

Education
Initiative in
Infectious
Disease

Expert Perspectives:
**Strategies for the
Management of
HIV/HCV Coinfection**
Monograph

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“ The HIV-treating community has begun to appreciate the frequency and severe consequences of coinfection with HCV. The interactions of these viruses and the resulting issues of liver impairment and drug-induced hepatotoxicity are challenging for experts in either infection, but pose particular difficulties as one attempts to treat both of these simultaneously. The monograph *Expert Perspectives* is a particularly worthwhile compilation of brief, readable, and well-referenced discussions on the epidemiology, natural history, and therapy of HIV/HCV coinfection. It should be consulted by any healthcare provider beginning to develop treatment programs for these patients.”

Paul Volberding, MD

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“ Coinfection with hepatitis C is rapidly becoming one of the most important complications in HIV-infected patients. This monograph provides excellent background information on the epidemiology, natural history, and emerging treatment options in this important disease.”

Michael S. Saag, MD

Professor of Medicine and Director, UAB AIDS Outpatient Clinic
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“ In general, it reads very well and provides very useful insights into the pathogenesis and therapy of HCV in the setting of HIV infection.”

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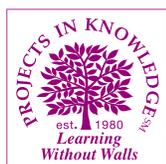
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Expert Perspectives: Strategies for the Management of HIV/HCV Coinfection

Table of Contents

Faculty/Contributors	ii
Introduction	iv
Faculty/Contributor Disclosure Information	iv
I. HIV/HCV Coinfections:	
Magnitude of the Problem	1
II. HCV Virology:	
Important Lessons Learned From HIV	4
III. Management of HIV Infection	
in HCV-Coinfected Patients	5
IV. Management of HCV Infection	
in HIV-Infected Patients	9
V. Managing Side Effects	
of Interferon and Ribavirin	14
VI. Special Challenges	
in Coinfected Patients	17
Overall Conclusions	20
Posttest	21
Evaluation	23
CME Information and Instructions	Back Cover



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Introduction

Overview

Expert Perspectives: Strategies for the Management of HIV/HCV Coinfection is part of Projects In Knowledge's Education Initiative in Infectious Disease, which was created to increase the knowledge base and improve the clinical skills of infectious disease specialists, other clinicians who treat HIV-infected patients, and physicians who manage hepatitis C virus (HCV)-infected patients throughout the United States. The overarching goals of Projects In Knowledge's Education Initiative in Infectious Disease are to:

- Increase physician knowledge of best practices in the field
- Enhance physicians' clinical skills
- Improve the ability of physicians to respond to the increasing demands for accountability and demonstrated outcomes
- Facilitate collaborative engagement among thought leaders and practitioners
- Provide a constructive forum in which infectious disease specialists, other clinicians who treat HIV-infected patients, and physicians in other specialties can address timely issues with representatives from diverse sectors of the healthcare enterprise
- Help patients and their families access a wide range of resources for information, education, and support

Methodology

The content of *Expert Perspectives: Strategies for the Management of HIV/HCV Coinfection* was developed during a meeting of a large, distinguished panel of clinicians who treat HIV-infected patients, hepatologists, gastroenterologists, and other experts engaged in research or treatment of HIV and/or HCV infection. At this meeting, several formats and techniques were used to gather information and establish consensus recommendations on difficult management issues.

Presentations were made by experts on a variety of topics pertaining to epidemiology of HCV and HIV/HCV coinfections, natural history of HCV infection, current standards for treatment of HCV and HIV infection, strategies for alleviating adverse effects of treatment, and overall disease management. Six small-group workshops convened to discuss key issues such as natural history in coinfecting patients, use of highly active antiretroviral therapy in coinfecting patients, patient evaluation, treatment issues specific to coinfecting patients, and management of adverse events. Consensus on these issues was then assessed using a written survey that included 23 multipart questions regarding relevant practice perspectives. These questions were prepared by the presenters and Projects In Knowledge. More than 50 experts participated in this comprehensive paper-based survey. This survey instrument was chosen to prevent individual responses from being influenced by those of other participants. Completed surveys were submitted at the close of the meeting or by mail shortly thereafter. The majority of the survey questions utilized a visual analogue scale from 1 to 5 (eg, from "strongly disagree" to "strongly agree" or "least important" to "most important"). The mean rating for each option was calculated.

Criteria for Inclusion on the Expert Perspectives Panel

Selection of members for the expert perspectives panel was based on a number of criteria. First, national and international thought leaders who have made profound contributions to the understanding of HIV/HCV through their research and participation in national and international science and public health forums were invited. Many of these distinguished leaders participated as presenters or as moderators of the small-group workshops. Second, invitations were made to authors of recently published clinical research and recipients of federal or industry research grants. Third, physicians currently participating in clinical trials and those who had participated in major trials within the last year were invited. Finally, invitations were sent to several clinicians who treat many HIV/HCV coinfecting patients and who offer the perspective of broad practical experience.

The majority of contributors (68%) were from eastern regions of the United States. Sixty-eight percent had at least 6 years in practice, with about one third having more than 20 years in practice. Forty-four percent practice in predominantly clinical academic settings, and 48% work in private solo or group practices. About one quarter of the practices specialize specifically in HIV, and 68% are general infectious disease practices. Respondents indicate that about one third of their current patients are infected with HCV alone, and 36.2% are infected with both HCV and HIV. Most (68.6%) of the HCV-infected patients seen by these physicians are referred to them by primary care physicians.

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I. HIV/HCV Coinfections: Magnitude of the Problem

HCV Infection: A Widespread Problem

Hepatitis C virus (HCV) is one of the most important causes of chronic liver disease in the United States.¹ It has been estimated that nearly 4 million Americans (about 1.8% of the population) are infected with HCV, and about 3 million are chronically infected.² In the United States, HCV infection disproportionately affects young persons (the highest prevalence is among those aged 30 to 49 years) and African Americans (Fig. 1).¹ The annual incidence of new infections has declined by >80% since 1989 to approximately 36,000 new infections per year; however, because of the long delay between viral infection and the appearance of liver damage, the impact of hepatitis C is expected to grow for many years to come. The number of people estimated to be living with HIV infection in the United States is about 750,000,³ although seroprevalence of HIV among intravenous (IV) drug users varies widely, depending on geography (eg, rates are higher in New York City than in Los Angeles). Worldwide, approximately 170 million people are infected with HCV,⁴ compared with more than 40 million persons infected with HIV.⁵

Survey Findings

Overall, the survey respondents recognized that HCV represents a serious problem in the United States today (Fig. 2).

HIV/HCV Coinfections Common Due to Shared Risk Factors

Overall, there may be 300,000 persons coinfecting with HCV and HIV in the United States, representing a significant proportion of persons with HIV infection.^{6,7} The high prevalence of coinfections with HIV and HCV is attributed to shared risk factors for transmission, most importantly, injecting drug use (IDU).

IDU is currently the major risk factor for acute HCV infection.¹ Infection occurs very rapidly after initiation of IDU, with about 60% to 90% of IDUs typically becoming infected within 6 months to 1 year of beginning use.⁸ Approximately 80% to 90% of long-term users of IV drugs are already infected with HCV, and approximately 15% to 20% of long-term users are infected with HIV.⁸

Nonparenteral risk factors for transmission (eg, sexual or vertical) are more important for HIV than HCV.^{9,10} Sexual transmission of HCV is rare between long-term steady partners; among persons with high-risk sexual practices, HCV has been linked to an increased number of sexual partners, failure to use condoms, persons with other sexually transmitted diseases, and sex with trauma. Unlike with HIV, men who have sex with men are at no higher risk of HCV infection than are heterosexuals with high-risk sexual practices.¹ The rate of perinatal transmission of HCV is 5% to 6%, but increases to 14% to 17% in persons coinfecting with HIV (Fig. 3A).¹

Fig. 1. Age-Specific Prevalence of HCV (NHANES III 1988–1994).

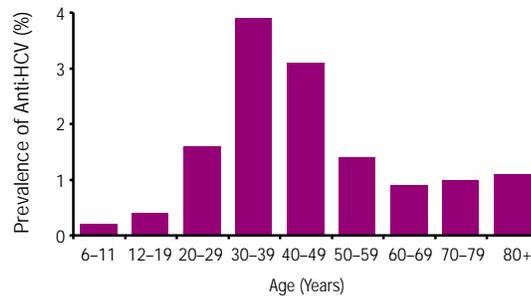
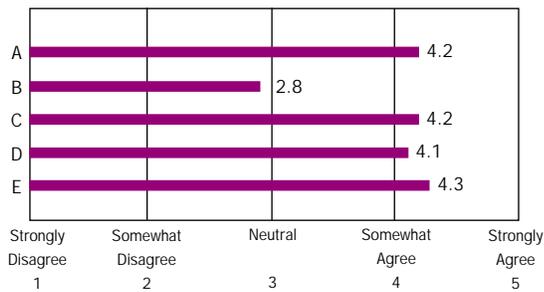


Figure adapted from data published in Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med.* 1999;341:556-562.

Fig. 2. Survey Findings: Hepatitis C Epidemiology and Magnitude of Problem.

