Liver Disease in HIV: An Update

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In the United States, it is estimated that 30% of the 800,000 people living with HIV are coinfected with the hepatitis C virus (HCV). Similar rates have been documented in Western Europe, although the actual number of HIV-infected individuals in some countries is not well defined. The magnitude and potential ramifications of HIV/HCV-coinfection are even more alarming in Spain, where Dr. Vincent Soriano suggested that at least half of the 130,000 HIV-positive people in the country are coinfected with HCV (Soriano, 2000). In turn, Spain has become a hotbed of coinfection research and has yielded studies that have helped to address some of the most important questions regarding follow-up and treatment facing clinicians today.

To appreciate the impact of liver disease on the lives (and deaths) of HIV-positive patients in the era of HAART, Dr. Soriano reviewed data from several European and American retrospective studies that have been published over the past few years. In one study evaluating the impact of end-stage liver disease in a cohort of HIV-infected patients—both before and after HAART came into widespread use—Dr. Luis Martín-Carbonero, Dr. Soriano, and their colleagues conducted a review of medical charts detailing hospital admissions at the Hospital Carlos III in Madrid between January 1996 and December 2000 (Martín-Carbonero, 2001). Discharge diagnosis, complications during the inpatient period, and the number and causes of death were recorded. A total of 1334 hospital admissions involving 875 HIV-infected patients were included in the analysis (three-quarters of these cases were associated with underlying HCV infection).

Overall, 158 (11.8%) were admitted because of liver disease complications, or developed complications of liver disease during their admission for another reason. Most interesting were the number and proportion of admissions over time. In 1996, prior to the widespread use of HAART, 31/330 (9.4%) admissions were related to liver disease. In 2000, however, 46/159 (29%) admissions were tied to liver complications. As for mortality rates, there were 54 deaths among admitted HIV-positive patients in 1996, five (9%) of which were related to liver disease. In 2000, there were 20 deaths, nine (45%) tied to liver disease. "In 2000, we had more deaths related to liver failure than we did to typical AIDS-related diseases," Dr. Soriano added. "Unfortunately, Madrid is by no means alone in this trend. It is going on across Europe and throughout North America." Studies with similar findings discussed by Dr. Soriano included one conducted in Brescia, Italy (Puoti, 2000), another conducted in Paris (Cacoub, 2001), and a third conducted in Boston (Bica, 2001) (see Table 1).

The Significance of HIV/HCV Coinfection

A large number of studies—many of which have been discussed in previous issues of *The PRN Notebook*—have demonstrated that HIV accelerates the clinical course of HCV disease. These studies, taken as a whole, add significant weight to the growing consensus that chronic HCV disease in HIV-infected patients truly is an opportunistic disease—an AIDS-defining illness now classified by the U.S. Centers for Disease Control.

In a Seville-based retrospective analysis of 547 intravenous drug users with chronic HCV infection, patients coinfected with HIV progressed to cirrhosis faster than their HIV-negative counterparts (Soto, 1997). Within ten years after being infected with HCV, 13/87 (14.9%) HIV-positive subjects developed cirrhosis, in comparison with 7/272 (2.6%) patients infected only with HCV. The study also reported that the mean interval from the estimated time of HCV infection to cirrhosis was significantly longer in HIV-negative than HIV-positive patients (23.2 vs. 6.9 years).

Table 1. Mortality Caused by End-Stage Liver Disease

	Pre-HAART Era		HAART Era	
	No. (%)	Year	No. (%)	Year
Brescia, Italy (Puoti, 2000)	35/305 (13%)	1987	16/46 (35%)	1996
Madrid, Spain (Martin-Carbonero, 2001; Soriano, 1999)	15/312 (4.8%)	1991–1995	9/20 (45%)	2000
Boston, Massachusetts (Bica, 2001)	3/26 (11.5%)	1991	11/22 (50%)	1998–1999
Paris, France (Cacoub, 2001)	21/1327 (1.6%)	1995	36/543 (7.8%)	1997

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Table 2. Hepatotoxicity of Antiretroviral Drugs

