

Pathogenesis and Treatment of Human Immunodeficiency Virus and Chronic Hepatitis C Virus Infection

Published online 16 May 2007 | Reprinted from *The PRN Notebook*® | Dr. James F. Braun, Editor-in-Chief
Meri D. Pozo, PhD, Managing Editor | Published in New York City by the Physicians' Research Network, Inc.®
John Graham Brown, Executive Director | For further information and other articles available online, visit
[HTTP://WWW.PRN.ORG](http://www.prn.org) | All rights reserved. ©MAY 2007

THE HEPATITIS C VIRUS (HCV) IS A SINGLE-STRANDED, ENVELOPED VIRUS OF the Flaviviridae family, identified in 1989. Usually, HCV persists as a chronic infection, potentially leading to cirrhosis, liver failure, and hepatocellular carcinoma (HCC) if untreated. In the United States and Europe, liver disease secondary to HCV is the leading indication for liver transplantation.

Due to overlapping transmission routes, HCV coinfection is common among HIV-infected persons. In the United States and Europe, HCV-associated end-stage liver disease has become a leading cause of death among HIV-infected persons (Bica, 2001; Rosenthal, 2003)

Virology

THE RNA GENOME IS APPROXIMATELY 9400 NUCLEOTIDES IN LENGTH, comprising 1 long open reading frame that encodes a polyprotein of 3010-3033 amino acids. This protein is cleaved into functionally distinct polypeptides during or after translation. The nucleocapsid and envelope proteins are encoded at the 5' end of the genome, while the nonstructural elements are located downstream. There are hypervariable regions (particularly in the E1 and E2 domains that code for envelope glycoproteins) that may be important antigenic sites. Their variability may be central in persistence of infection and immunopathogenesis. The hepatitis C virus replicates via an error-prone RNA-dependent RNA polymerase. Daily production of HCV exceeds 12 billion virions. Infections with HCV typically occur as a mixture of closely related viral populations known as quasispecies. There is a high degree of genetic variability, and the virus has evolved to optimize fitness in different hosts. There are at least 6 HCV genotypes, and hundreds of subtypes. Genotypes 1, 2, and 3 are the most common in the United States and Europe.

The HCV genotype is the most important pretherapy virologic predictor of outcome, regardless of HIV status (Fried, 2002; Manns, 2001; Carrat, 2004; Chung, 2004; Hadziyannis, 2004; Laguno, 2004; Torriani, 2004). Treatment is less effective for persons infected with HCV genotype 1, which is predominant in the United States (Blatt, 2000).

Epidemiology

CHRONIC HCV INFECTION IS AN IMPORTANT PUBLIC HEALTH CONCERN. Worldwide, 170 to 400 million people are thought to be infected with HCV, and a higher prevalence is found in Asia and Africa (Tossing, 2005). Population prevalence data are unavailable for many countries, but it is believed that 2% to 3% of the world's population is chronically infected. HCV is one of the 10 leading causes of infectious disease deaths worldwide, annually accounting for 250,000 deaths (Perz, 2006).

Geoffrey M Dusheiko, MD, FCP(SA), FRCP
Professor of Medicine, Royal Free and University College
School of Medicine | London, United Kingdom

Gabriel Ionescu, MD
Attending Physician, Division of Gastroenterology
St. Luke's-Roosevelt Hospital Center | New York, New York

Jason Bratcher, MD
Gastroenterology/HIV Fellow, Lenox Hill Hospital
New York, New York

Tracy Swan
Coinfection Project Director, Treatment Action Group
New York, New York

Globally, an estimated 4 to 5 million people are coinfecting with HIV/HCV (Alter, 2006). In the United States, 20%–30% (Sulkowski, 2000) and in Europe, 34% (Rockstroh, 2004) of all HIV-infected persons are coinfecting with hepatitis C, with much higher rates in hemophiliacs and injection drug users (IDUs). Among cohorts of HIV-seropositive IDUs, prevalence ranges from 70% to 90% (Garfein, 1996; Sherman, 2002; Bowker, 2004; Miller, 2004; Mohsen, 2005). Even though the rate of sexual transmission of HCV in heterosexual monogamous couples is exceedingly low, sexual transmission in both HIV-infected and -uninfected men who have sex with men (MSM) has now been documented (Danta, 2007).

In developed countries, individuals at risk of HCV infection include:

- Current and former injection drug users
- Health care workers who have had an occupational exposure to blood or blood products
- Individuals on hemodialysis, if facility does not practice adequate infection control
- Those who engage in high-risk sexual practices. (see Mark Danta, page 2 in this issue)
- Blood transfusion prior to 1992
- Sharing of paraphernalia in intranasal cocaine users
- Maternal/child transmission (C-section is recommended for HIV/HCV coinfecting women)
- Tattooing, when under unsterile conditions such as in prison with shared equipment, ink, inkwells

In developing countries, sources of HCV infection include all of the above and:

- Transfusions of unscreened blood
- Those who receive unsafe injections, or other parenteral exposure to blood
- Use of blood-contaminated implements for circumcision or surgery
- Traditional scarification
- Acupuncture under unsterile conditions
- Ear piercing

Natural History and Pathogenesis

MOST CASES OF CHRONIC HCV ARE ASYMPTOMATIC (SANANTONIO, 2003) and not preceded by an episode of clinically apparent jaundice (Calleri, 2007). In 15% to 45% of exposed individuals, acute HCV disease completely resolves, with clearance of HCV RNA from serum within 4 months (Di Bisceglie, 1991; Tremolada, 1992). Hepatitis C viral RNA becomes detectable in serum 7 to 21 days after exposure, while HCV antibodies are present from 20 to 150 days. Less than 20% of those infected have jaundice, and this usually correlates with RNA titers. In addition, a clinical syndrome may occur, consisting of jaundice, nausea, fatigue, myalgias, low-grade fevers, and upper abdominal discomfort. When present, it occurs within 2 to 12 weeks after exposure, lasting up to 12 weeks, and may not be related to viral titers (Orland, 2001). HCV-specific CD4+ and CD8+ T cells appear within 2 to 3 months following acute infection. A strong T cell response, with increased production of interferon-gamma (IFN- γ) and interleukin 2 (IL-2), was characteristic in HCV-monoinfected subjects who cleared viremia.

Approximately 55% to 85% of exposed individuals fail to spontaneously clear the virus and are at risk for liver damage as well as extrahepatic manifestations of HCV. Progression of HCV-induced liver disease has been associated with many systemic diseases and their complications, including autoimmune hepatitis, cryoglobulinemia, porphyria cutanea tarda, lymphocytic sialoadenitis and membranous glomerulonephritis. Data in support of a link between non-Hodgkins lymphoma and HCV (Gisbert, 2004) also exist but may be limited to MSM (Franceschi, 2006).

The pathogenetic mechanisms that result in chronic hepatitis are unknown; Tsai and colleagues proposed that abnormalities in early events, involving innate immunity, may lead to the impaired cellular immunity responses seen in those who develop persistent infection (Tsai, 1997). Thus, loss of sustained CD4+ reaction (Gerlach, 1999) and lower IFN- γ response to NS 3-5 proteins (Danta, 2006), lead to chronicity. In HIV-HCV coinfection, there is increased apoptosis of CD4+ and CD8+—naïve and memory cells, suggesting a permissive effect of HIV, regardless of viral load or CD4 counts, towards establishing chronic HCV infection. Furthermore, reduced activation of CD8+ memory cells is noted in coinfecting subjects (Yonkers, 2006).

In chronic HCV infection, fibrosis results from the activation of hepatic stellate cells by cytokines and other signalling molecules induced by the inflammatory process. These produce and deposit extracellular matrix proteins. Fibrosis begins around the portal tracts and gradually extends into the lobules towards the central veins. Hepatic steatosis is a concurrent factor in the progression to advanced fibrosis. Steatosis is associated with HCV genotype 3, and in patients with other genotypes, steatosis is associated with metabolic factors such as higher body mass index, type 2 diabetes, and hyperlipidemia (Castera, 2006).

HCV, with or without HIV, increases the risk of insulin resistance and diabetes (Duong, 2001; Mehta, 2003). The use of a protease inhibitor is an additional independent risk factor for developing hyperglycemia (Mehta, 2003). Insulin resistance is a common denominator for steatosis, fibrosis, and elevated circulating tumor necrosis factor (TNF), which adversely affect sustained virologic response (SVR) rates of genotype 1 HCV-infected patients (Romero-Gomez, 2005; 2006). In contrast to monoinfected patients, insulin resistance and diabetes were not contributing factors to fibrosis progression in HCV/HIV coinfecting patients (Merchante, 2006; Monto, 2006), although a recent report has shown hyperglycemic patients to be more likely to have advanced fibrosis (Barreiro, 2006).

At least 20% of those with chronic hepatitis will progress to cirrhosis after 20 years, increasing the risk of liver failure and HCC. The disease can more rapidly progress to cirrhosis in those with other hepatotoxic

risk factors, such as alcohol consumption of more than 50 grams per day, aging, and HBV and/or HIV coinfection. Approximately 10% to 20% of patients become cirrhotic within 10 years of infection. The initial presentation of older patients without access to medical care may be with advanced liver disease, cirrhosis, and/or HCC. Currently, HCV-induced cirrhosis is the most common indication for liver transplantation in the United States and Europe.

Effects of Coinfection

COINFECTION WITH HIV AFFECTS THE NATURAL HISTORY OF HCV INFECTION. Lower clearance rates (5% to 10%) are seen in HIV-seropositive individuals with acute HCV. HIV accelerates HCV disease progression. Cirrhosis is more prevalent among HIV-positive than -negative patients (Di Martino, 2001) and is emerging as a major cause of morbidity and mortality in patients with HIV/HCV coinfection (Rosenthal, 2003). Liver disease is now among the leading causes of hospital admissions for patients with HIV infection, and timely evaluation of HCV in these patients is crucial.

HCV is an independent risk factor for highly active antiretroviral therapy (HAART)—associated hepatotoxicity. This effect is generally outweighed by a reduction in the overall risk of liver-related mortality when HAART is administered; only 4% of HAART-treated patients require discontinuation of their HIV medication (Cooper, 2006). In a recent study, 2.7% of liver mortality was attributed to antiretrovirals, while HCC was responsible for 10% of liver-related events in the HAART era (Weber, 2006).