Regarding the extent of problems in the United States related to HCV infection and associated chronic liver disease, with which of the following statements would you agree?

- A. HCV infection is responsible for 40% of chronic liver disease.
- B. HCV-associated chronic liver disease often results in death.
- C. An estimated 8,000 to 10,000 deaths occur each year as a result of HCV-associated chronic liver disease.
- D. Persistent HCV infection develops in most persons (85% of the US population), including those with no biochemical evidence of active liver disease.
- E. HCV-associated chronic liver disease is the reason for most liver transplantations in the United States.



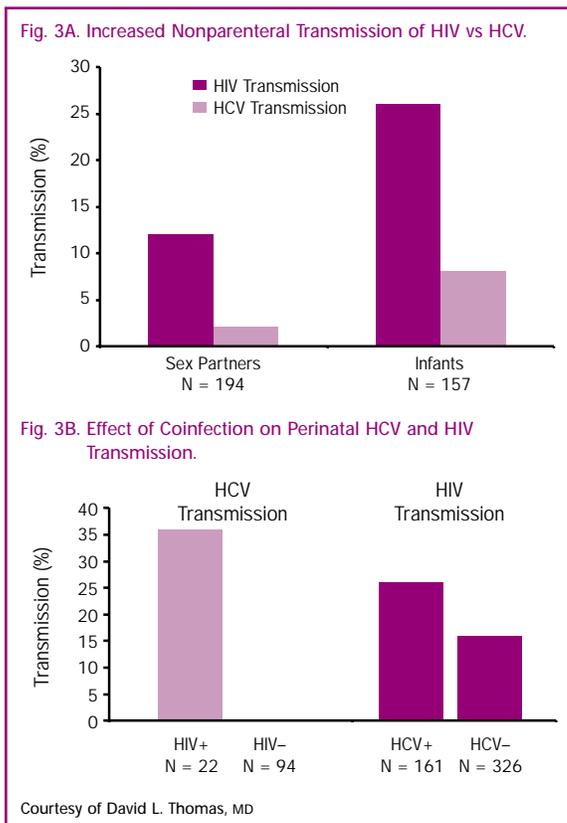
Coinfection with HIV and HCV may actually facilitate transmission of these viruses, at least perinatally (Fig. 3B).^{11,12} This may be attributable to the increased HCV viral load in patients coinfecting with HIV or other factors yet to be identified.¹³

Survey Findings

The survey respondents recognized IDU as the most important risk factor for HCV transmission (rating, 4.8 on a scale of 1 = not important to 5 = of major importance). Other risk factors for transmission, such as promiscuous sexual activity (rating, 3.4), blood transfusions (rating, 3.2), acquiring a tattoo (rating, 3.0), and working in a healthcare setting (rating, 2.4), were viewed as less important.

Hepatitis C: An Infectious Pathogen Causing Progressive Hepatic Fibrosis

In patients who are not coinfecting with HIV, HCV infection has a highly variable long-term prognosis. In general, chronic HCV infection is an insidious disease that progresses slowly with few symptoms in the first few decades. As a result, at least some studies suggest that many patients with HCV infection will do



well over the long term with low liver-related morbidity and mortality rates¹⁴; however, in a subset of patients, HCV infection will have more serious consequences. Approximately 70% of patients with acute hepatitis C develop biochemical evidence of chronic hepatitis, and $\geq 85\%$ of these will develop persistent viremia.¹ Hepatic fibrosis progresses with duration of infection, and cirrhosis develops in about 10% to 20% of infected individuals after about 20 to 30 years. In patients with cirrhosis, rates of hepatocellular carcinoma (HCC) are as high as 1% to 4% per year.¹ Chronic HCV infection is the leading reason for liver transplantation and the tenth leading cause of death in the United States, accounting for approximately 25,000 deaths/year.¹

The challenge for clinicians is to identify patients who merit treatment. Iron, fat, alcohol, age ≥ 40 years at time of infection, and male gender are critical cofactors that can lead to more rapidly progressive fibrosis in HCV infection.¹⁵ Patients with HCV infection should be instructed to limit or avoid alcohol consumption. Hepatotoxic medications also may contribute to liver damage associated with hepatitis C. Importantly, coinfection with HIV also predicts a poor prognosis (discussed further below), so treatment of HCV infection is needed in the majority of these patients.

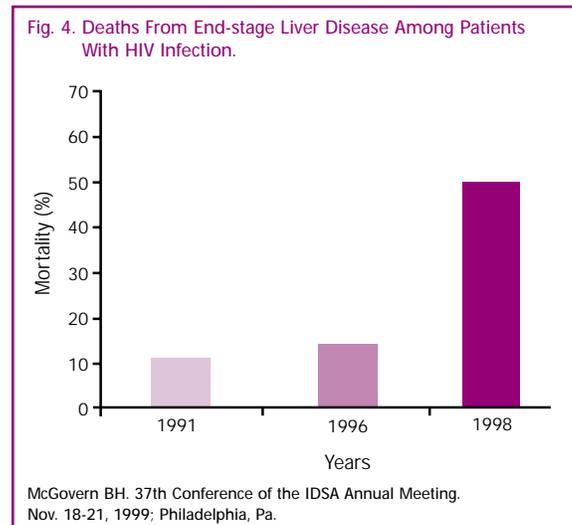
Increasing Relevance of HCV Infection Alone and in HIV-Infected Patients

During the next 20 years, those infected with HCV during the peak incidence period (1980s) will reach ages at which complications from chronic liver disease typically occur (usually between the ages of 31 and 50 years). The number of persons infected for more than 20 years is expected to continue to rise substantially, peaking at about 2015.¹⁶ It has been estimated that the proportion of HCV-infected patients

with cirrhosis will increase from roughly 15.6% in 1988 to more than 28.9% by 2018.¹⁷ Moreover, hepatic decompensation will increase 84%, HCC will increase 63%, and the death rate from complications of chronic hepatitis C is expected to triple.¹⁷ These epidemiologic changes will have dramatic economic costs as well: Direct and indirect costs of acute and chronic HCV infection were an estimated \$612 million in 1992 (Centers for Disease Control and Prevention, unpublished data) and are expected to reach \$10 billion in direct medical costs and an additional \$51 billion and \$20 billion from lost productivity due to premature death and disability, respectively.¹⁸ However, identification and treatment of all HCV-infected patients with compensated liver disease would reduce the number of cases of decompensated cirrhosis by 33.1% after 20 years.¹⁷

HCV infection is also of increasing relevance in patients with HIV infection. With the advent of highly active antiretroviral therapy (HAART), dramatic declines in morbidity and mortality from opportunistic diseases in patients with HIV infection have been observed over the past few years.¹⁹ As a result of this increasing longevity, mortality attributable to other underlying diseases such as HCV infection is increasing.²⁰⁻²³

For example, in a retrospective chart review of all causes of death in HIV+ patients in 1991, 1996, and 1998, end-stage liver disease was the leading cause of death in 1998, accounting for 11 of 22 deaths (50%). In contrast, only 7 years prior, liver disease accounted for only 11% of deaths, and in 1996 it had accounted for only 14% of deaths in HIV+ patients (Fig. 4). More than half of the patients who died from end-stage liver disease had undetectable HIV RNA or CD4 counts $>200/\text{mm}^3$ 6 months prior to death, underscoring the fact that liver disease, not HIV, was the cause of death. One third of patients in 1998 had discontinued HAART due to hepatotoxicity.²³



HIV infection is an important cofactor in HCV disease progression. Coinfection with HIV increases HCV viral loads, the rate of progression to fibrosis and cirrhosis (Fig. 5),²⁴⁻²⁷ and liver-related mortality in HCV-infected patients (Fig. 6).^{23,28} According to Lesens et al,²⁶ the risk of progressive liver disease is increased sevenfold for hemophilic patients with HIV/HCV

Fig. 5. Effect of HIV/HCV Coinfection on Fibrosis Progression Rate.

