

## Perspective

# HIV and Hepatitis C Virus Coinfection: Bad Bedfellows

*Hepatitis C virus (HCV) infection is common in HIV-infected individuals and is responsible for increasing morbidity in these patients. HIV infection increases HCV replication and accelerates progression of HCV disease. HCV infection increases the risk of antiretroviral-associated hepatotoxicity and the likelihood of withdrawal of antiretroviral treatment. HCV genotype 1 is the predominant genotype in HCV/HIV-coinfected individuals living in the United States. State-of-the-art treatment with peginterferon alfa plus ribavirin results in lower sustained HCV virologic response rates in patients with genotype 1 infection than in those infected with other genotypes. Data from studies of HCV infection treatment in coinfecting patients are discussed, as are prospects for future therapy. This article summarizes a presentation on HIV/HCV coinfection by Robert T. Schooley, MD, at the International AIDS Society–USA course in San Francisco in June 2005.*

In recent years hospitalizations associated with liver complications and injection drug use (IDU)-related complications among HIV-infected patients have increased. Much of the increased morbidity is associated with concurrent hepatitis C virus (HCV) infection. Recent estimates suggest that HCV infection is present in 30% of HIV-infected patients in the United States, 50% in Spain, 33% in Western Europe, and 50% in Thailand. In a cohort of 1955 patients in Baltimore, MD, HCV infection was present in 45% of HIV-infected patients, including 85% of those who acquired HIV through IDU, 14% of those infected through heterosexual sex, and 10% of those infected through male homosexual sex (Sulkowski, *Ann Intern Med*, 2003). HCV/HIV coinfection complicates management of both diseases.

### Effect of HIV Infection on HCV Disease

Studies of stored blood samples from HCV-infected patients with hemophilia who subsequently acquired HIV infection have shown a substantial increase in HCV RNA following HIV antibody seroconversion, suggesting a

marked effect of HIV in increasing HCV replication (Eyster, *Blood*, 1994). Other data indicate a dramatic effect of HIV infection in accelerating HCV disease. In one study in 413 HIV-seronegative patients and 116 HIV-infected patients with HCV infection, the 10-year incidence of cirrhosis was 2.6% in the former group versus 14.9% in the latter ( $P < .01$ ) and the mean time to cirrhosis was 23.2 years versus 6.9 years ( $P < .001$ ; Soto, *J Hepatol*, 1997). In a recent study by Sulkowski and colleagues in Baltimore (12th CROI, 2005), 67 HIV/HCV-coinfecting patients had paired biopsies scored using Ishak criteria. With a median time between biopsies of 2.8 years, an increase in fibrosis of 2 or more stages was observed in 17 patients (28%), whereas only 4 patients (7%), all with stage 1 fibrosis at baseline, had a decrease of 1 stage. A 2001 meta-analysis of 7 studies on the effect of HIV infection on HCV disease progression indicated a relative risk of progression to cirrhosis of 2.92 with coinfection versus HCV infection alone (Graham, *Clin Infect Dis*, 2001).

### Effect of HCV Infection on HIV Disease

There are some data to indicate that HCV coinfection somewhat blunts the CD4+ cell increase observed in HIV-

infected patients receiving potent antiretroviral therapy (Greub, *Lancet*, 2000), although there are conflicting findings in this regard. Further, the relatively small blunting effect that has been observed may not substantially affect the overall immunologic benefits of antiretroviral therapy. More important from the perspective of HIV treatment is the finding that coinfection with HCV increases the risk of antiretroviral-associated hepatotoxicity (Figure 1, top; Sulkowski, *Hepatology*, 2002). Antiretroviral therapy discontinuation rates have been found to be greater in coinfecting patients than in patients without HCV infection (Figure 1, bottom; Melvin, *AIDS*, 2000).

### Issues in Treatment of HCV Infection

An important factor to consider in treating and developing therapies for HCV infection is the high replication rate of HCV, which is 10- to 100-fold greater than that of HIV. Replication occurs via an RNA-dependent RNA polymerase that, like HIV reverse transcriptase, is prone to error in the genetic copying process. As a result, HCV generates great genetic diversity both in terms of viral subtypes and in terms of variants within the host. Indeed, the genetic variation between the closest related HCV viral subtypes is greater than that between the most distantly related HIV subtypes identified. Although these characteristics make the evolution of antiviral-resistant strains of HCV very likely, it is also the case that the virus, unlike HIV, does not replicate via a DNA intermediate inserted into the host-cell genome. Thus, resistance is not likely to be “archived” within host cells, and the response to subsequent use of the same antiviral(s) may not be jeopardized to the same extent as in the case of antiretroviral therapy.