Immune status and virologic control are critical in fibrogenesis. Factors that adversely impact fibrosis progression (Verma, 2006) include: decline of more than 10% in CD4 (Schiavini, 2006); nadir CD4 (Monto, 2006); current CD4 below 200 cells per mm³ (Di Martino, 2001), and HIV RNA above 50 copies per mL (Hernandez, 2006). Maintaining a CD4 count above 500 cells per mm³ may be associated with lower fibrosis progression rates. Successful HIV suppression in patients with CD4 levels below 500 cells per mm³ has also been associated with slower progression of fibrosis (Brau, 2006). Beneficial effects may be seen with any suppressive HAART regimen (Verma, 2006).

Antiretroviral agents for coinfecting patients should be carefully selected, since some are more likely to induce hepatotoxicity. Liver enzyme levels should be routinely monitored, and therapy stopped if symptoms develop or if liver function tests rise to greater than 5 times normal or to above 3.5 times the baseline values. In addition, other etiologies such as ethanol abuse, acute cholecystitis, or infection with hepatotropic viruses, like Epstein-Barr or cytomegalovirus (CMV) have to be ruled out (Sulkowski, 2003).

Stavudine and didanosine, nevirapine, and tipranavir—the latter in combination with enfuvirtide—have been associated with serious liver damage in persons with HIV alone (Maida, 2006). Stavudine and didanosine may deplete hepatocellular mitochondrial DNA, and have been associated with hepatic steatosis in HIV/HCV coinfecting patients (Mc Govern, 2006; Sulkowski, 2005; Walker, 2004).

The effect of HCV on HIV progression is poorly understood and is beyond the scope of this review.

Diagnostics

ANTI-HCV ANTIBODY IS USUALLY DETECTABLE WITHIN 3 WEEKS OF exposure, whereas HCV-RNA is detectable in blood 1 to 3 weeks after exposure (Orland, 2001; Netski, 2005). Patients with positive serology for antibodies against HCV should have a qualitative RNA level measured to confirm viremia. Up to 5.5% of coinfecting indi-

TABLE 1. Assays for Quantitation of HCV RNA in Serum

Assay	IU/L Conversion	Technique	Dynamic Range (IU/L)
Versant HCV RNA version # 3.0 Quantitative Assay	5.2 copies/mL	Semiautomated branched DNA assay	615–700,000
LCX HCV RNA Quantitative Assay	3.8 copies/mL	Semi-automated competitive rtPCR	25–2,630,000
SuperQuant	3.4 copies/mL	Semi-automated competitive rtPCR	30–1,470,000

Adapted from Pawlotsky JM. *Gastroenterology*. 2002;122:1554-1568.

viduals will display seronegative chronic HCV infection, in which there is negative serology and detectable HCV RNA (Bonacini, 2001). Elevated ALT, history of intravenous drug use and CD4 levels below 200 cells per mm³ are predictors of seronegative HCV (Chamie, 2006), and may indicate further screening for HCV RNA.

Two polymerase chain reaction (PCR)-based tests for qualitative detection of HCV RNA are currently approved by the FDA: Amplicor Hepatitis C Virus Test, version 2.0, and Cobas Amplicor Hepatitis C Virus Test, version 2.0 (Roche Molecular Systems, Branchburg, NJ), which have lower limits of detection of approximately 50 IU per mL. Of the quantitative tests (Table 1), only Versant HCV RNA version no. 3.0 is approved by the FDA. If HCV RNA is detected, baseline serum aminotransferases, bilirubin, alkaline phosphatase, prothrombin time, complete blood count (CBC) with differential, creatinine, and thyroid-stimulating hormone (TSH) should be measured in preparation for treatment. It is advisable to rule out other causes of liver disease such as hemochromatosis or autoimmune hepatitis.

Serum aminotransferases (AST and ALT) remain abnormal after 12 months in 60% to 85% of patients with posttransfusion or sporadic hepatitis. These enzymes decline from the peak values encountered in the acute phase of the disease, but typically remain abnormal by 2- to 8-fold. Serum ALT concentrations may fluctuate during the course of the disease, but they can also be intermittently or consistently normal. As chronic disease progresses, laboratory values continue to become more abnormal. Serum AST greater than ALT, hypoalbuminemia, thrombocytopenia, and prolonged prothrombin time all suggest cirrhosis.

A liver biopsy is helpful in grading the degree of inflammation and staging the degree of fibrosis. Biopsy has prognostic value, since all patients with initial periportal fibrosis are likely to develop cirrhosis after 2 decades of untreated infection (Yano, 1996). In patients with less-severe histologic disease who may never develop cirrhosis, careful clinical monitoring is an alternative to antiviral therapy. In addition, liver biopsy may be repeated in 5 years to assess progression rate (Strader, 2004) in monoinfected patients.

However, the benefits of liver biopsy have to be weighted in the light of sampling error (Regev, 2002) and against the risk of complications such as hemorrhage, puncture of adjoining organs, or mortality. Fatal hemorrhage may occur in up to 0.11% of all liver biopsies, with higher prevalence in malignant liver disease (McGill, 1990; Bravo, 2001).

As the efficacy of HCV therapy has improved, guidelines have been modified so that all patients with HCV should be evaluated for treatment (Strader, 2004; DHHS, 2006). This change in protocol has effectively reduced the need for liver biopsy, but it is still useful in making treatment decisions in select cases, such as patients with difficult to treat genotypes. For patients with genotypes 1 and 4, therapy should be individualized based on severity of liver disease,

as determined by either histology or clinical and laboratory signs of cirrhosis, such as spider angiomas, splenomegaly, jaundice, ascites, encephalopathy, hyperbilirubinemia, hypoalbuminemia, thrombocytopenia, and prolonged prothrombin time (PT)/ increased international normalized ratio (INR). However, the latter are signs of advanced liver disease, which may be avoided with earlier treatment.

Alternatives to biopsy, such as FibroScan® (FS, Echosens, France) and panels of serum markers of fibrosis (eg, FIBROSPECT®, Prometheus; FibroTest, Biopredictive), may eventually obviate the need for biopsy in all patients. Among these, FibroScan® determines liver stiffness, which is a noninvasive measure of fibrosis (Ziol, 2005), while FibroTest (Imbert-Bismut, 2001) and FIBROSPECT® (Christensen, 2006) are composite scores of serum markers of inflammation and fibrosis. These noninvasive methods are more accurate in predicting very mild fibrosis or cirrhosis and may help avert liver biopsy for patients whose liver histology may be at the extremes of the spectrum of inflammation and fibrosis.

Management

ALL PATIENTS WITH HCV SHOULD ALSO BE TESTED FOR HEPATITIS A VIRUS (HAV), HBV, and HIV. If negative, patients should be vaccinated against both HBV and HAV. The immune response to HAV vaccine is good, even in relatively immune-suppressed individuals, while successful HBV vaccination relies on relatively high CD4 counts (≥500 and on viral load below 1000). Revaccination should be attempted if antibodies to hepatitis B surface antigen titers are below 10 mIU per mL or if CD4+ levels rise above 500 per mm³ in the prior nonresponder (Laurence, 2005).

Treatment of chronic HCV has considerably improved over the last 10 years. A substantial proportion of patients can achieve serum viral eradication, although current treatments have limitations.

Comorbidities such as diabetes, cardiovascular and kidney disease, psychiatric history, and hematologic abnormalities must be considered before initiating treatment (Strader, 2004).

Pretreatment retinal examination is important, since a rare neuroretinitis (seen more often in patients with diabetes) may occur that is a medical emergency, necessitating discontinuation of treatment.

Alpha interferon is difficult to apply in decompensated cirrhosis (Child-Pugh class C) and may precipitate deterioration. Patients with signs of decompensated cirrhosis, such as jaundice, marked coagulopathy, spontaneous bacterial peritonitis, variceal bleeding and/or hepatic encephalopathy (Table 2) meeting Child-Pugh class C (Table 3) should be considered for liver transplantation.

A majority of coinfecting patients, with normal ALT, have mild fibrosis, while 30% may have moderate stage 2 fibrosis (Sanchez-Conde, 2006). Noninvasive markers are less accurate in coinfecting patients (Macias, 2006; Cacoub, 2006; Bourliere, 2006). A majority of coinfecting patients with normal ALT have mild fibrosis, while up to 30% have moderate stage 2 fibrosis (Sanchez-Conde, 2006). Untreated coinfecting patients may need to undergo liver biopsy more frequently than every 5 years. Over a 3-year time interval, a 2-stage progression has been noted on liver biopsy in 22% of patients with stage 1 fibrosis at baseline. Faster progression has been linked to persistently elevated AST and ALT (>100 IU/mL) (Sulkowski, 2006).

TABLE 2. Grading of Hepatic Encephalopathy

Grade	Level of Consciousness	Intellectual Function	Neurologic Findings	EEG
1	Lack of awareness Personality change Day/night sleep pattern reversal	Short attention span, forgetfulness, mild confusion, agitation	Uncoordination Mild asterixis tremor Impaired handwriting	Slowing (5–6 cps) Triphasic
2	Lethargic Inappropriate behavior	Disoriented	Asterixis Hypoactive reflexes	Slowing Triphasic
3	Asleep Rousedness	Loss of meaningful communication	Asterixis Hyperactive reflexes	Slowing Triphasic
4	Comatose	Absent	Decerebrate	Very slow (2–3 cps), delta

Adapted from Riordan SM. *N Engl J Med.* 1997;337:473-479.

TABLE 3. Child-Pugh Score Calculation and Interpretation

Child-Pugh Score Interpretation: Points			
	Class A:	5–6	
	Class B:	7–9	
	Class C:	10–15	
Points	1	2	3
Bilirubin	<2.0	2.0–3.0	>3.0
Albumin	>3.5	3.5–2.8	<2.8
PT prolongation (INR):	<4 seconds (<1.7)	4–6 seconds (1.7–2.3)	>6 seconds (>2.3)
Ascites	Absent	Mild-Moderate	Severe/Refractory
Encephalopathy	Absent	Mild (1–2)	Severe (3–4)

Points should be ascribed according to clinical and laboratory data and then added to establish Child-Pugh score and interpretation as stated above.