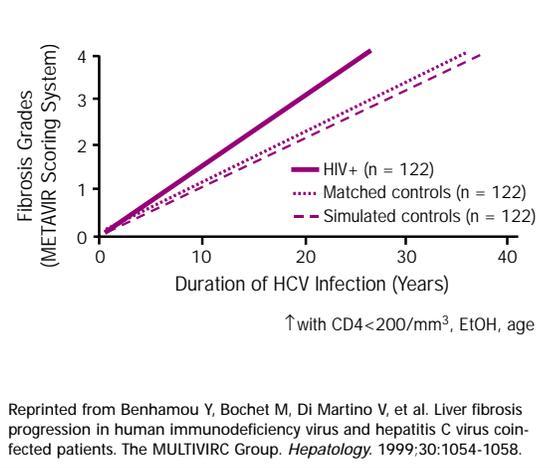
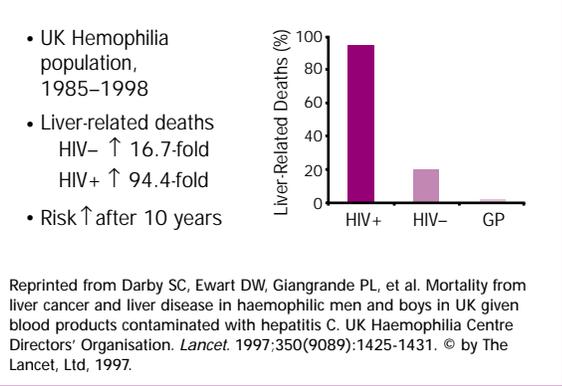


Fig. 6. HCV and HIV: Liver-Related Mortality.



coinfection compared with those with HCV alone. Darby et al²⁸ showed that HIV infection increased the rate of liver-related death after presumed exposure to HCV from 1.4% in HIV-uninfected men to 6.5%. Moreover, in this study, liver failure more frequently occurred within 10 years of the first exposure to HCV, suggesting a faster rate of progression.²⁸ Collectively, these data indicate that HCV acts as an opportunistic pathogen in patients with HIV infection, increasing both the incidence and severity of disease.²⁹ Effects of HCV infection on the course of HIV progression are more controversial, with one study showing no increased risk of progression³⁰ and another showing an increased risk of progression to AIDS (relative hazard [RH] 3.08) and death (RH 3.4) in patients with HCV genotype 1.³¹

The United States Public Health Service and the Infectious Disease Society of America have issued a set of guidelines for the prevention of opportunistic infections among patients who

are infected with HIV.³² With regard to HCV infection, the guidelines recommend the following:

- HIV-infected persons should be screened for HCV by enzyme-linked immunosorbent assay
- Patients should be advised on alcohol use
- Patients should be screened for hepatitis A virus IgG. If negative, they should be vaccinated
- Patients should be evaluated for liver disease and possible need for treatment
- Liver enzymes should be monitored after initiation of HAART

Conclusion

Long-term consequences of chronic hepatitis C are serious and are of increasing concern in patients with HIV infection. The high prevalence of coinfection and the worsened prognosis in patients with both viruses indicate that screening for HCV in HIV-infected persons, followed by implementation of effective treatment regimens for eligible patients, is necessary.

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II. HCV Virology: Important Lessons Learned From HIV

Lessons in Virology Learned From HIV

Important lessons in virology learned during the HIV epidemic are now proving relevant in dealing with hepatitis C virus (HCV). In the mid-1990s, Alan S. Perelson, PhD, and colleagues discovered that HIV replication occurred at astounding rates and that viral replication was the driving force behind HIV disease progression and antiviral drug failures.¹ This critical breakthrough, coupled with the development of new antiretroviral drugs, launched the era of combination drug therapy for HIV infection through suppression of viral replication and prevention of drug resistance. Subsequently, through the appropriate use of potent antiretroviral drug regimens, the rate of death from AIDS has fallen dramatically.

Potent combination therapies will probably be necessary to suppress viral replication and prevent drug resistance in HCV infection as well. The development of interferon alfa-2b/ribavirin combination therapy is the first step in the development of effective combination drug regimens to treat HCV infection. New drugs, such as HCV helicase and protease inhibitors, are in development for the treatment of HCV infection, although these agents are still several years away from clinical use. Therefore, combination therapy remains the standard of care and should be offered to all appropriate patients.

As new therapies are developed, the lessons learned from the treatment of HIV infection will become increasingly important. These lessons include the need for synergistic combinations of drugs that attack HCV at critical steps during its life cycle. Equally important to therapeutic success will be patient adherence to complex and, possibly, toxic drug regimens.

The Hepatitis C Virus

HCV is a spherical enveloped RNA virus of the Flaviviridae family, classified within the *Hepacivirus* genus. Its genome is a single-stranded linear RNA molecule of positive sense, consisting of a 5' noncoding region, a single large open reading frame, and a 3' noncoding region. The virus codes for the production of a 3,000 amino acid polyprotein.

HCV infection causes viral persistence and chronic disease in >80% of infected patients despite broad humoral and cellular immunologic responses to viral proteins. These responses may be thwarted by the high rate of mutation, which leads to the generation of a highly variable mixture of closely related genomes, referred to as quasispecies. This phenomenon persists and continuously evolves in infected individuals, mainly under the influence of host immune pressures. Even recovery from HCV infection does not protect against subsequent re-exposure to the virus.

HCV Similarities to HIV

There are many similarities between HCV and HIV. The most important of these are presented in Table 1.¹⁻⁴ There are also a few major differences between HIV and HCV. Unlike HCV

infection, HIV infection cannot be cured and is generally viewed as inevitably progressive. Also, viral load is a major prognostic indicator in HIV but not HCV infection.

Table 1. HCV and HIV Infections: Overview.

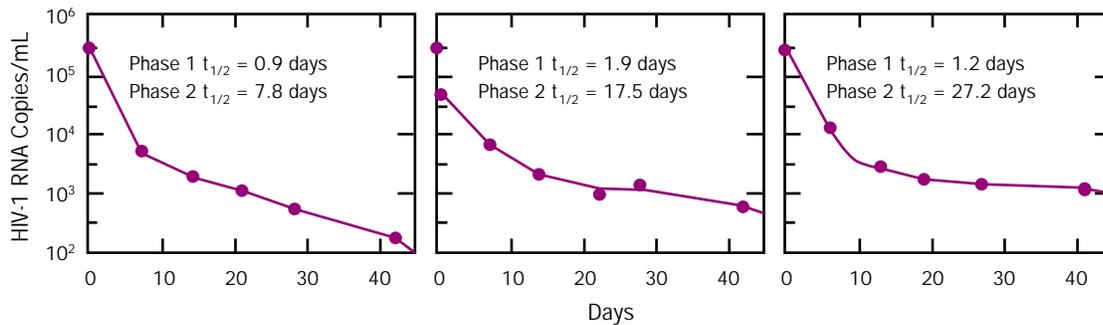
HCV	HIV
Single-stranded RNA virus—flavivirus	Single-stranded RNA virus—retrovirus
Worldwide	Worldwide
10 ¹² virions/day	10 ⁹ –10 ¹⁰ virions/day
6+ genotypes	11+ clades
Subclinical	Subclinical
Half-life 3 hours for genotype 1, 2 hours for genotype 2	Half-life <6 hours

Modeling the Response to Treatment

In response to treatment, HIV viral load falls dramatically (1 to 2 log decrease) over the first few weeks and then, in a second phase, declines more gradually and possibly becomes undetectable (Fig. 1).² A similar effect is seen in patients with HCV infection who respond to treatment: After a single dose of interferon, there is a pronounced dose-related drop in viral load during the first 24 hours (up to 95% decrease) followed by a slower, non-dose-dependent, second-phase decline with continued treatment.³⁻⁵ Interestingly, even patients who ultimately do not sustain a virologic response to interferon exhibit the first-phase decline.

The dramatic first-phase decline in virus is believed to be a result of interferon blocking the ability of infected cells to produce viral particles or to shed them from the cell. Mathematic modeling suggests that interferon-alfa incompletely blocks the production or release of virus, with a dose-dependent effect that reaches a maximum efficiency at about 10 MU/day.³

Fig. 1. Changes in Plasma HIV-1 RNA Level in Response to Therapy for Three Representative Patients.



Reprinted by permission from *Nature*. Perelson AS, Essunger P, Cao Y, et al. Decay characteristics of HIV-1-infected compartments during combination therapy. *Nature*. 1997;387:188-191. © 1997 Macmillan Magazines Ltd.

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III. Management of HIV Infection in HCV-Coinfected Patients

Hepatitis C virus (HCV) coinfection is not a contraindication for highly active antiretroviral therapy (HAART). With a few exceptions described in the rest of this section, management of HIV infection in patients coinfecting with HCV is largely the same as for those with HIV alone. However, staggered initiation of treatment for these two viruses is recommended, and careful monitoring is needed for hepatotoxicity associated with antiretroviral therapies.

Survey Findings

For the large majority of coinfecting patients, management of HCV infection will be carried out while HIV treatment is also in progress. Survey respondents indicated that 85.6% of their patients who are infected with both HIV and HCV are receiving treatment for HIV infection.

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Identifying Coinfection

Many HIV-infected patients are not aware that they are infected with HCV. As coinfection has important implications

with regard to prognosis and management, identification of HCV infection in patients with HIV infection is a crucial first step. Guidelines from the US Public Health Service and Infectious Disease Society of America recommend that all HIV-infected persons be screened for HCV by enzyme-linked immunosorbent assay (EIA).¹ If EIA is positive, or if it is negative but the patient has elevated liver enzyme levels, further assessment with PCR for HCV RNA is warranted.

Deciding Which Infection to Treat First

In most cases, when treatment for both infections is indicated, treatment of HIV infection is initiated first, particularly when liver disease is mild, because HIV infection is generally a more rapidly progressive disease, and a good response to HAART is more likely when it is initiated early (ie, when CD4 counts are high).² Indications for treatment of HIV infection include viral load >20,000 copies/mL or a CD4 count <350 to 500/mm³. For appropriate candidates, treatment of HCV infection is then initiated after HIV disease has stabilized.