Author	No.	Antiretroviral Therapy	HCV/HBV	CD4+ Cell Count (mm^3)	Incidence	Predictors
Rodríquez-Rosado, 1998	132	PI-based	62%	324	11%	HCV, alcohol
Sulkowski, 2000	211	PI-based	51%	109	12%	HCV, HBV, ↑CD4, ritonavir
	87	2 NRTI	61%	215	6%	HCV, HBV, ↑CD4
Saves, 1999	748	PI-based	41%	144	9%	HCV, HBV, previous cytolysis
	1249	2 NRTI	44%	234	6%	HCV, HBV, previous cytolysis
den Brinker, 2000	394	PI-based	22%	150	18%	HCV, HBV
Saves, 2000	1080	PI-based	30%	290	2%	HCV, HBV
Martínez, 2001	610	Nevirapine-based	51%	279	9.7%	HCV, time on antiretroviral drugs, previous cytolysis
Nuñez, 2001	222	HAART (PI, NNRTI)	40%	337	9%	HCV, age, alcohol

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In an earlier study conducted in Seville, rates of progression were evaluated in 76 HCV-infected patients, 32 (42.1%) of whom were coinfected with HIV (Sánchez-Quijano, 1995). Within 15 years after initial HCV infection, 8/32 (25%) HIV-positive patients developed cirrhosis, in comparison with only 2/31 (6.5%) patients in the HIV-negative group. HCV-RNA levels were also found to be almost ten times higher in the HIV-positive group, but this difference did not reach statistical significance in this small study population.

Also of significance are data indicating a more rapid progression to hepatocellular carcinoma (HCC) among HCV/HIV-coinfected patients. In one study discussed by Dr. Soriano, a group at Hospital Carlos III compared the medical records of seven coinfected patients with HCC to those of a control group consisting of patients with HCV-related HCC but no underlying HIV infection (Garcia-Samaniego, 2001). Among the coinfected patients, HCC was typically diagnosed at a young age (45 years old) and relatively soon after infection with HCV (17.8 years). Conversely, individuals in the control group were not likely to be diagnosed with HCC until they were older (69 years of age) and had been infected with HCV for almost three decades (28 years).

With respect to HCV-RNA dynamics in coinfected patients, HCV viral load levels are typically 1.5 to twofold higher than in HCV-monoinfected patients. Why this is so has not been established—underlying immune suppression resulting from HIV infection may certainly be a factor—nor is it clear whether the higher HCV titers are to blame for the more rapid course of hepatitis C in coinfected patients.

The Impact of HAART

WITH RESPECT TO THE IMPACT OF HAART ON HCV infection, Dr. Soriano pointed out that HIV-specific antiretroviral compounds have little, if any, direct effect against HCV. There is, however, some debate as to whether HAART offers any indirect benefits, perhaps in the form of immune reconstitution, which may slow the pathogenic effects of HCV on the liver. Two studies reported by Dr. Yves Benhamou of the Hôpital de la Pitié-Salpétrière in Paris and his colleagues suggest that HAART—including protease inhibitors—does lead to liver histology improvements in coinfected patients. Conversely, Dr. Sandro Vento and his colleagues of the University of Verona in Italy suggest that reconstitution of the immune response associated with antiretroviral therapy might increase hepatic necroinflammatory activity, thereby accelerating the course of HCV disease in patients coinfected with HIV. "We need more studies involving paired liver biopsies to learn more about this," Dr. Soriano said. "The immune reconstitution associated with HAART could be advantageous, or it could be making things worse. Until we've conducted prospective studies, it's very difficult to say which of these is true."

There is also the very real concern of hepatotoxicity associated with antiretroviral therapy, particularly among patients coinfected with HIV and HCV. Overall, studies have indicated that significant liver enzyme increases are seen in approximately 15% of individuals receiving antiretroviral drugs. Severe hepatotoxicity, leading to drug discontinuation, occurs in less than 10% of cases.

Dr. Soriano explained that most instances of hepatotoxicity can be classified under one of two categories. First there is early-onset hepatotoxicity, which is typically associated with immune-mediated hypersensitivity to a particular drug or combination of drugs. Such hypersensitivity reactions account for cases of transaminase elevations seen in HIV-positive individuals, who are at the same time experiencing noticeable allergic responses (e.g., fever, rash), a few days to weeks after therapy is initiated, though this may not be seen. This type of hepatotoxicity appears to be more common in individuals who have high CD4+ cell counts prior to initiating treatment and can almost always be traced to the use of either abacavir (Ziagen) or nevirapine (Viramune).

A second mechanism of HAART-related liver toxicity, which does not involve other organs, has a delayed onset, often several months after treatment is initiated, and represents a direct toxic effect of the

drug(s) being used. It is predictable—particularly in the setting of heavy alcohol use or in patients coinfected with either HCV or chronic HBV infection—and is likely dose-related and correlates with the length of time on therapy.