Combination Therapy with IFN alpha and Ribavirin

THE IFNS ARE A SYSTEM OF RELATED PROTEINS DERIVED FROM A multigene family that work via species-specific surface cell receptors. Interferon monotherapy induces a nonspecific cytokine response, Th1 and Th2, with sustained responders showing increased Th1 reactivity by augmented IFN- γ production at week 4 (Cramp, 2000).

Pegylated Interferons

LIMITATIONS IN THE EFFECTIVENESS OF IFN- α HAVE BEEN ATTRIBUTED to its rapid systemic clearance and short plasma elimination half-life ($t_{1/2}$) of about 8 hours. Pegylated (PEG) subcutaneous formulations of IFN- α have been developed by covalent attachment of recombinant IFN- α to branched 40- or 12-kD polyethylene glycol moieties (Kozlowski, 2001). These molecules protect the IFN protein from enzymatic degradation, thus reducing systemic clearance. Pegylation alters the pharmacokinetics and pharmacodynamics of IFN- α , leading to improved drug concentrations and sustained exposure. Pegylated IFNs have decreased volume of distribution (Vd) and a greater reduction in renal clearance compared with standard IFN.

Two versions, a 12-kD PEG IFN- α 2b (Peg-Intron[®], Viraferon PEG[®], Schering) and a 40-kD PEG IFN- α 2a (Pegasys[®], Roche) are approved for the treatment of hepatitis C, but only PEG IFN- α 2a is currently

approved by the FDA for the treatment of HCV in HIV coinfecting patients.

Although the 2 available PEG IFN products have different pharmacokinetic profiles and molecular structures, there do not appear to be major differences in their efficacy in the treatment of HCV mono-infection and HCV-HIV coinfection. However, no head-to-head studies have been conducted.

The aim of therapy is to achieve a sustained virological response (SVR : an undetectable HCV RNA 6 months after completion of therapy) and ultimately to reduce hepatic inflammation and severity of fibrosis. Response to treatment depends on genotype, baseline HCV RNA, and dosing and duration of treatment, age, and the stage of fibrosis, as well as clinical factors, such as comorbid conditions.

For mono-infected patients, 48 weeks of PEG IFN- α 2b (1.5 μ g/kg/wk) in combination with weight-based ribavirin (800 mg/d) achieved an overall SVR of 54% (42% for genotype 1 and 80% for genotypes 2 and 3), in comparison to an overall SVR of 47% with standard IFN- α 2b plus ribavirin. Analysis of response by weight-based dosing demonstrated that the optimum dose of ribavirin is 10.6 mg per kg per day, and those receiving this dose achieved an SVR of 48% for genotype 1 and 88% for genotypes 2 and 3 (Manns, 2001; Hadziyannis, 2004). Similar results have been obtained with PEG IFN- α 2a plus a fixed dose of ribavirin (Fried, 2002). For those mono-infected with genotypes 2 or 3, a reduced dose (800 mg/d) of ribavirin was adequate, as was only 24 weeks of combination therapy with PEG IFN and ribavirin (Hadziyannis, 2004). This finding has been extrapolated and applied to the use of PEG IFN- α 2b and ribavirin.

Ribavirin

RIBAVIRIN, A GUANOSINE NUCLEOSIDE ANALOGUE, SHOWS ONLY MODEST activity against HCV but increases the activity of standard and PEG IFN- α when the 2 are used in combination. The precise mode of action probably includes perturbation of intracellular nucleoside triphosphate pools. Ribavirin may also induce mutations in the HCV genome, affecting viral replication (Dixit, 2004).

Current Treatment Protocols

Monoinfected Patients

THE AIM OF THERAPY IS TO ACHIEVE AN UNDETECTABLE HCV RNA 6 MONTHS following therapy (SVR) and ultimately to reduce hepatic inflammation and severity of fibrosis. Pegylated IFN- α 2b is administered at a dose of 1.5 μ g per kg per week by subcutaneous injection. With this form of PEG IFN, ribavirin is coadministered according to the body weight of the patient for all genotypes in divided, oral daily doses. For patients who weigh less than 65 kg, the dose of ribavirin is 800 mg; for patients 65 to 85 kg, the dose is 1000 mg; and for patients over 85 kg, the dose is 1200 mg per day, divided in 2 doses. Pegylated IFN- α 2a (Pegasys®) is given at a fixed dose of 180 μ g per week. Coadministration of ribavirin in patients with genotype 1 is 1000 mg for those less than 75 kg and 1200 mg for those equal to or greater than 75 kg, in divided daily doses. Patients with genotypes 2 and 3 are treated with 800 mg of ribavirin. For genotypes 4, 5, and 6, there is insufficient evidence for treatment regimens and therapy needs to be individualized.

The pivotal studies suggested that a 24-week schedule for genotype 2 or 3 HCV-monoinfected patients is sufficient, whereas patients with genotype 1 require 48 weeks of therapy. Few patients with genotype 4 have been studied, but an SVR of 34% has been reported after a 48-week course of combination therapy, indicating that it should be treated in a similar manner to genotype 1 (Derbala, 2005). There are limited published data on treatment outcomes in patients with genotypes 5 and 6.

Patients with genotype 1 who do not show an early viral response (EVR; HCV RNA decline of at least 2 log₁₀ or undetectable HCV RNA after 12 weeks of therapy determined by quantitative PCR) have little opportunity of achieving an SVR, and therapy should be discontinued. For patients who achieve an EVR, HCV RNA should be measured at week 24. Patients who have detectable HCV RNA positive should stop therapy. Patients with genotype 2 or 3 have a high response rate to treatment (Strader, 2004) and, in those patients, HCV RNA testing at week 12 may not be cost-effective. However, testing at week 12 may avoid unnecessary medication for non-responders and may help to motivate patients who are responding to stay on treatment.

The most common, early adverse reactions of IFN include an influenza-like syndrome: chills, fever, malaise, muscle aches, and headaches. These symptoms may be ameliorated by acetaminophen (paracetamol), water, and exercise. Poor appetite, weight loss, increased somnolence, psychologic effects (irritability, anxiety, depression), hair loss, thrombocytopenia, and leukopenia are also common adverse effects.

Mild depression is not unusual and can often be treated with selective serotonin reuptake inhibitors (SSRIs), but a careful, pretreatment psychologic inventory is necessary to determine those who are at risk for developing severe depression. These patients may need structured psychologic support, which may delay or even preclude HCV treatment.

Dose reductions of IFN and/or ribavirin may be necessary, particularly in cirrhotic patients with low white cell and platelet counts due to portal hypertension and splenic sequestration. Unusual and severe adverse effects include seizures, acute psychoses, bacterial infections, and autoimmune reactions. Thyroid disease (both hyperthyroidism and hypothyroidism) is relatively common, can be seen in up to 5% of patients taking IFN, and can be permanent, requiring long-term therapy. Thyroid disease usually occurs in the setting of pre-existing antithyroid antibodies. Proteinuria, cardiomyopathy, skin rashes, interstitial lung disease, bone marrow suppression/aplasia and antibodies against IFN may also develop.

Although adverse effects are common, most are reversible and will resolve upon discontinuation of therapy. Occasionally, specialty referral is indicated for unusual reactions and growth factor supplementation

can also be instituted to avoid dose reduction or discontinuation due to anemia or leukopenia.

The major adverse effects of ribavirin are dose-dependent and include: reversible hemolytic anemia, myalgia (muscle pain), hyperuricemia, dyspepsia, and irritability. Patients should be carefully monitored for the above adverse effects clinically and serologically with CBCs, AST/ALT, uric acid, albumin, bilirubin, and thyroid function tests measured at least every 4 weeks. Any abnormal result should prompt immediate consideration and further investigation.

Due to the potential for ribavirin-induced teratogenicity, 2 methods of contraception should be reinforced prior to initiation of therapy and at each treatment-monitoring visit.

Dose reductions of IFN and/or ribavirin may be necessary, particularly in cirrhotic patients who develop anemia and/or leukopenia due to bone marrow suppression, or thrombocytopenia from portal hypertension and splenic sequestration.

Adherence to therapy is an important factor for improving SVR, but adverse effects necessitate dose reductions or discontinuation of therapy in 14% of patients. Aggressive management of adverse effects will help patients remain on HCV therapy.

Supportive therapies such as antidepressants, erythropoietin, and G-CSF have been demonstrated to reduce the incidence of IFN-induced depression, anemia and neutropenia, respectively. In anemic HCV-infected patients treated with ribavirin/IFN, epoetin alfa increases hemoglobin levels and maintains ribavirin dosing (Dieterich, 2003). Although these interventions can improve quality of life and enhance adherence, they have not yet been shown to benefit the SVR rate. Furthermore, they considerably add to the expense of therapy.