However, there are select cases in which treatment of HCV infection may need to precede treatment of HIV infection. In determining which virus to treat first, the physician should consider the pace and current stage of both diseases. For some patients, the potential consequences of advanced HCV infection may outweigh the need to treat early HIV infection. For example, John G. Bartlett, MD, recommends treating HCV infection first if the patient has rapidly progressive or severe hepatic disease and a CD4 cell count >350/mm³. If CD4 cells are >200/mm³, the goal is HCV eradication; patients should be treated like those who do not have HIV infection. If CD4 cells are <200/mm³, the goal is to foster tolerance of anti-HIV medication; reduce fibrosis, ALT, and HCV viral load; reduce risk of cirrhosis, hepatoma, and dying; and improve the quality of life. It may also be necessary to interrupt HAART to address hepatitis C in patients who experience flares of hepatitis while on HAART.

Effects of HAART on HCV

HIV protease inhibitors have no beneficial effect on HCV viral load.^{3,4} In fact, initiation of HAART may increase the alanine aminotransferase (ALT):aspartate aminotransferase ratio⁵ and HCV viral load for the first 3 to 4 months; however, these levels usually return to baseline by month 12.⁴ Unfortunately, this phenomenon can be disruptive to treatment of HIV infection: In a Boston cohort study, antiretroviral therapy was discontinued in 32% of coinfecting patients due to abnormal liver enzyme levels.⁶ On the other hand, there is evidence that coinfecting patients treated with protease inhibitors, especially those who have CD4 counts >200/mm³, have a slower rate of progression to liver fibrosis.⁷

Effects of Anti-HCV Treatment on HIV Infection

Interferon has minimal effect on HIV infection, potentially producing a 0.5-log reduction in viral load when used as monotherapy.⁸ Although interferon may produce a decrease in absolute number of CD4 cells, the percentage of CD4 cells may actually increase during interferon therapy⁹ and may be a more accurate assessment of immune function.⁹ Ribavirin inhibits phosphorylation of zidovudine, stavudine, and

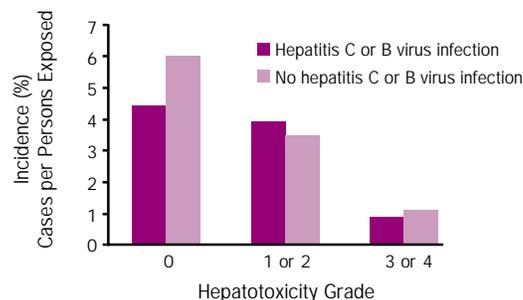
zalcitabine in vitro.¹⁰⁻¹⁴ However, the clinical significance of this interaction is unknown. Preliminary data have not detected clinically significant viral antagonism in patients receiving HAART.¹⁵ In vitro, ribavirin appears to enhance the anti-HIV activity of didanosine by increasing intracellular conversion to its active metabolite, but may also increase its toxicity in vivo.^{13,14} Hematologic toxicity (eg, ribavirin-associated anemia and interferon-associated neutropenia) can be countered with growth factors (erythropoietin and granulocyte colony-stimulating factor, respectively), but may affect compliance and tolerability with anti-HIV therapies.

HAART-Induced Hepatotoxicity

Many concerns have arisen surrounding the potential hepatotoxicity of antiviral medications used to treat HIV infection, particularly in patients infected with chronic viral hepatitis. Liver function abnormalities have frequently been observed in association with antiretroviral medications. Protease inhibitor regimens, in particular, can cause elevations of transaminases and bilirubin levels.

Recent studies indicate that liver toxicity from antiretroviral therapies is more common in HIV-infected patients with chronic hepatitis.^{16,17} For example, in an observational study conducted in Amsterdam, grade 3/4 hepatotoxicity developed in 18% of 409 patients treated with HAART.¹⁷ Of those with hepatotoxicity, 39% were coinfecting with hepatitis B virus (HBV) and 33% were coinfecting with HCV, versus 8% and 14% for the entire study population, respectively. Only 13% of the patients with hepatotoxicity had no markers for viral hepatitis. Moreover, in a prospective study by Sulkowski et al¹⁶ of patients with HIV infection, some of whom were also infected with HCV (52% of patients) or HBV (2.7% of patients), hepatotoxicity of any grade was seen in 54% of HCV-coinfecting patients compared with only 39% of patients with HIV alone ($P = 0.009$) (Fig. 1). However, severe hepatotoxicity was observed in a relatively small number of patients; in fact, 88% of patients who were coinfecting with HCV or HBV did not develop severe toxicity. Thus, although patients with HCV infection may be at increased risk of hepatotoxicity due to the use of antiretroviral medications, these drugs should not be withheld from coinfecting patients.

Fig. 1. Incidence Rate (Cases per Persons Exposed) of Hepatotoxicity During Antiretroviral Therapy, by Hepatitis C or B Virus Infection Status.



Reprinted from Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA*. 2000;283:74-80.

HAART-induced liver toxicity may involve both direct effects of the drugs on the liver (eg, through mitochondrial toxicity or effects on the cytochrome P450 enzyme system) and indirect effects of an improved immune system on the underlying hepatitis. Mitochondrial toxicity occurs because mitochondrial DNA has limited ability to repair mutations, such as those resulting from nucleoside reverse transcriptase inhibitors (NRTIs). Steatosis is a component of the reaction, and obese women are at the greatest risk. Mitochondrial toxicity, which is most common with stavudine, is rare and potentially fatal, but most patients can tolerate alternative NRTIs.

With regard to the indirect effects of HAART on liver toxicity, increases in the number of CD8 cells, resulting from immune restoration, may actually lead to flares in hepatitis not possible in a severely immunocompromised state.¹⁸ Increased activity of both HBV and HCV, including seroconversion, may represent an immune reconstitution syndrome; however, definitive evidence is not yet available.

Survey Findings

Survey respondents rated underlying HCV infection (rating, 4.3 on a scale of 1 = not likely to be involved to 5 = very likely to be involved) and interaction with the P450 cytochrome system (rating, 4.0) as the most likely factors to be involved in HAART-induced hepatotoxicity. Other contributing factors include underlying HBV infection (rating, 3.9), NRTI mitochondrial toxicity (rating, 3.9), and immune restoration with CD8 cell augmentation (rating, 3.5).

Hepatotoxicity of NRTIs

Initial reports of hepatic failure in patients taking zidovudine appeared in the early 1990s,^{19,21} resulting in a US Food and Drug Administration warning in 1993. Zidovudine-induced hepatotoxicity is characterized by abdominal pain, elevated liver enzyme and triglyceride levels, hepatomegaly, and lactic acidosis. It is seen most commonly in obese women.

Other NRTIs are less likely to produce hepatotoxicity. Didanosine in particular is rarely associated with hepatotoxicity, although such toxicity has been reported at doses >400 mg. Although extremely rare, stavudine can result in hepatic dysfunction. Zalcitabine has been associated with hepatomegaly and steatosis, lamivudine with HBV flare, and abacavir with elevated liver function tests and hypersensitivity.

Hepatotoxicity of Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Most of the hepatic reactions associated with use of NNRTIs are idiosyncratic. In the study by Sulkowski et al,¹⁶ severe hepatic toxicity occurred in patients taking dual NNRTIs only if they were HCV+.

In this class of drugs, the most significant hepatotoxicity is caused by nevirapine. Nevirapine produces a drug-induced hepatitis in 8% to 28% of patients,²² which is mediated by cytochrome P450 induction. It manifests as an elevated γ -glutamyltransferase level, usually during the first 2 months of therapy. In one trial, grade 3/4 toxicity (liver enzyme levels ≥ 5 times the upper limit of normal [ULN]) occurred in 15% of patients treated with nevirapine.²³

Delavirdine inhibits cytochrome P450 3A4 and therefore has the potential to interact with macrolides, azoles, and (with some advantage) protease inhibitors. Efavirenz is a mild inducer of cytochrome P450 enzymes. In phase III clinical trials of 53 patients with chronic viral hepatitis who received efavirenz, 13% developed grade 3/4 ALT elevations compared with only 5% of controls, but no patient developed fulminant hepatic failure.

Hepatotoxicity of Protease Inhibitors

All of the protease inhibitors inhibit cytochrome P450 3A enzymes. According to a presentation by Orenstein and Stewart,²⁴ protease inhibitors in general are associated with a 6% incidence of ALT levels ≥ 3 times the ULN. Median time to onset of elevated ALT levels is 8 weeks, with a 4-week mean time to resolution after treatment discontinuation. In the study by Sulkowski et al,¹⁶ nearly 88% of HCV-infected patients treated with protease inhibitors did *not* experience severe hepatotoxicity (grade 3/4).

In a study by Zylberberg and Pol²⁵ of 205 HIV-infected patients receiving protease inhibitor regimens, five patients (2.5%) developed severe acute hepatitis (ALT levels >5 times the ULN) with a mean duration of 3 months. Three of these five patients were taking indinavir and two were taking ritonavir. Four of the five patients (80%) had either HCV or HBV coinfection—a statistically significantly larger proportion than the 71 coinfecting patients (35.5%) out of the 200 patients who did not develop acute hepatitis while on protease inhibitors. In this small study, no relationship was found between acute hepatitis and immune restoration, baseline CD4 count, change in viral load, protease inhibitor type, and antiretroviral-naive status.