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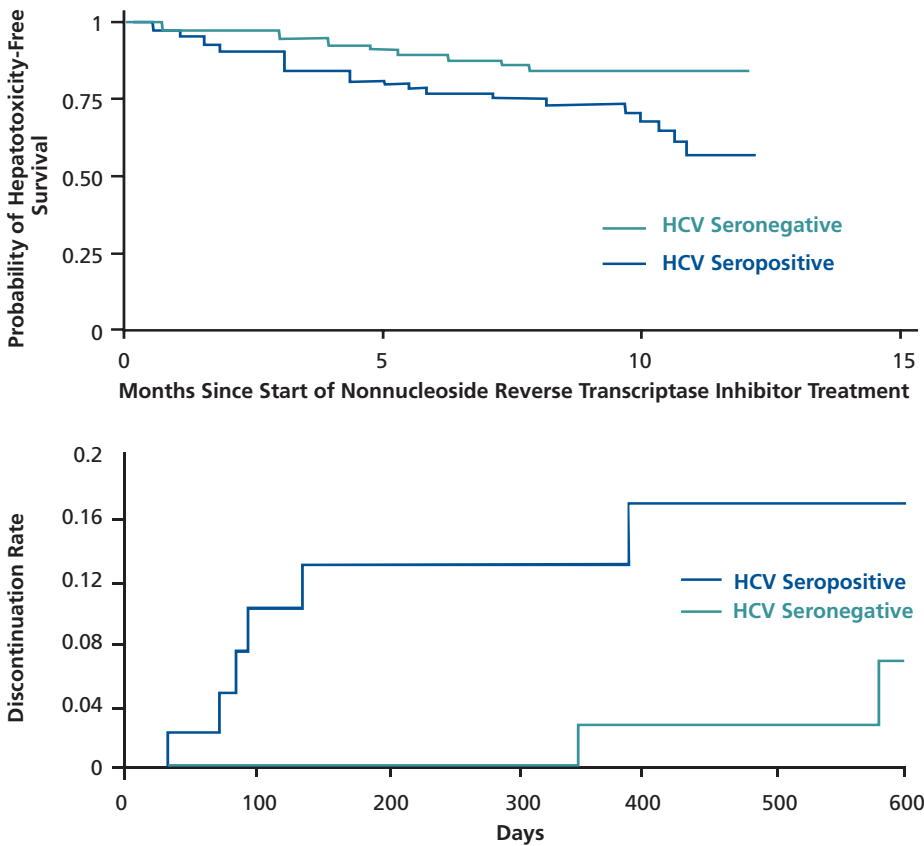


Figure 1. Top: Risk of associated hepatotoxicity in patients with or without hepatitis C virus (HCV) infection. Adapted from Sulkowski et al, *Hepatology*, 2002. Bottom: Rate of discontinuation of antiretroviral therapy due to hepatotoxicity in HCV-infected patients and in patients without HCV infection. Adapted from Melvin et al, *AIDS*, 2000.

Concentrations of anti-HCV drugs in the liver are key to achieving response.

Response to antiviral treatment for HCV infection is typically assessed in terms of end-of-treatment response (ETR)-HCV RNA levels below assay detection limits at the end of therapy, and sustained virologic response (SVR)-HCV RNA levels below the limit of assay detection at 24 weeks after the end of treatment. An SVR usually indicates a low risk of recurrence—that is, a high probability of virologic cure. Rates of ETR and SVR reported in the literature as of 2001 with interferon alfa, peginterferon alfa-2a, or peginterferon alfa-2b, with or without ribavirin, in patients without HIV infection are shown in Figure 2 (Shiffman, *Clin Liver Dis*, 2001). Although interpretation of these data must be qualified by the fact that there were differences in the study populations providing the data, they do pro-

vide some idea of the overall ability to achieve response with different regimens and the degree to which ETR is followed by either recurrence or SVR. The current state-of-the-art anti-HCV therapy treatment is peginterferon alfa plus ribavirin, which may be associated with an ETR rate of 60% or more and an SVR rate of approximately 50% in patients infected with HCV subtype 1 without HIV coinfection.