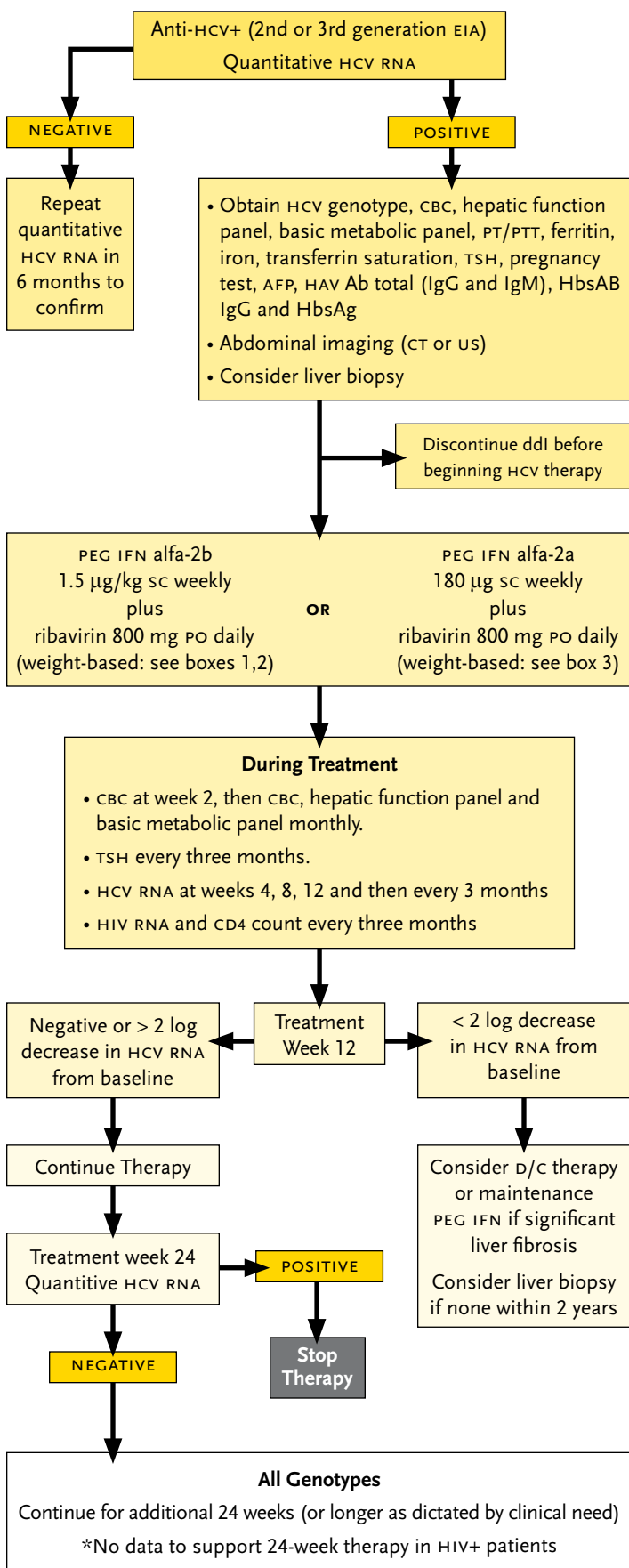
In addition to encouragement and support, patients should be advised to minimize or eliminate their intake of alcohol, since studies of interferon monotherapy reported a decrement in response to HCV treatment when alcohol was used, and alcohol consumption has been associated with higher HCV RNA.

Nonresponders to PEG IFN and ribavirin combination therapy, defined as patients whose HCV RNA levels remain stable on treatment, have a poor response to retreatment and, at present, no consensus exists regarding the management of this population. Those who relapse after standard IFN monotherapy, or standard IFN and ribavirin, may achieve an SVR when retreated with PEG IFNs and standard doses of ribavirin, particularly if they are nongenotype 1. As in naïve patients, treatment should be stopped if there is no retreatment EVR. Several major trials, including EPIC3 and HALT-C are currently investigating the long-term use of low-dose PEG IFN in nonresponders and those who relapse (ie, HCV RNA becomes undetectable on treatment but is detected again after discontinuation of therapy).

Current studies are investigating abbreviated courses of treatment for patients with genotype 1 and low viral loads (<400,000 IU/mL) who show a rapid viral response (RVR; negative HCV RNA by PCR at 1 month). Similarly, it may be possible to stop treatment at 16 weeks for patients with genotype 2 and 3 who have an RVR, while longer treatment may be needed for genotype 3 patients with HCV RNA above 800,000 IU/mL (von Wagner, 2005). Optimal dosing of ribavirin may be the key to achieving an RVR, since patients with HCV RNA levels higher than 800,000 IU per mL in genotype 3 may be more likely to relapse. Attractive as they may be, shorter courses of therapy are not universally accepted, since more studies are needed to determine the appropriate duration of treatment. Long-term follow-up on patients with SVR reveals ALT normalization and fibrosis and cirrhosis regression in a majority of patients with persistent HCV RNA in monocytes or liver tissue in extremely isolated cases (Maylin, 2006).

FIGURE 1. HIV/HCV Coinfection Management Algorithm

Courtesy of Hepatitis Resource Network (www.h-r-n.org).



Coinfected Patients

SEVERAL GUIDELINES HAVE ADDRESSED THE MANAGEMENT OF HCV/HIV coinfection (Strader, 2004; DHHS, 2006). Figure 1 provides a practical management algorithm for HIV-HCV coinfecting patients.

Treatment is generally more complex in coinfecting patients as a result of myelosuppression, drug interactions, antiretroviral-related hepatotoxicity, and advanced HIV disease. It is accepted that HCV treatment does not influence HIV progression or immune status, as the incidence of AIDS-defining events remained uniformly low, despite transient decrease in CD4 counts, while CD4+ percentage slightly increased (Torriani, 2004). In addition to HCV treatment, optimal immune status and effective HIV control should be achieved in an effort to slow fibrosis progression.

The indications for treatment are generally based on a combination of virologic findings and a full hepatic assessment. Most guidelines indicate that all HIV-positive patients with chronic HCV should be considered candidates for treatment (Strader, 2004; DHHS, 2006). Treatment is strongly recommended for patients with elevated serum aminotransferases, CD4 counts of greater than 350 cells per µL, HIV RNA less than 1000 copies per mL, and no alcohol intake, although the degree of fibrosis needs to be taken into account.

Similar to mono-infected patients, RVR is a strong predictor of SVR as long as dose reductions or discontinuation do not compromise the treatment course, and EVR is required to warrant a full course of therapy.

In a review of treatment practices, 70% of all coinfecting patients were ineligible for HCV treatment, primarily due to substance abuse, nonadherence with medical follow-up, advanced HIV disease, decompensated liver status, or medical comorbidities (Fleming, 2003). However, multidisciplinary models that incorporate mental health care and drug treatment (including methadone and buprenorphine) have successfully delivered HCV treatment to mono-infected and coinfecting patients with multiple diagnoses (Backmund, 2001; Schaefer, 2003; Van Thiel, 2003; Cournot, 2005; Litwin, 2005; Taylor, 2005; Sylvestre, 2005).

If possible, it is recommended that HIV management be optimized before commencing HCV treatment. Interferon may induce a slight decline in absolute CD4 count, but this does not appear to be of clinical significance.

Antiretroviral agents for HIV/HCV coinfecting patients should be carefully selected, since some are more likely to induce hepatotoxicity, depletion of hepatocellular mitochondrial DNA, and hepatic steatosis (Walker, 2004; Sulkowski, 2005; Mc Govern, 2006). Liver enzyme levels should be routinely monitored (Figure 2).

Box 1: Weight-based dosage of ribavirin used with PEG IFN-α 2b

<40 kg	600 mg daily
40–64 kg	800 mg daily
65–85 kg	1000 mg daily
86–105 kg	1200 mg daily
>105kg	1400 mg daily

Box 2: Weight-based dosage of PEG IFN-α 2b

Weight, kg	Redipen™ µg/0.5 mL	Volume, mL
<40	50	0.5
41–50	80	0.4
51–64	80	0.5
65–75	120	0.4
76–86	120	0.5
>85	150	0.5

Box 3*: Weight-based dosage of ribavirin used with PEG IFN-α 2a

<75 kg	1000 mg daily
>75 kg	1200 mg daily

*Trials to optimize response rates in mono- and coinfecting patients are ongoing. Results from the PRESCO trial indicate that weight-based ribavirin dosing, regardless of genotype, is associated with SVR in coinfecting patients.

FIGURE 2. Algorithm for HCV Treatment in HIV-Infected Patients

Before Starting Therapy

- ▶ **Review HIV disease status**
CD4 cell count (current and nadir), HIV RNA level
Antiretroviral therapy
Active opportunistic diseases
- ▶ **Examine comorbid conditions**
Psychiatric disease
Drug and alcohol use
Cardiopulmonary disease
Kidney disease
- ▶ **Measure complete blood count, serum creatinine concentration, and alanine and aspartate aminotransferase levels**
- ▶ **Measure plasma HCV RNA level (quantitative) to document that viremia is present**
- ▶ **Test for HCV genotype to help determine the probability of virologic response**
- ▶ **Consider a liver biopsy**
Assess the grade and stage of liver disease
Exclude other diagnosis
If biopsy is contraindicated or not available or patient declines, therapy can be given without liver biopsy
- ▶ **Counsel the patient about the relative risks and benefits of interferon- α plus ribavirin treatment**
Side effects should be thoroughly discussed

During Therapy

- ▶ **Pegylated interferon- α plus ribavirin combination therapy unless specific contraindications to the use of ribavirin (eg, uncontrolled cardiopulmonary disease or renal insufficiency)**
- ▶ **Reinforce the need to practice strict birth control during therapy and for 6 months thereafter**
- ▶ **Measure complete blood count and alanine and aspartate aminotransferase levels at weeks 2 and 4 and at 4- to 8-week intervals thereafter**
- ▶ **Adjust dose of interferon downward if a significant neutropenia occurs (absolute neutrophil count $<0.75 \times 10^9$ cells/L)**

- ▶ **Stop interferon if severe neutropenia occurs (absolute neutrophil count $<0.5 \times 10^9$ cells/L)**
- ▶ **Consider the concurrent administration of filgrastim in the management of interferon-associated neutropenia**
- ▶ **Adjust the dose of ribavirin downward (by 200 mg at a time) if significant anemia occurs (hemoglobin level <10 g/dL or hematocrit <0.3)**
- ▶ **Stop ribavirin if severe anemia occurs (hemoglobin level <8.5 g/dL or hematocrit <0.26)**
- ▶ **Consider the concurrent administration of epoetin- α (40,000 IU by subcutaneous injection weekly) in the management of treatment-related anemia**
- ▶ **Measure HIV RNA, absolute CD4 cell count, and CD4 percentage at 12-week intervals**
- ▶ **Evaluate for neuropsychiatric complications monthly (eg, depression screen)**
Consider use of antidepressants (eg, SSRI) and/or consultation with a mental health provider
- ▶ **Measure thyroid-stimulating hormone levels every 3 to 6 months during therapy**
- ▶ **Measure HCV RNA by PCR at 24 weeks**
- ▶ **If HCV RNA is still present, stop therapy or, if indicated, consider maintenance interferon- α monotherapy (maintenance interferon therapy has not been evaluated in coinfecting patients)**
- ▶ **If results of tests for HCV RNA are negative, continue therapy for at least an additional 24 weeks (some clinicians favor stopping therapy in persons with HCV genotype 2 or 3 infection; this approach has not been evaluated in coinfecting patients)**
- ▶ **At the end of therapy, test HCV RNA by PCR to assess whether there is an end-of-treatment response**

After Therapy

- ▶ **Six months after stopping therapy, test for HCV RNA by PCR**
If results of test for HCV RNA are still negative, the chance for a long-term virologic response is very high; relapses have rarely been reported after this point

HCV, hepatitis C virus; PCR, polymerase chain reaction; SSRI, selective serotonin reuptake inhibitor

Adapted from Sulkowski MS, Thomas DL. *Ann Intern Med.* 2003;138:197-207.