Ritonavir is the protease inhibitor most frequently associated with hepatocellular injury (3%–30%). Sulkowski et al¹⁶ observed a higher incidence of severe (grade 3/4) hepatotoxicity in patients using ritonavir compared with nucleoside analog regimens, indinavir, nelfinavir, and saquinavir (without concurrent ritonavir), and reported that ritonavir was responsible for nearly half of all cases of severe hepatotoxicity. Toxicity associated with ritonavir may be related to plasma levels, and is more likely to occur in the setting of immune reconstitution in which CD4 counts are rising and HIV viral load is decreasing.¹⁶

Clinical hepatitis is rare in patients treated with saquinavir. However, when ritonavir and saquinavir are combined, hepatotoxicity is increased in patients with underlying viral hepatitis evidenced by abnormal baseline liver enzyme levels. Risk is increased when ritonavir is used at a dose of ≥ 600 mg (the usual recommended dose of ritonavir is 200–400 mg).

Severe hepatotoxicity is uncommon with nelfinavir. Hyperbilirubinemia occurs in 10% of patients treated with indinavir.²⁶ This reflects indirect bilirubin and is of no consequence except possibly for pregnant women. Amprenavir produced grade 3/4 hepatotoxicity in 4% to 6% of patients in clinical trials.²⁷

**Table 1. Survey Findings:
Selecting Treatment for HIV in Patients Coinfected With HCV**

Drug	1 Avoid Using	2	3	4	5 First Choice	Mean Rating
Lamivudine	4%	4%	17%	35%	39%	4.0
Didanosine	5%	10%	24%	48%	14%	3.6
Co-trimoxazole	5%	0%	45%	41%	9%	3.5
Nelfinavir	5%	9%	32%	41%	14%	3.5
Stavudine	0%	5%	41%	50%	5%	3.5
Azithromycin	0%	14%	45%	32%	9%	3.4
Amprenavir	4%	13%	39%	39%	4%	3.3
Dapsone	9%	9%	35%	35%	13%	3.3
Saquinavir	9%	22%	30%	26%	13%	3.1
Zidovudine	14%	19%	14%	43%	10%	3.1
Clarithromycin	5%	18%	50%	23%	5%	3.0
Fluconazole	0%	26%	57%	13%	4%	3.0
Indinavir	13%	3%	30%	22%	4%	2.7
Ritonavir	44%	28%	4%	12%	12%	2.2

Survey Findings

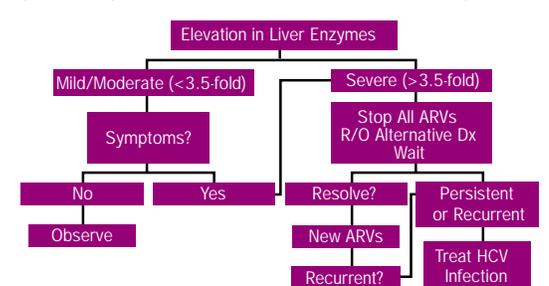
In an HIV-infected patient with known chronic active hepatitis, survey respondents rated lamivudine as a top choice for inclusion in treatment regimens and said they would generally avoid ritonavir, presumably because of the high incidence of hepatotoxicity (Table 1).

Management of HAART-Associated Hepatotoxicity

When significant hepatotoxicity does develop in coinfecting patients, the following issues should be considered: (1) the potential cause(s) of the abnormality, (2) the possibility of changing antiviral medications in an effort to decrease toxicity while maintaining antiretroviral effect, (3) the prevention of additional hepatotoxicity from other sources, and (4) the necessity of treating the underlying viral hepatitis. Options for ongoing management include (Fig. 2):

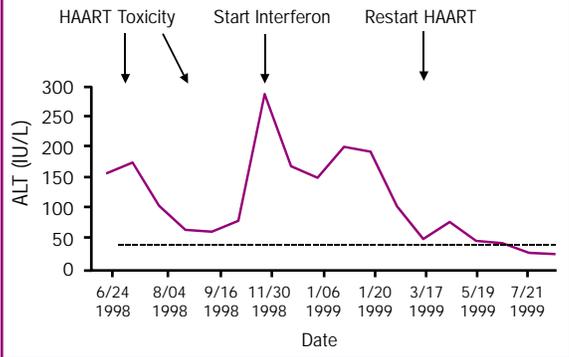
- Continuing with the current regimen but monitoring more closely
- Switching to a different protease inhibitor
- Switching from a protease inhibitor regimen to a protease inhibitor-sparing regimen in patients with good viral control (preliminary evidence suggests that viral suppression remains stable, pill burden decreases, and there is no increase in adverse effects)
- Treating the underlying chronic hepatitis (Fig. 3)

Fig. 2. Management of HAART-Associated Hepatotoxicity.



ARVs = antiretrovirals; R/O = rule out, Dx = diagnosis
Courtesy of Mark S. Sulkowski, MD.

Fig. 3. HAART-Associated Hepatotoxicity: Role for HCV Therapy?



Survey Findings

Survey respondents said that in coinfecting patients with HAART-induced hepatotoxicity, it would be highly appropriate to obtain markers for HBV (rating, 4.4 on a scale of 1 = not appropriate to 5 = highly appropriate), to switch to non-protease inhibitor regimens (rating, 4.2), or to treat the underlying HCV infection (rating, 4.2). However, they also considered it appropriate to switch to a different protease inhibitor (rating, 3.8) or to continue to treat with HAART if liver enzyme levels remained <5 times the ULN (rating, 3.8). In patients coinfecting with HIV and HCV who experience a second flare of liver enzyme abnormalities during HAART, survey respondents said it would be most appropriate to discontinue all antiretroviral therapy and manage HCV infection with interferon/ribavirin in patients with evidence of active chronic HCV infection on liver biopsy before reintroducing antiretroviral therapy 1 month later (rating, 3.8). Alternatively, physicians could discontinue the current antiretroviral therapy and try an alternate antiretroviral regimen (rating, 3.1). There was less support for waiting until completion of interferon/ribavirin to reintroduce antiretroviral therapy (rating, 2.3).

Conclusions

HIV-infected patients should be screened for markers of viral hepatitis, including HCV. HAART, including protease inhibitor therapy, should not be withheld in coinfecting patients. Most coinfecting patients can tolerate HAART without evident hepatotoxicity. Liver enzyme levels should be monitored closely in coinfecting patients treated with HAART, particularly during the first 3 months of treatment, and any significant increases should be further evaluated. Flares of hepatitis do not prohibit use of HAART in coinfecting patients, but physicians should minimize use of other potentially hepatotoxic drugs, should counsel patients against consuming alcohol, and should monitor clinical and laboratory parameters carefully. Suppression of HCV disease activity by treating with combination therapy may be necessary if aggressive therapy for HIV is warranted. If CD4 cells are >200/mm³, the goal is HCV eradication; patients should be treated like those without HIV infection. If CD4 cells are <200/mm³, the goal is to foster tolerance of anti-HIV medication; reduce fibrosis, ALT, and HCV viral load; reduce risk of cirrhosis, hepatoma, and dying; and improve the quality of life. Further research is needed on the impact of antiretroviral therapy and immune reconstitution on the course of HCV disease.

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IV. Management of HCV Infection in HIV-Infected Patients

Evaluating Patients for Treatment

All patients with a diagnosis of hepatitis C virus (HCV) infection should undergo further evaluation and be considered for treatment. Irrespective of HIV status, patients should be provided with information regarding prevention of transmission of HCV, avoidance of alcohol and other hepatotoxins, and the potential benefits and risks of treatment for HCV infection, and should be given an opportunity to make an informed decision regarding therapy.

The presence of psychiatric illness or active substance abuse should be addressed prior to initiating treatment for HCV infection. Psychiatric disorders complicate the treatment of HIV/HCV infections in several ways: (1) mental illness is a risk factor for the acquisition of HCV and HIV; (2) depression is a relatively common side effect of some medications widely used to treat HIV or HCV infections (eg, interferon); and (3) mental illness can decrease patient compliance with treatment. Treatment of preexisting mood disorders before initiation of therapy for HCV infection is essential in order to increase the likelihood that the patient will be able to tolerate and comply with treatment for HCV and/or HIV infections. With appropriate psychiatric treatment, coinfecting patients can be successfully maintained on therapy for HCV infection. Interferon is contraindicated, however, for suicidal patients.

Although liver biopsy is not required before initiation of therapy, it is the gold standard for assessment of liver injury to determine prognosis and individualize treatment. Treatment is strongly favored in patients with stage ≥ 2 fibrosis (regardless of genotype). Conversely, careful observation is a viable option in patients with stage 0 or 1 fibrosis, especially if they have a long disease duration and/or genotype 1. Patients are usually accepting of biopsy, as it is only minimally invasive and briefly painful and is associated with low rates of morbidity (bleeding, 1%; septicemia, $<0.1\%$; bile leak, 0.1%) and mortality (0.01%–0.05%).^{1,2} Valid reasons for not performing a liver biopsy include high risk of bleeding, patient refusal, and presence of ascites, cholangitis with extrahepatic biliary obstruction, or morbid obesity.