There are actually three types of direct liver toxicity. Ritonavir and nevirapine, for example, have been shown to cause direct hepatocellular damage, through mechanisms that are not entirely understood (usually associated with elevated transaminases +/- hyperbilirubinemia and an ALT/alkaline phosphatase ratio >5). Alternatively, indinavir is associated with cholestasis (associated with elevated alkaline phosphatase +/- hyperbilirubinemia and an ALT/alkaline phosphatase ratio <2). There is also the link between mitochondrial toxicity and steatosis, a type of liver damage believed to be associated with the use of nucleoside reverse transcriptase inhibitors.

Because NNRTIs do not require intracellular phosphorylation to exert their blocking action on HIV, there has been an interest in measuring plasma levels of nevirapine to determine if elevated drug concentrations might be behind the risk of liver toxicity in HIV-monoinfected and HIV/HCV-coinfected patients. In a case-control study conducted at Hospital Carlos III in Madrid, 70 patients taking nevirapine-based regimens were classified into two groups, one including patients who developed any grade of hepatotoxicity, and a control group that included subjects without transaminase elevations. Patients were also stratified according to the presence of HCV infection (González de Requena, 2002).

The peak in transaminase levels among the 33 subjects in the first group was reached after approximately six months of beginning treatment. Transaminase levels were mildly to moderately elevated in 70% of patients, twenty-three of whom were HCV-positive. The median nevirapine plasma concentrations—measured using high-performance liquid chromatography—in subjects who developed transaminase elevations was significantly higher than in controls (6.25 µg/mL vs. 5.2 mg/mL, respectively [P=0.025]). When HCV infection was also included in the analysis, both higher nevirapine plasma levels and HCV seropositivity were found to be independent factors predicting hepatic injury. Moreover, in patients with both chronic HCV and nevirapine plasma levels above 6 mg/mL, the risk of liver toxicity was approximately 92%.

Might underlying HCV infection be responsible for the elevated nevirapine levels in coinfected patients? Apparently not, says another recent study conducted at Hospital Carlos III, the results of which will soon be published in *AIDS*. As explained by Dr. Soriano, a member of the study team, median nevirapine plasma concentrations panned out to be lower (5.8 mg/mL) in the 32 HCV-positive patients enrolled, compared to the median level (6.1 mg/mL) found in the 38 HCV-negative patients included in the analysis.

"We know that HCV is an independent risk factor associated with hepatotoxicity," Dr. Soriano reiterated. "We now have reason to believe that higher nevirapine plasma levels are also associated with increased hepatotoxicity, independent of underlying HCV infection. Interestingly, HCV coinfection itself does not enhance nevirapine levels. The effect of HCV on nevirapine levels may only be evident in patients with end-stage liver disease." Might therapeutic drug monitoring be useful in HIV/HCV-coinfected patients receiving nevirapine? Not necessarily, Dr. Soriano argues, "there's really no indication for this type of monitoring in noncirrhotic patients."

Treatment Issues and Emerging Guidelines

THE PRIMARY GOAL OF HCV TREATMENT IS TO maintain an undetectable HCV viral load—particularly six months after therapy is completed—to allow for fibrosis regression and the reversal of extrahepatic complications. There is also the public health component of HCV treatment: to render patients avirimic, thus reducing their chances of passing the virus on to others.

Unfortunately, information has long been limited as to how best to achieve these goals in HIV/HCV-coinfected patients. True, much clinical trial data—beginning with monotherapy studies involving standard