Factors that can affect response rates are shown in Figure 3. HCV genotype 1, the predominant type in the United States, is associated with lower response rates than are genotypes 2 and 3, which predominate in Europe. Other factors affecting response include pretreatment plasma HCV RNA level, age, race, weight (likely reflecting differences in drug exposure with standard dosing), alanine aminotransferase level (activated enzymes are a favorable sign), histol-

ogy, dose of ribavirin, and sex (also likely reflecting differences in drug exposure via body size). Among these factors, several are of particular concern in treating HIV-coinfected patients. Patients with coinfection are more likely to have infection with HCV genotype 1, higher pretreatment plasma HCV RNA levels, and more advanced liver histology, and they are less likely to tolerate full doses of ribavirin because of drug interactions with antiretroviral agents.

Results of APRICOT, a trial of HCV infection treatment in HIV-coinfected patients, have recently been reported (Torriani, *N Engl J Med*, 2004). In this trial, coinfecting patients received interferon alfa 3 MIU 3 times weekly plus ribavirin 800 mg daily (n = 285); peginterferon alfa 180 µg once weekly (n = 286); or peginterferon alfa 180 µg once weekly plus ribavirin 800 mg daily (n = 289) for 48 weeks and were

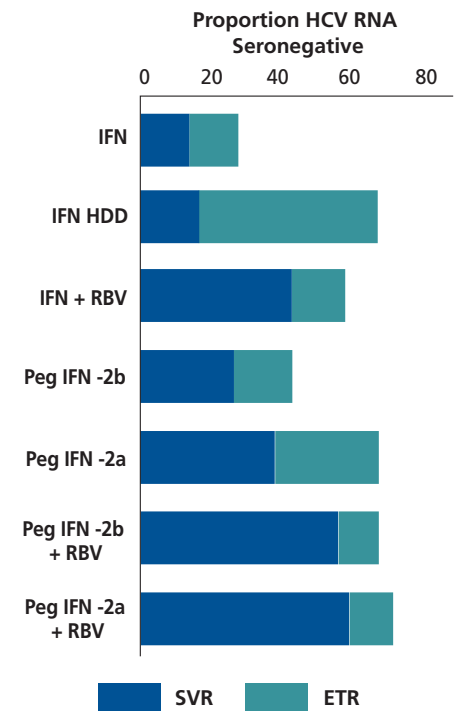
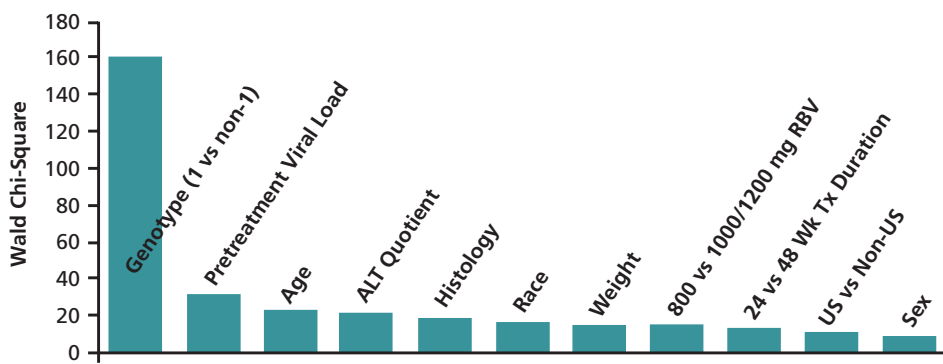


Figure 2. End-of-treatment response (ETR) and sustained virologic response (SVR) rates in hepatitis C virus (HCV)-infected patients without HIV infection, according to treatment. IFN indicates interferon alfa; HDD, high dose daily; RBV, ribavirin; Peg IFN, peginterferon alfa. Adapted from Shiffman, *Clin Liver Dis*, 2001.