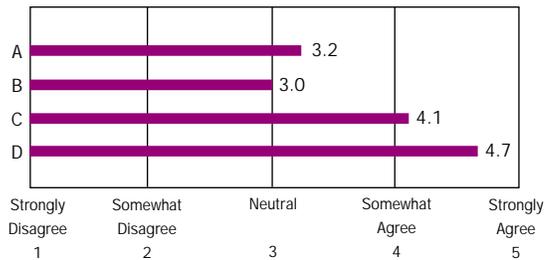
Survey Findings

Liver biopsy is not always needed before treatment of HCV infection is initiated. If the histologic results would not alter patient management, biopsy may not be necessary. Although survey respondents consider liver biopsy to be the most important tool in predicting outcome of chronic hepatitis C (Fig. 1), less than half (41.7%) of their HCV-infected patients (with and without HIV coinfection) have undergone liver biopsy.

Fig. 1. Survey Findings: Natural History of HCV Infection and Liver Biopsy.

In your opinion, which of the following is useful in predicting the outcome of chronic hepatitis C infection?

- A. Quantitative HCV RNA PCR (viral load)
- B. ALT
- C. HCV genotype
- D. Liver histology



Panelists were most likely to **postpone** treatment for patients with untreated depression (rating, 4.6 on a scale of 1 = least critical to consider to 5 = most critical to consider) or ongoing substance abuse (rating, 4.4), or if the patient has irregular follow-up visits (rating, 4.3), ischemic heart disease (rating, 4.3), plans to conceive a child (rating, 4.2), or uncontrolled HIV viral load (rating, 4.1). They were unlikely to postpone treatment if the patient has normal alanine aminotransferase (ALT) levels (rating, 2.9), has substance abuse that has been in remission for >1 year (rating, 2.8), does not want a liver biopsy (rating, 2.8), or has low HCV viral load (rating, 2.6). Some clinicians would postpone treatment if the patient's liver biopsy shows moderate inflammation and bridging (septal) fibrosis (rating, 3.5) or minimal inflammation and no fibrosis (rating, 3.7), or if the patient is homeless (rating, 3.9).

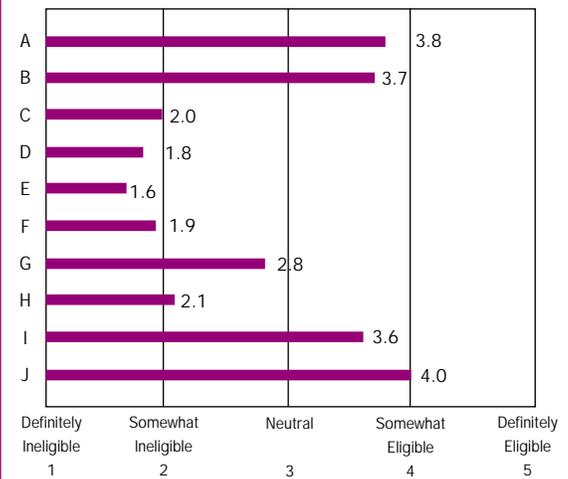
Respondents were likely to **avoid** treatment of HCV infection in patients with <100 CD4 cells/ mm^3 , no symptoms, and viral

load <50 copies/mL, and in patients with clinical AIDS with past opportunistic infections and viral load <50 copies/mL (Fig. 2).

Fig. 2. Survey Findings: When to Avoid Treatment.

Based upon your experience, which of the following factors would make an HIV/HCV coinfecting patient *definitely ineligible* for treatment of HCV?

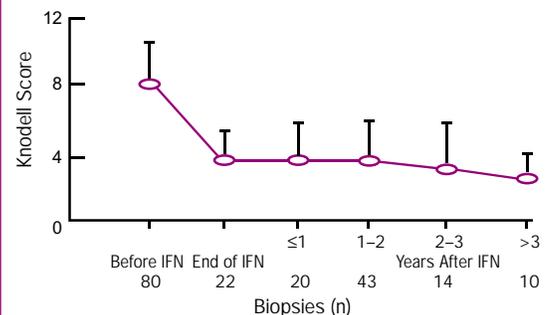
- A. CD4+ cells $<100/\text{mm}^3$, no symptoms, viral load <50 copies/mL
- B. Clinical AIDS with past opportunistic infections, viral load <50 copies/mL
- C. AIDS with multiple active opportunistic infections
- D. Major depression with multiple suicide attempts
- E. Active ischemic heart disease
- F. Decompensated liver cirrhosis (ascites)
- G. On hemodialysis
- H. Malignancy
- I. Treatment for depression
- J. Histologic evidence of cirrhosis without signs of decompensation



HCV: A Curable Disease

Unlike HIV infection, HCV infection appears to be a curable disease in a significant proportion of non-HIV+ patients. Individuals with a sustained virologic response (ie, no detectable HCV RNA 6 months after therapy) maintain the response and experience histologic improvement long term (Fig. 3).^{3,4} Thus, the primary goal for treatment of HCV infection is to eradicate the virus. Secondary goals are to reduce HCV RNA titer (in the absence of viral eradication),

Fig. 3. Viral Eradication and Histologic Progression.



Reprinted from Marcellin P, Boyer N, Gervais A, et al. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. *Ann Intern Med.* 1997;127:875-881.

hepatic inflammation/necrosis, and risk of hepatocellular carcinoma; to slow the progression of the disease to cirrhosis; and to postpone or avoid the need for liver transplantation.

The Current Standard of Care for HCV Infection

It is now more than 1 year since standard treatment for chronic HCV infection advanced from interferon monotherapy to combination therapy with interferon/ribavirin. With combination therapy, 40% of treatment-naïve patients,^{5,6} 49% of interferon relapsers,⁷ and 15% to 30% of interferon nonresponders⁸⁻¹⁴ achieve sustained virologic response. Histologic improvement (ie, a decrease in inflammatory score of ≥ 2 points) occurs in 86% of patients who achieve a sustained virologic response and 39% of patients who relapse or do not respond to interferon/ribavirin.⁵

Viral genotype is the single most powerful predictor of sustained response. With interferon/ribavirin, HCV genotype 1-infected patients have sustained response rates of 25% to 30% (with slightly better rates in those few patients with low viral loads), and patients with genotype non-1 HCV infection achieve sustained response rates of 60% to 65%.^{5,6} In patients with low viral loads, response rates are similar with 24 versus 48 weeks of treatment (Table 1). Other predictors of good response to treatment include age <40 years at infection and female gender.⁶ Although African Americans have rather poor response to interferon monotherapy, associated predominantly with >95% prevalence of HCV genotype 1, sustained response rates to interferon/ribavirin are about 21%.¹⁵

Table 1. Combination of Viral Load and Genotype

Genotype	Viral Load	Sustained Response (%)	
		48 Weeks	24 Weeks
2, 3	<2 million	64	60
2, 3	>2 million	64	67
1	<2 million	36	35
1	>2 million	28	8

Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon alfa-2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alfa-2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet*. 1998;352:1426-1432.

The duration of treatment for HCV infection should be customized according to HCV genotype and other prognostic factors. Patients infected with HCV genotype 1 and high viral loads should be treated for 48 weeks if the HCV RNA is negative at 24 weeks. Although the existing data suggest that patients with genotype 1 and low viral loads can stop therapy at 24 weeks, some clinicians prefer to continue to 48 weeks in all genotype 1 patients. For genotype non-1 infections, 24 weeks of interferon/ribavirin is sufficient for most patients regardless of initial viral load. Exceptions may include patients with cirrhosis or advanced fibrosis, whom some clinicians treat for 48 weeks because this is another adverse response predictor.¹⁶ Virologic response is determined by PCR for HCV RNA after 6 months of treatment. Persistence of HCV RNA 6 months after onset of treatment means that subsequent response is extremely unlikely to occur and cessation of therapy should be considered. Other important clinical and laboratory assessments are listed in Table 2.

Table 2. Clinical and Laboratory Assessments

- Baseline
 - HIV load, CD4 (%), CBC, chemistry panel, HCV load
 - Screen comorbid disease
 - Consider alcohol and depression screen
 - Consider antidepressant prophylaxis
- 12-week intervals
 - HIV load and CD4 (%)
 - Evaluate for drug-drug interactions
 - Screen for IFN-associated thyroid dysfunction (TSH)
- Anti-HCV activity
 - Week 12: HCV RNA >1 log reduction
 - Week 24: HCV RNA undetectable
 - Reevaluate goals of therapy based on virologic response and drug tolerability; if no response:
 - Stop treatment
 - Maintenance IFN
- At week 2
 - CBC
 - Anemia: epoetin alfa
- 4-week intervals
 - CBC, chemistry panel
 - Evaluate mood, weight, adverse effects

CBC = complete blood count, IFN = interferon, TSH = thyroid-stimulating hormone

The optimal approach to patients who have either relapsed following, or not responded to, interferon/ribavirin remains unclear. Those who have relapsed after only 6 months of combination therapy may benefit from retreatment for 12 months. There is no evidence that prolonging therapy beyond that time increases efficacy. For nonresponders to interferon/ribavirin, several lines of evidence are creating interest in maintenance therapy with the goal of retarding the progression of disease and preventing cirrhosis and hepatocellular carcinoma. Maintenance therapy is discussed in more detail in Section VI: Special Challenges in Coinfected Patients.