Coadministration of didanosine (ddI) and ribavirin should be avoided because of an increased risk of lactic acidosis (Lafeuillade, 2001) and/or pancreatitis (Salmon-Ceron, 2001), while AZT in conjunction with ribavirin increases the risk of anemia (Alvarez, 2006).

Use of stavudine (d4T) during HCV treatment is associated with weight loss and lipoatrophy (Perez Olmeda, 2003).

As with HCV monoinfection, the primary goal of HCV treatment for coinfecting patients is SVR. However, even in the absence of SVR, benefits of treatment have been shown and may include: reduction in the risk of HCC (Soriano, 2004); reduction in the risk of HAART-associated hepatotoxicity (Uberti-Foppa, 2003); and delay or reversal of fibrosis progression (Lissen, 2006).

The treatment regimen is the same as in monoinfected patients: PEG IFN and ribavirin. Although SVR is less likely for coinfecting patients, if HIV is well controlled and HCV therapy is tailored by response

to treatment and weight-based ribavirin dosing, response can be optimized. Four randomized, controlled trials have been published that examine the efficacy of PEG IFN and ribavirin for treatment of HCV in patients coinfecting with HIV (Tables 4 and 5). In general, the mean or median CD4 counts were high and more than 80% were undergoing HAART. Response rates ranged from 27% to 40%, which was better than that seen with standard IFN (12%–21%), but worse than that observed in monoinfected patients undergoing combination therapy (Carrat, 2004; Chung, 2004; Laguno, 2004; Torriani, 2004).

In coinfection genotype and baseline RNA also exerted a strong effect upon response rates. Higher SVRs were observed in patients with genotypes 2 and 3, as well as in patients with genotype 1 and lower viral loads. Better outcomes were also noted in young patients (aged younger than 40 years) without cirrhosis, those with elevated aminotransferases, and those with low or undetectable HIV RNA. In the APRICOT study, a

TABLE 4. PEG IFN + Ribavirin Trials in HIV-HCV Coinfected Patients

Characteristic	Chung, 2004 ACTG	Torriani, 2004 APRICOT	Carrat, 2004 RIBAVIC	Laguno, 2004
Location	United States	International	France	Spain
Design	PEG 2a + RBV vs STD 2a + RBV	PEG 2a + RBV vs PEG 2a + placebo vs STD 2a + RBV	PEG 2b + RBV vs STD 2b + RBV	PEG 2b + RBV vs STD 2b + RBV
PEG Dose	180 µg	180 µg	1.5 µg/kg	100–150 µg
Ribavirin	600 mg/d starting dose in 200-mg monthly increments up to a total dose of 1000 mg/d	800 mg/d	800 mg/d	800–1200 mg/d
Weeks	48	48	48	48
Undetectable HIV RNA	61%	60%	70% <400	70% <200
HCV RNA > 800,00 IU	83%	72%	Not reported	47%
Genotype 1	77%	61%	48%	55%
Fibrosis Cirrhosis	11%	12%	39%	29%
Adverse Effects Management	PEG/RBV dose reduction	PEG/RBV dose reduction Erythropoietin G-CSF	PEG/RBV dose reduction	PEG/RBV dose reduction

G-CSF, granulocyte-colony stimulating factor; PEG, pegylated interferon; RBV, ribavirin; STD, standard interferon.

TABLE 5. Response in Coinfected Patients

Reference	Regimen	Genotype 1 SVR	Genotype 2 and 3 SVR
Chung, 2004 ACTG	PEG 2a + RBV	14%	73%
	STD 2a + RBV	6%	33%
Torriani, 2004 APRICOT	PEG 2a + RBV	29%	62%
	STD 2a + RBV	7%	20%
Carrat, 2004 RIBAVAC	PEG 2b + RBV	17%	44%
	STD 2b + RBV	6%	43%
Laguno, 2004	PEG 2b + RBV WB	38%	53%
	STD 2b + RBV	7%	47%

PEG, pegylated interferon; RBV, ribavirin; STD, standard interferon; WB, weight based.

baseline CD4 percentage higher than 19.1%, and baseline HCV RNA below 400,000 IU per mL predicted higher SVR in genotype 1 patients (Dieterich, 2006). In addition, an early increase in CD4 cell percentage, after 1 month of treatment, was found to predict viral response (Neau-Cransac, 2005).

Differences in SVR rates among the studies include patient characteristics—such as general health status and race—and study design and ribavirin dose. It is possible that higher relapse rates occurred due to a lower dose of ribavirin (800 mg).

Questions remain regarding best dosing and duration of HCV treatment in HIV/HCV coinfecting patients. In February of 2006, PEG IFN-α 2a with 800 mg of ribavirin was approved for HIV/HCV coinfecting patients based on data from the APRICOT Study Group Trial (Torriani, 2004). The study conservatively dosed ribavirin at 800 mg daily in an attempt to prevent dose reduction or discontinuation due to anemia. Discontinuation of treatment was observed in 12% to 17% of patients and supplemental hemopoietic factors were required in 60% of patients taking zidovudine who developed anemia.

Higher doses (up to 1200 mg) are approved for mono-infected patients, and some coinfecting patients may derive similar benefit from a more aggressive regimen. Furthermore, APRICOT found that coinfecting patients have a higher rate of relapse and may need 48 weeks of treatment, regardless of HCV genotype. As with HCV mono-infection, coinfecting patients who fail to achieve an EVR have little, if any chance of achieving an SVR (Ballesteros, 2004; Laguno, 2007).

HCV treatment may have histologic benefits, even in the absence of SVR. Studies based on paired liver biopsies, taken before and after HCV treatment, showed improved histology in a majority of treatment responders and in up to 40% of patients who did not achieve SVR (Lissen, 2006; Soriano, 2006).

In HIV-coinfecting patients, SVR appears to be equally durable. Soriano and colleagues reported no HCV rebound among 77 patients who achieved SVR (minimum 6 month and mean of 58 months of long term follow-up). In addition, no liver decompensation or HCC are in this analysis (Soriano, 2004).

Liver transplantation in HIV-suppressed coinfecting patients has become an option for decompensated liver disease (see <http://clinicaltrials.gov/ct/show/NCT00074386?order=1>). However, survival beyond 4 years was noted to be poorer than in HCV mono-infected, and related to pretransplant Model for End-Stage Liver Disease (MELD) score and to posttransplant HAART intolerance, presence of HIV RNA above 400 and CD4 counts below 200 (Ragni, 2003; Duclos, 2006). In addition, HCV had a more severe course after orthotopic liver transplantation (OLT) (Duclos, 2006). It is likely that patient selection for current treatments will be based on prediction models, in establishing risk-benefit ratio, in difficult-to-treat cases, such as genotype 1 coinfecting patients, with advanced fibrosis.

New Strategies and Treatments on the Horizon

IN VITRO, HCV IS EXCEEDINGLY DIFFICULT TO CULTURE, BUT THE RECENT development of an HCV replicon system, and the production of robust cell culture models allow for a more detailed investigation of HCV replication (Lindenbach, 2005; Wakita, 2005). Currently, there is a robust pipeline in clinical and preclinical development.

In HCV mono-infection, different treatment strategies are being explored. Extension of treatment with PEG IFN- α 2a plus ribavirin from 48 to 72 weeks considerably increases the rate of SVR in patients with detectable viremia at week 4 of treatment (Sanchez-Tapias, 2006). Treatment of overweight and obese patients could achieve SVR rates similar to lean subjects by dosing ribavirin using a weight-based scheme (1200 mg/day for weight 85–105 kg, 1400 mg/day for 105–125 kg) (Jacobson, 2006). Concerns about inducing anemia with higher ribavirin doses were addressed in a recent study, showing that pre-emptive treatment with erythropoietin at the onset of combination therapy with PEG IFN- α 2b and high-dose ribavirin (>13 mg/kg), significantly increased SVR and decreased the incidence of anemia (Shiffman, 2005). It also allowed maintenance of higher doses of ribavirin, while preserving quality of life (Sulkowski, 2005).

In HIV/HCV coinfection, higher doses of ribavirin (1000 mg/day for patients weighing less than 75 kg and 1200 mg/day for those more than 75 kg) in addition to PEG IFN- α 2a, for 48 weeks, led to better SVR rates for all genotypes, when compared with historic APRICOT data. However, prolonging treatment to 72 weeks for genotype 1 led to more adverse effects and to treatment discontinuation (Nunez, 2006), likely negating the slight increase in SVR.

Long-term, low-dose PEG IFN- α 2b led to improvements in fibrosis and inflammation scores in HCV nonresponders with advanced fibrosis or cirrhosis (Kaiser, 2006).

Two trials, Slam C and HRN 004, are exploring PEG IFN maintenance in coinfecting patients with advanced fibrosis who failed current treatment regimens, and are addressed towards stopping fibrosis progression.

Important progress is being made in the development of new treatments, particularly in new specific inhibitors of hepatitis C. Infergen® (Valeant Pharmaceuticals), also known as consensus IFN (IFN alphacon-1), appears to be a promising therapy for mono-infected and coinfecting nonresponders (Bacon, 2006; Leevy, 2005). In a difficult-to-treat group with genotype 1 and advanced fibrosis, consensus interferon led to an end-of-treatment response of 19% with 15 μ g per day and ribavirin (Bacon, 2006).

Viramidine® (taribavirin hydrochloride; Valeant Pharmaceuticals), a prodrug of ribavirin, may cause less hemolytic anemia due to its preferential uptake by the liver, which effectively reduces the plasma concentration of ribavirin and exposure to red blood cells. Phase 3 studies using 600 mg twice daily have shown that, although taribavirin results in a lower incidence of anemia, it is less effective than weight-based ribavirin. Recently, it was shown that achieving taribavirin levels higher than 18 mg per kg yields an SVR rate similar to that of standard ribavirin treatment, with a lower rate of anemia (Jacobson, 2006). A phase 2 trial will be looking at safety and efficacy of weight-based taribavirin.