**Figure 3.** Factors associated with sustained virologic response to treatment with peginterferon alfa plus ribavirin (RBV) according to a multiple logistic model in 1737 hepatitis C virus monoinfected patients. The Wald chi-square is proportional to the square of the risk associated with each factor noted on the x-axis. ALT indicates alanine aminotransferase; RBV, ribavirin. Adapted from FDA Antiviral Drugs Advisory Committee Proceedings, 2002.

observed to week 72. Patients had to have stable HIV disease, with or without antiretroviral treatment, and they had to have a CD4+ cell count of at least 100/ $\mu$ L. Those with CD4+ cell counts of 100/ $\mu$ L to 200/ $\mu$ L were also required to have a plasma HIV RNA level below 5000 copies/mL. On intent-to-treat analysis, SVR defined as HCV RNA below 50 IU/mL at week 72 occurred in 12% of the interferon alfa plus ribavirin group, 20% of the peginterferon alfa group, and 40% of the peginterferon alfa plus ribavirin group ( $P < .001$  versus both other groups). ETR and SVR rates were lower in patients with HCV genotype 1 infection than in those with genotype 2 or 3 infection (Figure 4).

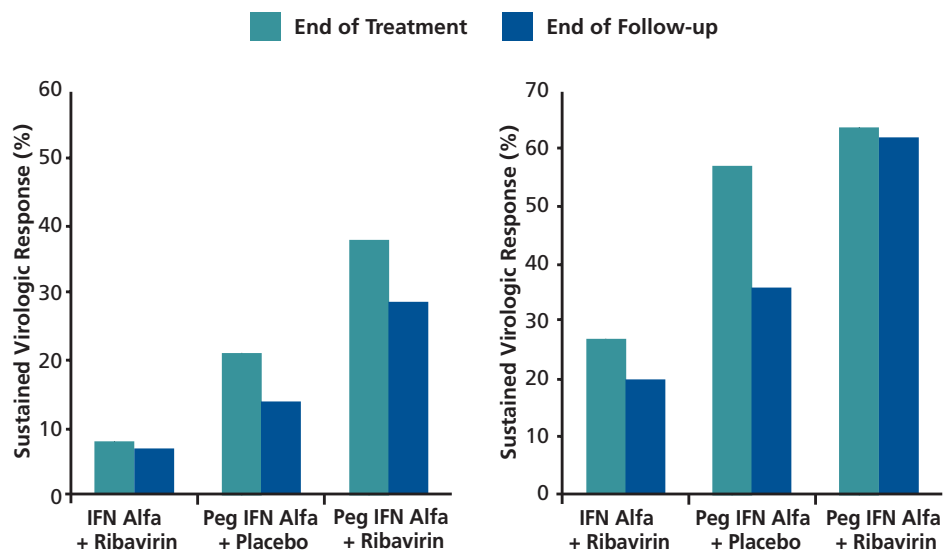
A number of studies have shown the value of early virologic response in predicting long-term response. In APRICOT, reduction of HCV RNA to undetectable levels or by at least 2  $\log_{10}$  copies/mL at 12 weeks occurred in 71% of patients receiving peginterferon alfa-2a plus ribavirin; of these, 56% had an SVR. Of the 29% of patients without such early virologic response, 98% had no SVR. This negative predictive value of 98% was similar to that observed in other trials of antiviral therapy for HCV infection and suggests that the absence of response at 12 weeks may permit sparing the patient the remainder of the treatment course if the patient is experiencing significant toxic effects.

However, even partial response to treatment can improve HCV infection course, so the absence of full suppression of HCV replication should not routinely prompt cessation of therapy.

It is recognized that CD4+ cell counts decrease during interferon alfa treatment, and decreases were observed in all treatment groups in APRICOT (Figure 5). These decreases are usually not accompanied by changes in CD4+ cell percentage, however, and levels in the treatment groups in APRICOT increased at the

end of the treatment period. It is also known that interferon alfa has anti-HIV activity, and decreases in HIV RNA of up to 1  $\log_{10}$  copies/mL were observed in the trial.