There is some controversy about the need for biopsy and treatment in HCV-infected patients with normal ALT levels. Although these patients tend statistically to have milder degrees of liver disease on biopsy, there are patients who exhibit surprising degrees of fibrosis.^{17,18} Preliminary data regarding treatment of patients with normal ALT levels with interferon/ribavirin show rates of sustained response comparable to those of typical HCV-infected patients with high ALT levels.¹⁹

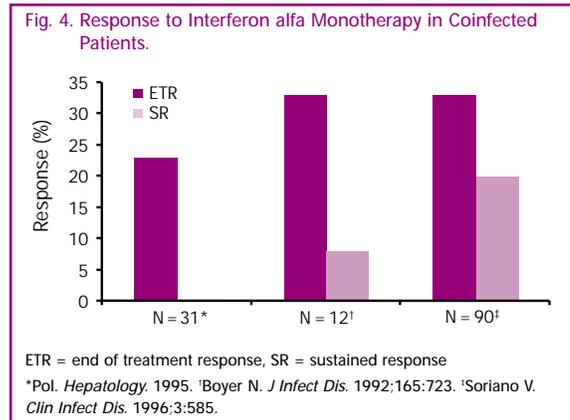
Survey Findings

The panelists indicated that 42.3% of their patients infected with HCV alone are being treated. They have treated nearly three quarters with interferon/ribavirin and only 4% with interferon alone. The other 24% have been referred to a gastroenterologist. None of the panelists is waiting for other therapies or using alternative therapies to treat HCV infection. Combination therapy with interferon/ribavirin remains the standard of care for the treatment of patients with HCV infection, and should not be withheld from patients who are appropriate candidates for treatment in anticipation of these new agents.

Panelists indicated that nearly half of their patients with HCV infection are receiving interferon/ribavirin combination therapy. None of the panelists is waiting for the appearance of as-yet unapproved therapies before initiating treatment.

Treatment of HCV Coinfection in Patients With HIV

It is increasingly clear that HIV/HCV coinfection is associated with a tendency for more rapidly progressive liver disease compared with patients with HCV infection alone. Thus, hepatologists, as well as their colleagues who treat HIV disease, have recognized the need to treat HCV infection more aggressively in HIV-infected patients. Rates of sustained response to interferon monotherapy in HIV/HCV-coinfected patients have varied from 0% to 20% (Fig. 4).²⁰⁻²²



Trials of combination therapy in HIV/HCV coinfecting patients are in progress, and preliminary data from prospective, non-randomized trials have been promising.^{23,24} In a study of 37 consecutive patients (10 of whom had cirrhosis) with a median of 343 CD4 cells/mm³, HCV RNA was undetectable at week 12 of treatment in eight (35%) of 23 patients treated with interferon/ribavirin versus one (7%) of 14 treated with interferon alone.²³ This study demonstrated no increase in HIV RNA level in 14 patients receiving ribavirin concurrently with either zidovudine or stavudine. Six patients discontinued treatment due to adverse events, predominantly psychiatric effects. Nearly 50% of patients had anemia and required the use of erythropoietin. In a second trial, 10 (50%) of 20 HCV/HIV-coinfecting patients (mean CD4 count, 150 cells/mm³; cirrhosis in nine patients) had no detectable HCV RNA after 6 months of treatment with interferon/ribavirin (Table 3).²⁴ There were no reports of significant adverse events.

Table 3. Interferon/Ribavirin Therapy in HIV-Infected Persons

- French, prospective, nonrandomized trial
 - 20 patients standard interferon/ribavirin
 - 9 cirrhosis
 - Mean CD4 350 ± 15/mm³
- Virologic response at 6 months of treatment
 - 10 patients HCV RNA undetectable
 - Genotype 1 (5 patients) and 3 (5 patients)
- No reports of significant adverse effects

Landau A, Batisse D, Van Huyen JPD, et al. Efficacy and safety of combination therapy with interferon- α 2b and ribavirin for chronic hepatitis C in HIV-infected patients. *AIDS*. 2000;14:839-844.

Good control of HIV infection may also help to slow the progression of liver disease. In a retrospective cohort study, Benhamou et al²⁵ showed that patients treated with protease inhibitors had a slower rate of fibrosis (odds ratio 2.4), but

this remains controversial. However, as discussed, the impact of highly active antiretroviral therapy (HAART) on HCV-related liver disease is poorly understood and, in some cases, HAART hepatotoxicity may actually contribute to worsening of liver disease.

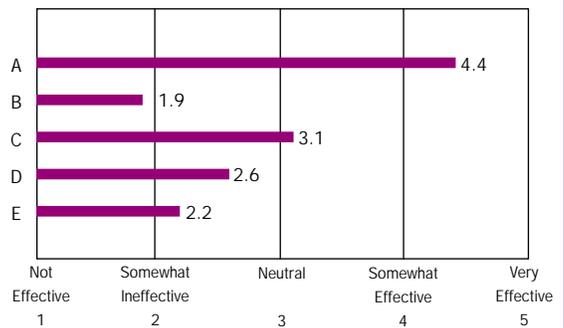
Survey Findings

Nearly one quarter of the panelists' patients who are infected with both HIV and HCV are receiving treatment for HCV infection. Interferon/ribavirin received the highest rating as treatment for HCV infection in coinfecting patients (Fig. 5). Overall, the panelists apparently treat HCV infection in these patients the same as they do in patients without HIV infection, as they reported that over three quarters are treated with interferon/ribavirin and only 4% are treated with interferon alone. However, fewer (only 12%) have been referred to a gastroenterologist, and 8% are simply being observed.

Fig. 5. Survey Findings: Preferences for Treatment of HCV in HIV-Infected Patients

To provide optimal therapy for your HIV/HCV-coinfecting patients, how would you rate the following treatment options?

- A. Treat patients with interferon/ribavirin.
- B. Treat patients first with interferon. Add ribavirin if HCV RNA is still detectable in plasma after 3 months of treatment.
- C. Refer patients to a nearby site conducting an HIV/HCV-coinfection clinical trial.
- D. Refer patients to a hepatologist for treatment.
- E. Do not treat. Wait until more data on safety and efficacy of combination therapy in your setting are available.



Other General Management Issues

Management of HCV infection in HIV-infected patients should also include the following general measures^{26,27}:

- Education regarding the prevention of liver damage
- Advice to avoid consumption of alcohol and, if necessary, referral for alcohol treatment and relapse-prevention programs
- Vaccination against hepatitis A and B viruses in susceptible patients
- Caution against initiating new medications, including over-the-counter, herbal, or alternative medications, without consulting a healthcare provider
- Monitoring of serum liver enzyme levels if the patient is taking concomitant HAART for treatment of HIV infection, as these drugs may result in hepatotoxicity (see previous section)

- Information about other support resources that are available, such as educational materials (including self-help books and videos), patient newsletters, and national organizations
- Vigilant monitoring of serum lactic acid level for nucleoside analogue toxicity

Optimal management of HCV infection in patients with HIV infection requires a multidisciplinary team headed by the HIV care provider. Other important members of this team include gastroenterologists/hepatologists, psychiatrists/psychologists, nurses, nurse practitioners (NPs), and physician assistants (PAs). Physician extenders (eg, NPs, PAs) can offer essential supportive care by discussing with patients many aspects of treatment, such as disease symptoms, physician orders, treatment options, and side effects, and helping patients to interpret the results of clinical laboratory tests. The healthcare team should also include an extended range of other support providers, such as family and friends, coworkers, support groups, and clergy.

A Look Into the Future: Advances in HCV Therapy

The next advance in therapy for HCV infection is expected to be the use of long-acting pegylated interferons. Polyethylene glycol conjugates of interferon alfa will offer greater patient convenience (once-weekly dosing) and improvements in response rates compared with standard interferon monotherapy.²⁸ However, pegylated interferon monotherapy will not produce response rates as high as are currently achieved with interferon/ribavirin combination therapy. It is likely that the combination of pegylated interferon/ribavirin will produce sustained response rates comparable or superior to the rates typically observed with conventional interferon alfa-2b. Until this is conclusively demonstrated, combination therapy with standard interferon/ribavirin is apt to continue to be first-line therapy for treatment-naïve patients and interferon relapsers, and pegylated interferon monotherapy will be recommended for patients in whom ribavirin is contraindicated or as maintenance therapy for nonresponders.

The next generation of pharmacologic therapies for HCV infection is likely to comprise additions to the current two-drug therapy. All of these new therapies are at least several years away from full evaluation and commercialization. Potential new therapies include interleukin-10, protease inhibitors, helicase inhibitors, polymerase inhibitors, ribozyme therapy, interferon gene therapy, therapeutic vaccines, antisense nucleotides, and interfering peptides/proteins. The next decade is promising for the development of improved therapies for HCV infection.