Albuzeron® (albinterferon alpha 2b; Human Genome Sciences), which is currently in phase 2 and 3 trials, is an 85.7-kD protein consisting of IFN- α that is genetically fused to human serum albumin. This process extends the half-life of the medication, allowing for dosing intervals of up to 2 to 4 weeks. In a recent report, nonresponders to prior IFN- α underwent treatment with a combination of albinterferon alpha 2b and weight-based ribavirin. This led to an SVR rate of 28%, at a dose of 900 mg bi-weekly, with 15% of genotype 1 patients experiencing an SVR at 1200 mg monthly (Nelson, 2006).

Several new enzymatic inhibitors of hepatitis C virus show some promise in phase 1 and 2 studies. Valopicitobine (Idenix Pharmaceuticals), or NM283, is a prodrug of the polymerase inhibitor MN107, which competitively inhibits HCV RNA polymerase. As an orally administered daily dose, valopicitobine causes a rapid decline in HCV RNA concentrations in animal models, with a mean viral load reduction after 7 days of 1.05 log₁₀ and 0.83 log₁₀ in the high- and low-dose groups, respectively. Results from a phase 2 study of IFN and valopicitobine in nonresponders were disappointing, since none achieved SVR; final results from a trial in naïve patients are expected in mid-2007 (Afdal, 2007).

The protease enzymes may represent dual therapeutic agents as they suppress virus replication and improve host IFN responsiveness. VX-950 (Vertex Pharmaceuticals), a peptidomimetic protease inhibitor of the hepatitis C NS3-4A protease, has shown promise in phase 1 and 2 studies, but genomic analysis of HCV sequences after only a few weeks of monotherapy have shown a rapid emergence of resistance. A triple-drug, phase 2 study of VX-950 (Vertex Pharmaceuticals) (in combination with PEG IFN and ribavirin) resulted in undetectable HCV RNA (<10 IU/mL) in all 12 patients after 28 days of treatment (Lawitz, 2006). Further studies are ongoing to assess the efficacy of 12- and 24-week treatment of VX950 at a dose of 750 mg every 8 hours. The study designs include combination protocols of the protease inhibitor with either PEG IFN alone (double therapy) or PEG IFN and ribavirin (triple therapy). The ketoamide SCH 503034 (Schering-Plough Corporation) is another peptidomimetic protease inhibitor that was shown to inhibit HCV replication *in vitro*. Phase 2 studies in combination with IFN- α 2b and, now, ribavirin, are in progress. Future use of HCV protease inhibitors in PI-exposed HIV-positive patients, may be impacted by the emerging mutations of NS3 protease domain, leading to HCV-PI resistance (Morsica, 2006).

Other novel drugs that are being tested include nuclease-resistant ribozymes, which inhibit RNA translation, and antisense inhibitors, which reduce production of proteins necessary for HCV replication. An inhibitor of hepatocyte apoptosis—PF-0349—was reported to markedly decrease ALT and AST in HCV patients with advanced fibrosis. Histology outcomes need to be studied (Shiffman, 2006). A cyclophyllin antagonist produced an almost 4-log drop in HCV RNA and 1-log drop in HIV RNA, after 15 days, in a phase 1 trial in coinfecting patients (Flisiak, 2006).

Similarly, several vaccines were tested, designed to stimulate an immune response to envelope proteins, with antiviral and antifibrotic effects (Leroux-Roels, 2004; DiBisceglie, 2005). As an adjunctive therapy, a new oral platelet growth factor (eltrombopag, GlaxoSmithKline), allowed a majority of thrombocytopenic patients (median 55,000) to start and reach 12 weeks of PEG IFN treatment, in contrast to a minority—6%—achieving similar endpoint at 12 weeks in the placebo group (McHutchison, 2006).

Conclusions

HCV TREATMENT IN HIV-INFECTED PATIENTS IS COMPLEX AND DIFFICULT FOR patients to tolerate, but promising results have been attained with PEG IFN and ribavirin combination therapy. Interferon will continue to be the backbone of HCV treatment for some time. In the future, HAART-like triple-therapy may prove to increase efficacy and tolerability, and, hopefully, shorten the duration of treatment. It is likely that resistance testing will guide treatment decisions using new antiviral agents. Trials of new treatment strategies involving current drugs and new agents in coinfecting patients should expand the understanding of the most appropriate treatment protocols in this population.