Treatment of HCV infection in coinfecting patients also has been examined in the AIDS Clinical Trials Group (ACTG) 5071 study. In this trial, 132 patients received interferon alfa plus ribavirin ( $n = 66$ ) or peginterferon alfa plus ribavirin for 48 weeks, and were followed up for 72 weeks. Ribavirin was started at 600 mg daily and the dose was increased by 200 mg each month to a maximum of 1000 mg daily, if tolerated. Patients were on stable antiretroviral therapy and had CD4+ cell counts above 100/ $\mu$ L and plasma HIV RNA levels below 10,000 copies/mL, or they were antiretroviral-naïve and had CD4+ cell counts above 300/ $\mu$ L. This trial was conducted in the United States and thus had a greater proportion of patients with HCV genotype 1. The trial also had more African-American patients, a group that has lower rates of response to interferon alfa-based treatment. Among patients with genotype 1 infection, ETR occurred in 6% of the interferon alfa/ribavirin group and



**Figure 4.** Virologic response at the end of 48 weeks of treatment and at the end of 72 weeks of follow-up in HIV/hepatitis C virus (HCV) coinfecting patients with HCV genotype 1 infection (left) or genotypes 2 and 3 infection (right) according to treatment in the APRICOT trial. Virologic response is defined as an HCV RNA level below 50 IU/mL. IFN indicates interferon; Peg IFN, peginterferon. Adapted from Torriani et al, *N Engl J Med*, 2004.

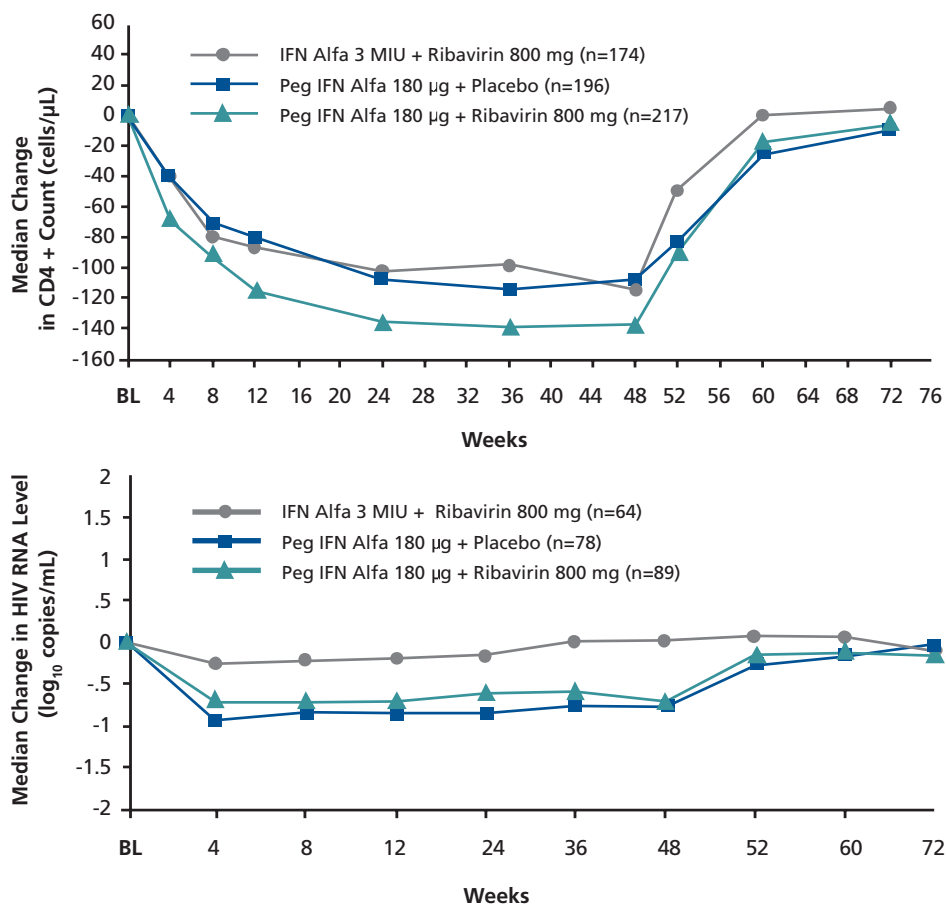


Figure 5. Median change from baseline in CD4+ cell count (top) and mean change from baseline in plasma HIV RNA (bottom) in HIV/hepatitis C virus coinfecting patients, according to treatment in the APRICOT trial. IFN indicates interferon; Peg IFN, peginterferon. Subjects received 48 weeks of treatment. Data are from Torriani et al, *N Engl J Med*, 2004.

29% of the peginterferon alfa/ribavirin group, and SVR occurred in 6% and 14%, respectively (Chung, *N Engl J Med*, 2004). The lower SVR rate in patients with HCV genotype 1 infection in this study than in the APRICOT trial may also be related to the more cautious use of ribavirin in the ACTG 5071 trial.

