4 cell counts are below 200 cells per mm$^3$. In all 3 major trials, CD4 cell count was not a significant predictor of outcome in multivariate analyses. However, patients in all of the studies tended to cluster tightly around CD4 cell counts of approximately 500 cells per mm$^3$, making it difficult to analyze the effects of CD4 cells on treatment response across a wide range of CD4 cell count values. In the RIBAVIC trial, the investigators performed an analysis to compare end of treatment responses for patients with CD4 cell counts below 500 cells per mm$^3$ to patients with high cell counts. For PEG-IFN and standard IFN groups, there was a significantly lower likelihood of virologic response after 48 weeks in the patients with low CD4 cell counts at baseline.23

OBSTACLES TO TREATMENT IN HIV-COINFECTED PATIENTS

Coinfection of HIV and HCV represents a significant obstacle to the treatment of both viral infections. Sulkowski et al have shown the risk of ART-associated hepatotoxicity for HIV treatment during approximately 1 year of follow-up is significantly greater among patients with HCV infection than among patients who are HCV negative (Figure 2).24 It also has been shown that HCV infection is associated with increased likelihood of early HAART discontinuation and that elevated alanine aminotransferase and aspartate aminotransferase levels often result in treatment discontinuation by physicians.25 In addition, there are also barriers to the treatment of HCV created by HIV infection. In 1 study of 149 patients who had HCV with HIV, only 28% were thought to be eligible for HCV treatment.26 ESLD was a disqualification for treatment of 12% of patients. The recognition of ESLD is a significant issue among infectious disease specialists. Once a patient becomes decompensated, it is generally too late to consider treatment, although in patients with HCV infection alone, there are some very late treatment trials under way. At present, patients with ESLD should be referred to a transplant center that is considering or evaluating patients with HIV for transplantation.

Another reason given for not treating HCV infection is the presence of AIDS, which was noted for 13% of patients. In these patients, treatment would usually focus first on the HIV infection and reducing the risk of AIDS complications. In addition, those patients probably have a lower likelihood of response. Nonadherence to treatment was considered a reason for ineligibility in 23% of patients, and drug use was cited for 23% of patients. Although a patient who is actively sharing needles may not be a good candidate for therapy, intravenous drug use should not necessarily prevent treatment in all cases. Many individuals who inject drugs are careful not to share needles and are very adherent to medication regimens. Psychiatric reasons were considered grounds for ineligibility in 21% of cases. Although the labeling for IFN indicates that there are significant risks of depression, psychiatric illness that is well controlled should not be considered an absolute contraindication to therapy.

![Figure 2. Hepatotoxicity Grade According to NVP or EFV Use](https://example.com/figure2.png)

There are also other issues that may limit the treatment of HCV infection in patients with HIV. Many clinicians lack experience with the use of these agents and with the management of psychiatric complications related to IFN use. A dose-related hemolytic anemia is associated with ribavirin, which is generally manageable with the use of growth factors or by reducing the ribavirin dose. Neutropenia can occur, but it is not a significant issue for most patients and can be managed using granulocyte colony-stimulating factor if necessary. Weight loss can occasionally be significant, and patients are encouraged to use dietary supplements (eg, Ensure or Boost).

The 3 large clinical trials of HIV/HCV treatment previously described provide some important lessons about maintaining patients on long-term therapy. In the RIBAVIC trial, in which clinicians generally did not have a great deal of experience with the agents, there was a 36% dropout rate during the course of treatment. However, in the ACTG trial, in which hepatologists worked with infectious disease specialists throughout the course of treatment, the dropout rate was only 12%, which is comparable to the dropout rate observed in clinical trials of patients with HCV infection alone. Many clinicians have been concerned about the potential for decreased CD4 cell counts in patients with HIV who receive IFN therapy, and decreases in CD4 cell counts do occur in patients who receive PEG-IFN or conventional IFN. This decrease is typically transitory, with maximum loss of CD4 cell number occurring at weeks 24 to 48, and returning to baseline values at 72 weeks. This decrease in CD4 cell number has not been associated with an increase in the risk of opportunistic infections.

There also is potential concern about drug interactions for patients who are receiving treatment for HIV and HCV. In an in vitro study, ribavirin interfered with the ability of zidovudine to suppress HIV replication. The clinical importance of interaction is limited, as single-agent zidovudine is no longer widely used. Ribavirin also interacts with didanosine metabolism, resulting in elevated didanosine levels and the development of mitochondrial toxicity. This interaction has been a significant cause of pancreatitis, lactic acidosis, and fulminate hepatic failure, and both drugs now carry “black box” warnings that they should not be used together.

CONCLUSIONS

The prevalence of HIV/HCV coinfection is high. Coinfection is associated with increased likelihood of morbidity and mortality. Treatment options for HCV infection are effective, but coordinating the use of antiretroviral agents and PEG-IFN must be individualized for each patient. AIDS complications may make it difficult to complete a course of IFN therapy. Individualized management of adverse events is also critical to the completion of treatment protocols. Physician experience with the therapies also helps patients to complete what is often a very difficult course of therapy. Some AIDS medications should be used with caution in patients with HCV.

REFERENCES