Figure 1. Pretreatment Evaluation of HCV Infection In Coinfected Patients

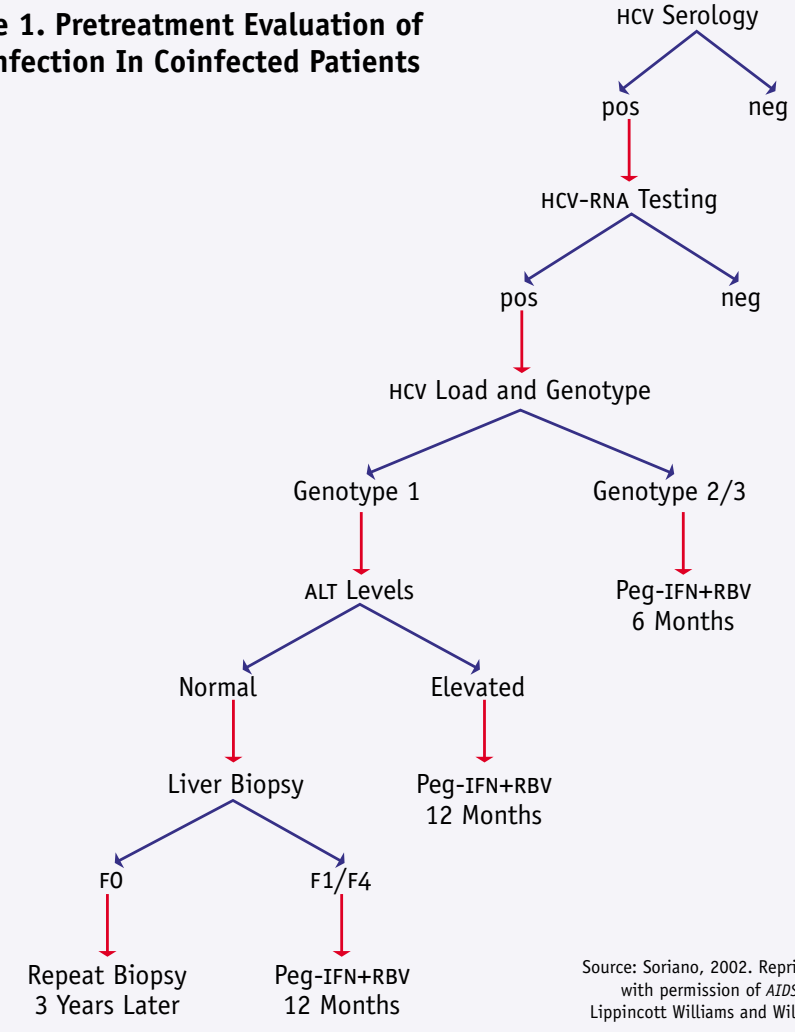

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Table 3. Sustained Virologic Responses to Pegylated Interferon in HIV-Negative Patients with Chronic HCV

	No. of patients	Overall response (%)	Genotype 1 (%)	Genotype 2 (%)
Roche (Fried, 2001)				
Standard interferon + ribavirin	444	45	37	46
Pegasys	224	30	21	56
Pegasys + ribavirin	453	56	46	76
Schering-Plough (Manns, 2001)				
Standard interferon + ribavirin	505	47	33	79
Peg-Intron 1.5/0.5 + ribavirin	514	47	34	80
Peg-Intron 1.5 + ribavirin*	511	54	42	82

*Considering only patients who received a ribavirin dose greater than 10.6 mg/kg, the figures are 6.1% for the overall response rate, 48% for genotype 1 and 88% for genotypes 2/3.

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alpha-interferon and more recent evaluations of pegylated alpha-interferon combined with ribavirin—has been generated over the past four years. But there has been little in the way of a consensus-derived standard-of-care—a blueprint, of sorts, for clinicians to draw upon when faced with questions related to the who, when and how of treatment in their patients coinfected with HIV and HCV.

Fortunately, a consensus has now been reached. On April 18, 2001, an international panel of experts—including Drs. Soriano, Mark Sulkowski, Christine Katlama, Douglas Dieterich, and Thierry Poynard, to name a handful of participants—met in Paris to present research and practice protocols and to produce a set of recommendations that might be applied to the care of all coinfected patients with access to newer technologies and treatments. Dr. Soriano spent the better part of his lecture time reviewing the data and the recommendations, published in the April 12, 2002, issue of *AIDS* (Soriano, 2002).

Whom to Treat?

AS SUMMARIZED IN THE *AIDS* EDITORIAL, A VAriety of strategies have been proposed to determine which coinfected patients require treatment. In the past, many clinicians were quick to order a liver biopsy and to prescribe treatment based on its results. While there is no doubting the clinical importance of liver biopsies, it may be equally important to consider other parameters.

A liver biopsy that produces a result of no fibrosis (F0) or non-significant inflammatory activity is generally not an indication for immediate treatment. In contrast, a fibrosis score of F2 to F4, which indicates significant fibrotic activity likely associated with inflammation, is an indication to begin treatment. A fibrosis score of F1 may be more difficult to claim categorically as an indication either for or against immediate treatment. However, in addressing this question in HIV-negative individuals, a recent cost-effectiveness analysis concluded that immediate therapy is warranted (Wong, 1998).