References

- Afdhal N, O'Brien C, Godofsky E, et al; Valopicitobine 04 Study Group. Valopicitobine (NM283), alone or with PEG-Interferon, Compared to PEG-Interferon/ribavirin (PEGIFN/RBV) retreatment in patients with HCV-1 infection and prior non-response to PEGIFN/RBV: One-year results. 42nd Annual Meeting of the European Association for the Study of the Liver. April 11th-15th, 2007. Barcelona, Spain. Abstract 6.
- Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med.* 1999;341:556-562.
- Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol.* 2006;44(1 Suppl):S6-S9.
- Alvarez D, Dieterich DT, Brau N, Moorehead L, Ball L, Sulkowski MS. Zidovudine use but not weight-based ribavirin dosing impacts anaemia during HCV treatment in HIV-infected persons. *J Viral Hepat.* 2006;13:683-689.
- Backmund M, Meyer K, Von Zielonka M, Eichenlaub D. Treatment of hepatitis C infection in injection drug users. *Hepatology.* 2001;34:188-193.
- Bacon B, Regev A, Ghalib R, et al. Use of daily alfacon-1 (Infergen) plus ribavirin in patients infected with Hepatitis C virus who are non-responders to previous pegylated interferon plus ribavirin therapy: 24-week and end-of-treatment data from the Direct Trial. 17th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. October 27-31, 2006. Abstract LB18.
- Ballesteros AL, Franco S, Fuster D, et al. Early HCV dynamics on Peg-interferon and ribavirin in HIV/HCV co-infection: indications for the investigation of new treatment approaches. *AIDS.* 2004;18:59-66.
- Barreiro P, Labarga A. Factors associated with progression of liver fibrosis in HIV/HCV co-infected patients: influence of antiretrovirals and metabolic disturbances. VIII Annual International Congress on Drug Therapy in HIV-infection (HIV8). Glasgow, United Kingdom. November 12-16, 2006. Abstract P313.
- Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis.* 2001;32:492-497.
- Blatt LM, Mutchnick MG, Tong MJ, et al. Assessment of hepatitis C virus RNA and genotype from 6807 patients with chronic hepatitis C in the United States. *J Viral Hepat.* 2000;7:196-202.
- Bourliere M, Penaranda G, Renou C, et al. Validation and comparison of indexes for fibrosis and cirrhosis prediction in chronic hepatitis C patients: proposal for a pragmatic approach classification without liver biopsies. *J Viral Hepat.* 2006;13:659-670.
- Bowker SL, Soskolne CL, Houston SC, Newman SC, Jhangri GS. Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) in a Northern Alberta population. *Can J Public Health.* 2004;95:188-192.
- Brau N, Salvatore M, Rios-Bedoya CF, et al. Slower fibrosis progression in HIV/HCV co-infected patients with successful HIV suppression using antiretroviral therapy. *J Hepatol.* 2006;44:47-55.
- Bravo AA, Sheth SG, Chopra S. Liver biopsy. *N Engl J Med.* 2001;344:495-500.
- Cacoub P, Carrat F, Bedossa P, et al. Independent assessment of non-invasive liver fibrosis biomarkers in HIV-co-infected patients: the Fibrovis Study. 17th Annual Meeting of the American Association for the Study of Liver Diseases, Boston, Massachusetts. October 27-31, 2006. Abstract 215.
- Calleri G, Cariti G, Gaiottino F, et al. A short course of pegylated interferon- α in acute HCV hepatitis. *Journal of Viral Hepatitis* 2007;14:116-121.
- Carrat F, Bani-Sadr F, Pol S, et al, ANRS HCO2 RIBAVIC Study Team. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *JAMA.* 2004;292:2839-2848.
- Castera L. Steatosis, insulin resistance and fibrosis progression in chronic hepatitis C. *Minerva Gastroenterol Dietol.* 2006;52:125-134.
- Chamie G, Bonacini M, et al. Factors associated with seronegative hepatitis C virus infection in HIV-infection. XVI International AIDS conference. Toronto, Canada. August 13-18, 2006. Abstract WEP0046/13774.
- Christensen C, Bruden D, Livingston S, et al. Diagnostic accuracy of a fibrosis serum panel (FIBROSPECT II) compared with Knodell and Ishak liver biopsy scores in chronic hepatitis C patients. *J Viral Hepat.* 2006;13:652-658.
- Chung RT, Andersen J, Volberding P, et al, AIDS Clinical Trials Group A5071 Study Team. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med.* 2004;351:451-459.
- Cooper CL, Breaux C, Laroche A, Lee C, Garber G. Clinical outcomes of first antiretroviral regimen in HIV/hepatitis C virus co-infection. *HIV Med.* 2006;7:32-37.
- Cournot M, Glibert A, Castel F, et al. Management of hepatitis C in active drugs users: experience of an addiction care hepatology unit. *Gastroenterol Clin Biol.* 2004;28:533-539.
- Cournot M, Glibert A, Castel F, et al. Management of hepatitis C in active drugs users: experience of an addiction care hepatology unit. *Gastroenterol Clin Biol.* 2004;28:533-539.
- Cramp ME, Rossol S, Chokshi S, Carucci P, Williams R, Naoumov NV. Hepatitis C virus-specific T-cell reactivity during interferon and ribavirin treatment in chronic hepatitis C. *Gastroenterology.* 2000;118:346-355.
- Department of Health and Human Services (DHHS). Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services. October 10, 2006;1-113. Available at: <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentsGL.pdf>. Accessed: March 21, 2007.
- Derbala M, Amer A, Bener A, Lopez AC, Omar M, El Ghannam M. Pegylated interferon-alpha 2b-ribavirin combination in Egyptian patients with genotype 4 chronic hepatitis. *J Viral Hepat.* 2005;12:380-385.
- Di Bisceglie AM, Frey S, Gorse et al. A phase I safety and immunogenicity trial of a novel E1E2/ME59C.1 hepatitis C vaccine candidate in healthy HIV-negative adults. *Hepatology.* 2005;42:750A.
- Di Bisceglie AM, Goodman ZD, Ishak KG, Hoonagale JH, Melpolder JJ, Alter HJ. Long term clinical and histopathological follow-up of chronic post-transfusion hepatitis. *Hepatology.* 1991;14:969-974.
- Di Martino V, Rufat P, Boyer N, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. *Hepatology.* 2001;34:1193-1199.
- Dieterich DT, Opravil M, Sasadeusz J. Effect of baseline CD4+ on the efficacy of Peg-interferon alpha-2a plus ribavirin: Findings from APRIOT. XLVI Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, California. September 27-30, 2006. Abstract H-1888.
- Dieterich DT, Wasserman R, Brau N, et al. Once-weekly epoetin alfa improves anemia and facilitates maintenance of ribavirin dosing in hepatitis C virus-infected patients receiving ribavirin plus interferon alfa. *Am J Gastroenterol.* 2003;98:2491-2499.
- Dixit NM, Layden-Almer JE, Layden TJ, Perelson AS. Modelling how ribavirin improves interferon response rates in hepatitis C virus infection. *Nature.* 2004;432:922-924.
- Duclos VJ, Feray C, Sebagh M, et al. Survival and prognostic factors in a large cohort of HIV-HCV coinfected patients transplanted in a single centre. 17th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. October 27-31, 2006. Abstract 772.
- Duong M, Petit JM, Piroth L, et al. Association between insulin resistance and hepatitis C virus chronic infection in HIV-hepatitis C virus-coinfected patients undergoing antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2001;27:245-250.
- Fleming CA, Craven DE, Thornton D, Tumilty S, Nunes D. Hepatitis C virus and human immunodeficiency virus coinfection in an urban population: low eligibility for interferon treatment. *Clin Infect Dis.* 2003;36:97-100.
- Flisiak R, Horban A, Kierkus J, et al. The cyclophilin inhibitor DEB10-025 has a potent dual anti-HIV and anti-HCV activity in treatment-naïve HIV/HCV co-infected subjects. 17th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. October 27-31, 2006. Abstract 1130.
- Franceschi S, Polesel J, Rickenbach M, et al. Hepatitis C virus and non-Hodgkin's lymphoma: Findings from the Swiss HIV Cohort Study. *Br J Cancer.* 2006;95:1598-1602.
- 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.
- Gale M Jr, Blakely CM, Kwieciszewski B, et al. Control of PKR protein kinase by hepatitis C virus nonstructural 5A protein: molecular mechanisms of kinase regulation. *Mol Cell Biol.* 1998;18:5208-5218.
- Garfein RS, Vlahov D, Galai N, Doherty MC, Nelson KE. Viral infections in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. *Am J Public Health.* 1996;86:655-661.
- Gerlach JT, Diepolder HM, Jung MC, et al. Recurrence of hepatitis C virus after loss of virus-specific CD4(+) T-cell response in acute hepatitis C. *Gastroenterology.* 1999;117:933-941.
- Gisbert JP, Garcia-Buey L, Arranz R, et al. The prevalence of hepatitis C virus infection in patients with non-Hodgkin's lymphoma. *Eur J Gastroenterol Hepatol.* 2004;16:135-138.
- Hadziyannis SJ, Sette H Jr, Morgan TR, et al; PEGASYS International Study Group. Peginterferon-alpha 2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med.* 2004;140:346-355.
- Hernandez MD, Logush-Pinto L, Rodriguez-Torres M. In HIV/HCV-coinfected patients, the duration of highly active antiretroviral therapy does not predict fibrosis progression rate or fibrosis stage. 17th Annual Meeting of the American Association for the Study of Liver Diseases, Boston, Massachusetts. October 27-31, 2006. Abstract 248.
- Imbert-Bismut F, Ratzliff V, Pieroni L, Charlotte F, Benhamou Y, Poinard T; MULTIVIRC Group. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet.* 2001;357:1069-1075.
- Jacobson I, Pockros P, Benhamou Y, et al. Impact of telivirgin and ribavirin exposure on efficacy and anemia rates when combined with pegylated interferon alfa-2b in the treatment of chronic HCV. 17th Annual Meeting of the American Association for the Study of Liver Diseases, Boston, Massachusetts. October 27-31, 2006. Abstract 1133.
- Jacobson IM, Brown RS, Freilich B, et al. Response to peginterferon alfa-2b and ribavirin for chronic hepatitis C in patients with body weight >125 kg: results from the WIN-R trial. 17th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. October 27-31, 2006. Abstract 369.
- Kaiser PS, Hass H, Lutze B, Sauter B, Gregor M. Long-term low-dose treatment with pegylated interferon alpha-2b leads to a significant reduction in fibrosis and inflammatory score in chronic hepatitis C non-responder patients with fibrosis or cirrhosis. 17th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. October 27-31, 2006. Abstract 1145.
- Khakoo S, Glue P, Grellier L, et al. Ribavirin and interferon alfa-2b in chronic hepatitis C: assessment of possible pharmacokinetic and pharmacodynamic interactions. *Br J Clin Pharmacol.* 1998;46:563-570.
- Kozlowski A, Charles SA, Harris JM. Development of pegylated interferons for the treatment of chronic hepatitis C. *BioDrugs.* 2001;15:419-429.
- Lafeuillade A, Hittinger G, Chadapaud S. Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. *Lancet* 2001;357:280-281.
- Laguno M, Murillas J, Blanco JL, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. *AIDS.* 2004;18:F27-36.
- Laguno M, Larrousse M, Murillas J, et al. Predictive value of early virologic response in HIV/hepatitis C virus-coinfected patients treated with an interferon-based regimen plus ribavirin. *J Acquir Immune Defic Syndr.* 2007;44:174-178.
- Laurence JC. Hepatitis A and B immunizations of individuals infected with human immunodeficiency virus. *Am J Med.* 2005;118(Suppl 10A):75S-83S.
- Lawitz EJ, Rodriguez-Torres M, Muir A, et al. 28 days of the hepatitis C protease inhibitor VX-950, in combination with PEG-interferon-alpha-2a and ribavirin, is well-tolerated and demonstrates robust antiviral effects. *Gastroenterology.* 2006;131:950-951.
- Levy C, Chalmers C. Sustained virological response (SVR) to retreatment with IFN alfacon 1+ ribavirin in HCV/HIV coinfected patients who had failed 12 weeks of peg ifn alfa 2 + ribavirin therapy. 56th Annual Meeting of the American Association for the Study of Liver Diseases. San Francisco, California. November 11-15th, 2005. Abstract 1268.
- Leroux-Roels G, Depla E, Hulstaert F, et al. A candidate vaccine based on the hepatitis C E1 protein: tolerability and immunogenicity in healthy volunteers. *Vaccine.* 2004;22:3080-3086.
- Lindenbach BD, Rice CM. Unravelling hepatitis C virus replication from genome to function. *Nature.* 2005;436:933-938.
- Lissen E, Clumeck N, Sola R, et al. Histological response to pegIFNalpha-2a (40kD) plus ribavirin in HIV-hepatitis C virus co-infection. *AIDS.* 2006;20:2175-2181.
- Litwin AH, Soloway I, Gourevitch MN. Integrating services for injection drug users infected with hepatitis C virus with methadone maintenance treatment: challenges and opportunities. *Clin Infect Dis.* 2005;40(Suppl 5):S339-S345.
- Macias J, Giron-Gonzalez JA, Gonzalez-Serrano M, et al. Prediction of liver fibrosis in human immunodeficiency virus/hepatitis C virus coinfected patients by simple non-invasive indexes. *Gut.* 2006;55:409-414.
- Maida I, Nunez M, Rios MJ, et al. Severe liver disease associated with prolonged exposure to antiretroviral drugs. *J Acquir Immune Defic Syndr.* 2006;42:177-182.

- Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*. 2001;358:958-965.
- Martin-Carbonero L, Benhamou Y, Puoti M, et al. Incidence and predictors of severe liver fibrosis in human immunodeficiency virus-infected patients with chronic hepatitis C: A European collaborative study. *Clin Infect Dis*. 2004;38:128-133.
- Maylin S, Martinot-Peignoux, Boyer N, Ripault MP. Sustained virologic response is associated with eradication of hepatitis C virus and fibrosis regression in patients treated for chronic hepatitis C. LVII Annual Meeting of the American Association for the Study of Liver Diseases (AASLD). Boston, Massachusetts. October 27-31, 2006. Abstract 1B9.
- McGill DB, Rakela J, Zinsmeister AR, Ott BJ. A 21-year experience with major hemorrhage after percutaneous liver biopsy. *Gastroenterology*. 1990;99:1396-1400.
- McGovern BH, Ditelberg JS, Taylor LE, et al. Hepatic steatosis is associated with fibrosis, nucleoside analogue use, and hepatitis C virus genotype 3 infection in HIV-seropositive patients. *Clin Infect Dis*. 2006;43:365-372.
- McHutchison JG, Afdhal NH, Dusheiko G, et al. Eltrombopag, an oral platelet growth factor, facilitates initiation of interferon therapy in subjects with HCV associated thrombocytopenia: results from a phase II placebo controlled, double-blind, dose ranging study. LVII Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. October 27-31, 2006. Abstract 1B3.
- Mehta SH, Brancati FL, Strathdee SA, et al. Hepatitis C virus infection and incident type 2 diabetes. *Hepatology*. 2003;38:50-56.
- Merchante N, Macias J, Ramayo E, et al. Insulin resistance is not associated with liver fibrosis progression in HIV/hepatitis C virus-coinfected patients. *J Virol Hepat*. 2006;13:449-456.
- Miller CL, Wood E, Spittal PM, et al. The future face of coinfection: prevalence and incidence of HIV and Hepatitis C Virus coinfection among young injection drug users. *J Acquir Immune Defic Syndr*. 2004;36:743-749.
- Mohsen AH, Murad S, Easterbrook PJ. Prevalence of hepatitis C in an ethnically diverse HIV-1-infected cohort in south London. *HIV Med*. 2005;6:206-215.
- Monto A, Kakar, S, Dove, LM, et al. Contributions to hepatic fibrosis in HIV-HCV coinfectd and HCV monoinfected patients. *Am J Gastroenterol*. 2006;101:1509-1515.
- Morsica G, Bagaglio S, Alagna L, et al. Mutations in the natural strains of NS3 protease domain of HCV in HIV/HCV coinfectd patients under antiretroviral therapy including or not HIV protease inhibitors. LVII Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. October 27-31, 2006. Abstract 436.
- National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C: 2002—June 10-12, 2002. *Hepatology*. 2002;36(5 Suppl 1):S3-20.
- Neau-Cransac M, Foucher J, Ledinghen VD, Bernard PH, Legrand E, Lafon ME. Modifications of T-lymphocyte subsets before and during interferon and ribavirin treatment for chronic hepatitis C infection. *Viral Immunol*. 2005;18:197-204.
- Nelson D, Rustgi V, Balan V, Sulkowski J et al. Sustained virological response rates with albumin interferon alpha-2b, in combination with ribavirin in non-responders to prior interferon therapy: interim results from a phase 2 study. LVII Annual Meeting of the American Association for the Study of Liver Diseases, Boston, Massachusetts. October 27-31, 2006. Abstract 1136.
- Netski DM, Mosbrugger T, Depla E, et al. Humoral immune response in acute hepatitis C virus infection. *Clin Infect Dis*. 2005;41:667-675.
- Núñez M, Garcia-Samaniego J, Romero M, et al. The PRESCO trial: impact of higher ribavirin doses and longer duration of therapy with peginterferon alfa-2a plus ribavirin in HIV-infected patients with chronic hepatitis C. LVII Annual Meeting of the American Association for the Study of Liver Diseases, Boston, Massachusetts. October 27-31, 2006. Abstract 365.
- Núñez M, Soriano V, Lopez M, et al. Coinfection with hepatitis C virus increases lymphocyte apoptosis in HIV-infected patients. *Clin Infect Dis*. 2006;43:1209-1212.
- O'Leary JG, Chung RT. Management of hepatitis C virus coinfection in HIV-infected persons. *AIDS Read*. 2006;16:313-316, 318-320.
- Orland JR, Wright TL, Cooper S. Acute hepatitis C. *Hepatology*. 2001;33:321-327.
- Pawlotsky JM. Diagnostic tests for hepatitis C. *J Hepatol*. 1999;31(Suppl 1):71-79.
- Pawlotsky JM. Molecular diagnosis of viral hepatitis. *Gastroenterology*. 2002;122:1554-1568.
- Perez-Ormeda M, Nunez M, Romero M, et al. Pegylated IFN-alpha2b plus ribavirin as therapy for chronic hepatitis C in HIV-infected patients. *aids*. 2003;17:1023-1028.
- Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol*. 2006;45:529-538.
- Qurishi N, Kreuzberg C, Luchters G, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. *Lancet*. 2003;362:1708-1713.
- Ragni MV, Belle SH, Im K, et al. Survival of human immunodeficiency virus-infected liver transplant recipients. *J Infect Dis*. 2003;188:1412-1420.
- Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol*. 2002;97:2614-2618.
- Rehermann B, Nascimben M. Immunology of hepatitis B virus and hepatitis C virus infection. *Nat Rev Immunol*. 2005;5:215-229.
- Riordan SM, Williams R. Treatment of hepatic encephalopathy. *N Engl J Med*. 1997;337:473-479.
- Rockstroh J, Konopnicki D, Soriano V, et al; and EuroSIDA study group. Hepatitis B and Hepatitis C in the EuroSIDA cohort: Prevalence and effect on mortality, AIDS progression and response to HAART. XIth Conference on Retroviruses and Opportunistic Infections. San Francisco, California. February 8 -11, 2004. Abstract 799.
- Romero-Gomez M, Del Mar Vilorio M, Andrade RJ, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology*. 2005;128:636-641.
- Romero-Gomez M. Hepatitis C and insulin resistance: steatosis, fibrosis and non-response. *Rev Esp Enferm Dig*. 2006;98:605-615.
- Rosenthal E, Poiree M, Pradier C, et al. GERMIVIC Joint Study Group. Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study). *AIDS*. 2003;17:1803-1809.
- Salmon-Ceron D, Chauvelot-Moachon L, Abad S, Silbermann B, Sogni P. Mitochondrial toxic effects and ribavirin. *Lancet* 2001;357:1803-1804.
- Sanchez-Conde M, Berenguer J, Miralles P, et al. Liver biopsy findings for HIV infected patients with chronic hepatitis C and persistently normal levels of alanine aminotransferase. *Clin Infect Dis*. 2006;43:640-644.
- Sanchez-Tapias JM, Diago M, Escartin P, et al. TeraViC-4 Study Group. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology*. 2006;131:451-460.
- 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.
- Schiavini M, Angeli E, Mainini A, et al. Risk factors for fibrosis progression in HIV/HCV coinfectd patients from a retrospective analysis of liver biopsies in 1985-2002. *HIV Med*. 2006;7:331-337.
- Sherman KE, Rouser SD, Chung RT, Rajcic N. Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. *Clin Infect Dis*. 2002;34:831-837.
- Shiffman ML, Hubbard S, Wilson M, et al. Treatment of chronic Hepatitis C virus (HCV) genotype 1 with peginterferon alfa-2b (PEGASIS), high weight based dose ribavirin (RVN) and Epoetin alfa (EPO) enhances sustained virologic response (SVR). *Hepatology*. 2005;42(5):Abstract 67045.
- Simmonds P. Viral heterogeneity of the hepatitis C virus. *J Hepatol*. 1999;31(Suppl 1):54-60.
- Soriano V, Labarga P, Ruiz-Sancho A, Garcia-Samaniego J, Barreiro P. Regression of liver fibrosis in hepatitis C virus/HIV-co-infected patients after treatment with pegylated interferon plus ribavirin. *AIDS*. 2006;20:2225-2227.
- Soriano V, Maida I, Nunez M, et al. Long-term follow-up of HIV-infected patients with chronic hepatitis C virus infection treated with interferon-based therapies. *Antivir Ther*. 2004;9:987-992.
- Strader DB, Wright T, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. *Hepatology*. 2004;39:1147-1171.
- Sulkowski M, Mehta S, Torbenson M, Higgins Y, Moore R, Thomas D. Significant liver disease progression among HIV/HCV coinfectd persons with minimal fibrosis on initial liver biopsy. LVII Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. October 27-31, 2006. Abstract 164.
- Sulkowski MS, Dieterich DT, Bini EJ, et al; for the HIV/HCV Coinfection Study Group. Epoetin alfa once weekly improves anemia in HIV/hepatitis C virus-coinfectd patients treated with interferon/ribavirin: a randomized controlled trial. *J Acquir Immune Defic Syndr*. 2005;39:504-506.
- Sulkowski MS, Mast EE, Seeff LB, Thomas DL. Hepatitis C virus infection as an opportunistic disease in persons infected with human immunodeficiency virus. *Clin Infect Dis*. 2000;30(Suppl 1):S77-S84.
- Sulkowski MS, Mehta SH, Torbenson M, et al. Hepatic steatosis and antiretroviral drug use among adults coinfectd with HIV and hepatitis C virus. *AIDS*. 2005;19:585-592.
- Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected person. *Ann Intern Med*. 2003;138:197-207.
- Sylvestre DL. Treating hepatitis C virus infection in active substance users. *Clin Infect Dis*. 2005;40(Suppl 5):S321-S324.
- Taylor LE. Delivering care to injection drug users coinfectd with HIV and hepatitis C virus. *Clin Infect Dis*. 2005;40(Suppl 5):S355-S361.
- Torriani FJ, Ribeiro RM, Gilbert TL, et al. Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) dynamics during HCV treatment in HCV/HIV coinfection. *J Infect Dis*. 2003;188:1498-1507.
- Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. APRIOT Study Group. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV infected patients. *N Engl J Med*. 2004;351:438-450.
- Torti C, Lapadula G, Puoti M, et al. Influence of genotype 3 hepatitis C coinfection on liver enzyme elevation in HIV-1-positive patients after commencement of a new highly active antiretroviral regimen: results from the EPOKA-MASTER Cohort. *J Acquir Immune Defic Syndr*. 2006;41:180-185.
- Tossing G. Management of chronic hepatitis C in HIV-co-infected patients—results from the First International Workshop on HIV and Hepatitis Co-infection, 2nd-4th December 2004, Amsterdam, Netherlands. *Eur J Med Res*. 2005;10:43-45.
- Tremolada F, Cassin C, Alberti A, et al. Long-term follow-up of NANB (type C) post-transfusion hepatitis. *J Hepatol*. 1992;16:273-281.
- Tsai SL, Liaw YF, Chen MH, Huang CY, Kuo GC. Detection of type 2-like T-helper cells in hepatitis C virus infection: implications for hepatitis C virus chronicity. *Hepatology*. 1997;25:449-458.
- Uberti-Foppa C, De Bona A, Morsica G, et al. Pretreatment of chronic active hepatitis C in patients coinfectd with HIV and hepatitis C virus reduces the hepatotoxicity associated with subsequent antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2003;33:146-152.
- Van Thiel DH, Anantharaju A, Creech S. Response to treatment of hepatitis C in individuals with a recent history of intravenous drug abuse. *Am J Gastroenterol*. 2003;98:2281-2288.
- Verma S, Wang CH, Govindarajan S, Kanel G, Squires K, Bonacini M. Do type and duration of anti-retroviral therapy attenuate liver fibrosis in HIV-hepatitis C virus-coinfectd patients? *Clin Infect Dis*. 2006;42:262-270.
- von Wagner M, Huber M, Berg T, et al. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterology*. 2005;129:522-527.
- Wakita T, Pietschmann T, Kato T, et al. Production of infectious hepatitis C virus in tissue culture from a cloned viral genome. *Nat Med*. 2005;11:791-796.
- Walker UA, Bauerle J, Laguno M, et al. Depletion of mitochondrial DNA in liver under antiretroviral therapy with didanosine, stavudine, or zalcitabine. *Hepatology*. 2004;39:311-317.
- Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. 2006;166:1632-1641.
- Yano M, Kumada H, Kage M, et al. The long-term pathological evolution of chronic hepatitis C. *Hepatology*. 1996;23:1334-1340.
- Yonkers NL, Rodriguez B, Post AB, et al. HIV Coinfection Impairs CD28-Mediated Costimulation of Hepatitis C Virus-Specific CD8 Cells. *J Infect Dis*. 2006;194:391-400.
- Zioli M, Handra-Luca A, Kettaneh A, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. *Hepatology*. 2005;41:48-54.