Pegylated interferon alfa and ribavirin therapy is not without significant toxic effects. Successful therapy requires ongoing support of the patient and anticipatory management of toxicities. Virtually every patient can be expected to experience flu-like symptoms including fatigue, headaches, and myalgias with interferon alfa-based therapies (Aspinall et al, *Aliment Pharmacol Ther*, 2004). These symptoms are manageable in most patients if patients are adequately prepared for

them in advance, and few patients must cease therapy solely because of flu-like symptomatology. The most frequent causes of discontinuation of therapy stem from depression and bone marrow suppression. Patients who are otherwise candidates for interferon alfa-based therapies should be assessed for depression prior to therapy. Depression occurs during therapy in 35% to 40% of patients and can usually be managed with antidepressants. Selective serotonin reuptake inhibitors and tricyclic antidepressants have each been used with excellent success in this setting. Bone marrow suppression from interferon alfa-based therapy may cause granulocytopenia, thrombocytopenia, or anemia. Ribavirin therapy exacerbates the anemia since it causes hemolysis of red blood cells. Although these hematologic

complications are readily reversible with dose reduction of the interferon alfa or ribavirin, reductions in doses of either medication significantly reduce rates of SVR (Fried et al, *N Engl Med*, 2002). Thus, practitioners should not be hesitant to use granulocyte colony-stimulating factor and erythropoietin in the management of granulocytopenia and anemia, respectively.

Based on current knowledge, it generally can be recommended that patients with early HIV infection be considered for HCV treatment to obtain virologic cure prior to the initiation of antiretroviral therapy. In later HIV infection, the potential for obtaining an SVR is lower, but treatment of HCV infection should be considered in order to reduce the HCV disease progression risk and to permit the initiation of antiretroviral therapy. Overall, factors favoring the institution of anti-HCV therapy include infection with genotypes other than genotype 1, earlier HIV disease, and the presence of fibrosis on liver biopsy. Factors complicating therapy include infection with HCV genotype 1, ongoing substance abuse, psychiatric disorders, later HIV disease, the toxic effects of interferon alfa and ribavirin, and current antiretroviral therapy.

### Approaches in Development

The future will bring improved therapies for HCV infection. Potential targets for drug development include the HCV protease and polymerase enzymes. Development of inhibitors of the HCV protease enzyme has proven difficult because of the long and shallow enzyme-binding site on the protein to which it cleaves. Investigation of the protease inhibitor BILN 261 compound showed that inhibition is possible, with treatment producing up to 3 log<sub>10</sub> copies/mL decreases in HCV RNA in patients with HCV genotype 1 infection and generally smaller and less consistent reductions in those with non-genotype 1 infection over short-term administration (Lamarre, *Nature*, 2003; Reiser, *Hepatology*, 2005); however, the molecule is difficult to synthesize. The

protease inhibitor VX-950 is easier to synthesize and appears to exhibit greater activity. In a phase Ib dose-ranging study, a median HCV RNA reduction of 4.4 log<sub>10</sub> copies/mL was achieved at a dose of 750 mg every 8 hours after 14 days of treatment. At the highest dose, 4 of 8 patients had undetectable HCV RNA levels, whereas viral rebound was observed at lower dose levels in some patients. The polymerase inhibitor NM283 (valopicitabine) was found to produce small reductions in HCV genotype 1 RNA levels, with the greatest reduction being somewhat more than 1 log<sub>10</sub> copies/mL when the highest dose tested was administered with an antiemetic. In a phase IIa trial, valopicitabine produced a 1.9-log<sub>10</sub>-copy/mL reduction in HCV RNA when used alone, and the combination of valopicitabine and peginterferon alfa produced a reduction of 4.5 log<sub>10</sub> copies/mL over 24 weeks of treatment.

## Summary

Increased morbidity from HCV infection in HIV-infected patients, with increasing numbers of patients requiring treatment, is expected. It is hoped that effective small-molecule inhibitors of HCV can be developed that will permit a reduced reliance on interferon alfa and ribavirin as primary components of anti-HCV therapy. Given the high replication rate of HCV and its ability to generate wide genetic variation, combination therapy will likely be required for predictable effective suppression of the virus.

*Presented by Robert T. Schooley, MD, in June 2005. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Schooley in September 2005.*

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