A combination of biochemical fibrosis markers has recently been proposed as an indirect method for scoring fibrosis without liver biopsy (Imbert-Bismut, 2001). These markers include: alpha-2 macroglobulin, alpha-2 globulin (or haptoglobin), gamma globulin, apolipoprotein A1, gamma glutamyltranspeptidase, and total bilirubin. As titillating as it may sound to be able to follow HCV-infected patients without the need for repeated liver biopsies, Dr. Soriano warned that these data have yet to be confirmed in prospective studies or validated in patients coinfected with HIV and HCV. "Liver biopsy is still the best tool we have to stage the disease and to exclude other causes of liver damage," he said.

There is also the question of how often liver biopsies should be repeated in coinfected patients with baseline biopsy results showing no signs of fibrosis. Among HCV-monoinfected patients, Dr. Soriano said that repeated liver biopsies are typically recommended every five years, until a fibrosis score of F2 or higher warrants the initiation of treatment. However, in HIV/HCV-coinfected patients, the progression from F0 to F4 is faster than in HCV-monoinfected patients; thus many experts suggest reducing the interval between liver biopsies to three years.

An algorithm summarizing the most beneficial way to proceed in the pretreatment evaluation of HCV infection in HIV-positive patients can be seen in Figure 1.

When to Treat?

REITERATING THE PUBLISHED RECOMMENDAtions, Dr. Soriano stressed that efforts to treat chronic HCV infection should be initiated before patients begin HAART. There are several reasons for this. First, HCV is considered an opportunistic infection and its treatment should be given priority over the more general protective effects of antiretroviral therapy. Second, successful HCV treatment may reduce the heightened risk of HAART-associated hepatotoxicity typically associated with chronic HCV infection. Third, there is evidence to suggest that HCV infection may stunt or alter the immune reconstitution response to HAART. Fourth, patients are less likely to feel burdened or overwhelmed if their treatments for HIV and HCV do not need to be taken at the same time. Finally, there is a reduced likelihood of interactions—such as overlapping toxicities (e.g., anemia associated with ribavirin and zidovudine [Retrovir]

or pancreatitis associated with ribavirin and didanosine [Videx])—if treatments for both conditions are started separately.

How to Treat?

UNTIL RECENTLY, DAILY OR THREE-TIMES-weekly injections of alpha-interferon, combined with daily oral doses of ribavirin, were considered the best option available, with sustained response rates between 30% and 35%. While interferon remains a vital component of anti-HCV combination therapy, attention has now shifted to the pegylated interferons—formulations of alpha-interferon that have been covalently bonded to polyethylene glycol (peg). This modification allows for a slower release of alpha-interferon and the possibility of maintain-

CONSENSUS STATEMENTS FROM THE HIV-HCV INTERNATIONAL PANEL

1. HCV infection is now a leading cause of morbidity and mortality in HIV-infected individuals in developed countries.

2. Screening for HCV antibodies should be performed on all HIV-infected individuals, in order to facilitate the prevention of liver disease progression and to allow for the active consideration of HCV treatment.

3. HCV treatment should be recommended primarily on the basis of the fibrosis score obtained by liver biopsy (alternatively using fibrosis markers). A fibrosis score of F1–F4 is generally an indication for treatment. However, treatment might be considered without biopsy in individuals with HCV genotypes 2 or 3, because their response rate is very high with combination therapy.

4. The CD4 cell count and plasma HIV-RNA level should be reviewed together when considering a patient as a candidate for HCV therapy. Individuals with CD4 cell counts greater than 500 cells/mm,^{3} regardless of the HIV-RNA level, are good candidates for treatment. Likewise, patients with CD4 cell counts between 200 and 500 cells/mm^3 may also benefit from HCV treatment if they have plasma HIV-RNA levels below 5000 copies/ml. A CD4 cell count below 100 cells/mm^3 should be considered a relative contraindication for HCV therapy. These patients are at high risk of developing classical AIDS-defining conditions. Antiretroviral treatment should be the priority in such patients. Once the CD4 cell count rises above 200 cells/mm,^{3} such patients can be reconsidered as candidates for HCV therapy.

5. Active substance abuse must be addressed before beginning HCV therapy. Candidates should not be active intravenous drug or alcohol users. Enrollment into drug and alcohol treatment programs should be encouraged. Patients on a methadone maintenance therapy program are candidates for HCV treatment.

6. Patients with a history of severe depression must be monitored closely throughout therapy. Antidepressants may be recommended in patients developing mild depression symptoms, and treatment should be discontinued in cases of severe depression or suicidal ideations. For some patients, psychiatric consultation should be considered before HCV treatment.

7. HCV therapy should not be initiated in the presence of an active opportunistic infection.

8. Based on limited data, the treatment of HCV infection in HIV-positive individuals should be the same as regimens recommended for HIV-negative individuals. The ribavirin dose should be based on body weight, and the dose should be maintained at at least 10.6 mg/kg per day. Likewise, Peg-IFN should be weight-based for Peg-Intron (Schering–Plough) at 1.5 µg/kg/week and at a fixed dose of 180 mg/week for Pegasys (Roche).

9. Serum HCV-RNA measurement by PCR or other nucleic acid testing should be performed at least after 24 weeks on treatment. If HCV RNA is undetectable, treatment should be continued for an additional 24 weeks in patients with HCV genotypes 1 or 4. In patients with HCV genotypes 2 or 3, treatment might be discontinued. In all cases, if HCV RNA is detectable after 24 weeks, treatment should be discontinued. The benefit of continuing with maintenance therapy should be examined in the context of clinical trials.

10. Serum ALT levels should not be used as the primary parameter to assess treatment efficacy.

11. Clinicians should be cautious when using ribavirin with zidovudine or didanosine, and should consider close clinical and laboratory monitoring during therapy (e.g., hemoglobin levels with zidovudine and amylase with didanosine). Whenever possible, other antiretroviral drugs should be recommended.

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ing sustained plasma levels of the drug with more effective viral suppression. Schering Plough's 12 kDa branched-pegylated IFN-α-2b (Peg-Intron) was approved in January 2001, and a New Drug Application (NDA) in support of Hoffmann-La Roche's 40 kDa branched-pegylated IFN-α-2a (Pegasys) is now under review. [EDITOR'S NOTE: *A detailed review of data from clinical trials assessing the safety and efficacy of standard alpha-interferon and pegylated interferon—both alone and combined with ribavirin—can be found in "HCV and HIV: Challenges and Opportunities," an article summarizing a lecture delivered by Dr. Douglas Dieterich appearing in the March 2001 issue of* The PRN Notebook.]

In HIV-negative patients, combinations of pegylated interferon and ribavirin were associated with sustained virologic response rates of up to 42% in those with genotype 1 and up to 80% in those with genotype 3 (see Table 3). In HIV-positive patients, studies evaluating pegylated interferon and ribavirin are still under way. One such trial is the French randomized RIBAVIC-ANRS HC02 study. As of April 2002, 239 patients have been randomly assigned to receive either standard interferon doses (3 million IU TIW) plus ribavirin (800 mg/day) or pegylated interferon (1.5 µg/kg/week) combined with ribavirin for 48 weeks. A little closer to home is ACTG 5071, a randomized comparison of standard interferon and pegylated interferon—both in combination with ribavirin—currently closed to enrollment with 134 patients accrued. Dr. Soriano anticipates that preliminary data from both studies will begin trickling down later this year.

While the selection of the most effective treatments available will definitely have an impact on the overall success of treatment, there are also host and viral matters to consider. As explained in the consensus paper, there are essentially five independent predictors of sustained virologic responses to therapy. First, chronic infection associated with genotype 2 or 3 is the most important predictor. Sadly, genotype 1—the most common HCV genotype in the United States—is considered to be the most unresponsive to treatment. Second, pretreatment HCV-RNA levels below 3.5 million copies/mL are more likely to be knocked down and maintained at undetectable levels than higher HCV viral loads. Third, patients with minimal liver damage—damage that does not exceed portal fibrosis—are also much more likely to respond effectively to therapy. Fourth, individuals under the age of 40 appear to respond to therapy better than older individuals. Finally, women are more likely to benefit than men, though this is probably related to issues of body weight and not gender, per se.

Another point raised by Dr. Soriano, which is also raised in the published recommendations, pertains to the duration of interferon/ribavirin therapy in coinfected patients. It appears that 24 weeks is a crucial time point at which to assess a given patient's response to treatment and to determine how much longer he or she should continue therapy. If HCV-RNA is positive at 24 weeks, treatment should be discontinued and other therapeutic strategies considered. If PCR is negative, and the patient has fewer than four predictors of response (see above), treatment should be continued for an additional six months. If, however, the patient has four or more predictors, treatment may be discontinued at 24 weeks. prn

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