Conclusions

Treatment of HCV infection with interferon/ribavirin should be considered for patients who are at the greatest risk for progression to cirrhosis (ie, those with persistently elevated ALT levels, detectable HCV RNA, and histologic findings of portal or bridging fibrosis, or at least moderate inflammation

Table 4. Summary of General Recommendations for Management of HCV Infection in HIV-Infected Patients

- Evaluate all HIV/HCV-infected patients for HCV therapy
- Consider the following in assessing candidates for treatment and deciding how aggressively to treat
 - Laboratory and histologic findings
 - Severity and duration of liver disease
 - Likelihood of response to treatment
 - Comorbidities (eg, chronic obstructive pulmonary disease, depression, other psychiatric illness)
 - Contraindications to treatment
 - Alcohol use
 - Psychiatric disorders
 - Status of HIV disease
 - Life expectancy
 - Patient attitude
- Strongly advise patients with HCV infection to abstain from alcohol consumption
- Vaccinate susceptible patients against hepatitis A and B viruses, pneumococcus, and influenza virus
- Consider interferon/ribavirin combination therapy for HCV-infected patients with
 - Stable HIV disease (including adequate CD4 count), with the goal of viral eradication
 - Advanced liver disease, with the goal of halting or delaying disease progression
 - HAART hepatotoxicity, with the goal of reducing the toxicity and re-establishing aggressive treatment for HIV infection
- Avoid interferon/ribavirin combination therapy for HCV-infected patients with
 - Decompensated cirrhosis (consider liver transplantation)
 - Major contraindications, such as severe depression
- Manage side effects of interferon/ribavirin, including depression and cytopenia (see Section V)
- Individualize duration of therapy according to patient and viral characteristics
- Evaluate response to treatment at 6 months and consider long-term treatment in nonresponders with advanced liver disease
- Use a team approach to treatment

or necrosis).²⁷ Overall treatment recommendations are summarized in Table 4. Preliminary data regarding the efficacy and safety of interferon/ribavirin in HIV-infected patients are promising, and data supporting the enhanced efficacy of interferon/ribavirin versus interferon monotherapy in non-HIV patients are compelling. In patients who have stable HIV disease, high CD4 counts, and undetectable viral levels, HCV infection should be managed the same as in patients without HIV infection, with the goal of eradicating HCV. Treatment of HCV infection is probably also justifiable in HIV-infected patients with advanced liver disease in order to delay clinical and histologic progression, and in patients who experience hepatotoxicity while on HAART in order to permit continuation or reinitiation of aggressive HIV treatment. New therapies for HCV infection are in development, although these agents still require considerable clinical testing before their role in the treatment of coinfecting patients is understood. At present, interferon/ribavirin combination therapy may be considered the standard of care for the safe and effective treatment of HCV infection among coinfecting patients.

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V. Managing Side Effects of Interferon and Ribavirin

In the treatment of hepatitis C virus (HCV) infection, vigilance on the part of the clinician is essential for prevention and appropriate treatment of any adverse events that develop in order to ensure compliance and achievement of treatment goals. Although numerous, the side effects of interferon rarely pose serious danger to patients if appropriate monitoring takes place. When ribavirin is added to interferon, additional

adverse effects can occur, but the improved efficacy usually outweighs these risks. Toxicity of interferon/ribavirin is usually reversible. Nevertheless, full disclosure to patients of potential side effects remains a critical element in the overall management of chronic HCV infection.

Managing Side Effects of Interferon

Flulike Symptoms and Fatigue

Flulike symptoms (eg, fever, myalgias, headaches, chills, and nausea) and fatigue are common adverse events of interferon but can be ameliorated by premedication with acetaminophen or (in the absence of contraindications) a nonsteroidal agent,

such as ibuprofen or an antihistamine. Other general measures that may help relieve these and other common side effects of interferon include administering the drug early in the evening, engaging in light aerobic exercise, drinking decaffeinated fluids, and employing comfort measures.

Psychiatric Effects

Depression is the single most common reason for discontinuation of treatment for HCV infection.¹ However, with the appropriate treatment, symptoms of depression in most patients with interferon-induced depression can be controlled.

All patients receiving interferon must be carefully monitored for depression. It is often helpful to speak to the patient's spouse or significant other to gain further insight into changes in the patient's mood and behavior. Patients who report depression should be queried specifically about suicidal ideation. Most patients can continue therapy, although dosage adjustment or treatment discontinuation is sometimes needed.

Interferon-induced depression may be treated using the same strategies that are commonly employed to treat depression in patients who are not being treated with interferon. All antidepressants currently marketed have similar response rates and discontinuation rates in clinical trials. They are distinguished by side effects and toxicities, and to a lesser extent by drug-drug interactions. Selective serotonin reuptake inhibitors (SSRIs) and related compounds are safer and easier to use than the older tricyclic antidepressant (TCA) compounds, but are no more efficacious. Some patients find the side effects of SSRI drugs, or some of the atypical drugs, easier to tolerate, but other patients find the TCAs preferable. The clinician's effort should be to find a drug that is effective and tolerable for the individual patient. TCAs are sedating and therefore enhance sleep. Their anticholinergic properties cause constipation but decrease diarrhea. TCAs also have a salient effect on neuropathic pain. Virtually no studies have been done on use of SSRIs or TCAs in patients receiving hepatitis C treatment with interferon/ribavirin, but they have been effective in clinical experience. Studies are clearly needed to guide therapeutic decisions. Psychotherapy (especially cognitive-behavioral therapy), stress reduction techniques, and support groups can also be useful. Consultation with or referral to a mental health specialist is often helpful.

Thyroid Dysfunction

In about 5% of patients, thyroid toxicity manifests as thyroiditis and may be irreversible. It is usually accompanied by thyroid antibodies and generally appears after 3 to 6 months of treatment. Monitoring of thyroid function tests, including thyroid-stimulating hormone (TSH), is recommended at baseline and every 3 months. The most common pattern of thyroid toxicity is an asymptomatic rise in levels of TSH that may evolve to symptomatic hypothyroidism, which can be managed with thyroid supplements. If TSH levels are monitored closely, some patients will show a subclinical drop in TSH before the hypothyroid phase supervenes. Less commonly, patients may develop sustained hyperthyroidism requiring beta blockers and/or ablative therapy.

The degree to which cessation of interferon prevents irreversible thyroid dysfunction is unclear. A major factor to

be considered in deciding whether to continue treatment is the ability to adequately treat the thyroid dysfunction.

Hematologic Effects

Interferon may induce neutropenia and/or thrombocytopenia, which are dose related. These cell-count reductions are of particular concern when polymorphonuclear cell (PMN) count drops to $<1,000/\text{mm}^3$ and the platelet count reaches $<50,000/\text{mm}^3$. In some instances, when neutropenia limits treatment, filgrastim (granulocyte colony-stimulating factor) may be useful. Otherwise, dose reduction or treatment discontinuation may be necessary (Table 1). The addition of ribavirin to interferon reduces the risk and severity of thrombocytopenia.

Table 1. Guidelines for Interferon Dose Modification

	Dose Reduction	Permanent Discontinuation of Treatment
White blood count	$<1.5 \times 10^9/\text{L}$	$<1.0 \times 10^9/\text{L}$
Neutrophil	$<0.75 \times 10^9/\text{L}$	$<0.5 \times 10^9/\text{L}$
Platelet count	$<50 \times 10^9/\text{L}$	$<25 \times 10^9/\text{L}$

Reprinted from Maddrey WC. Safety of combination interferon alpha 2b/ribavirin therapy in chronic hepatitis C-relapsed and treatment-naive populations. *Semin Liver Dis.* 1999;19(suppl 1):67-75.

Ophthalmologic Effects

Retinopathy is a rare adverse effect of interferon. A baseline fundoscopic examination by an ophthalmologist is advisable before initiating antiviral treatment in patients with diabetes or long-standing hypertension. Ophthalmologic consultation is indicated during therapy in patients who complain of visual impairment, such as spots or field deficits. Since retinopathy is sometimes irreversible,² strong consideration must be given to discontinuing therapy when retinopathy occurs.

Other Adverse Effects

Other adverse effects of interferon include diarrhea, insomnia, anorexia, cutaneous reactions (either local or systemic), exacerbation of preexisting psoriasis, frontotemporal alopecia (mostly in women), hearing loss, and peripheral neuropathy. These effects are generally reversible and can be managed with standard therapies (eg, antidiarrheals, sleep-promoting agents). Rarely, angina may be exacerbated and seizures may occur in patients with a history of seizure disorder. Cardiac arrhythmias are another possible effect but are usually benign.

Managing Side Effects of Ribavirin

Teratogenic Complications

Because ribavirin has been shown to be teratogenic in animal models,³ women of childbearing age must be screened for pregnancy just before initiation of treatment and monthly during therapy. Rigorous contraception with two forms of birth control must be practiced by both male and female patients receiving ribavirin, and conception in the patient or the patient's partner(s) must be avoided until at least 6 months posttherapy.

Hemolytic Anemia

Dose-related hemolysis is a consistent consequence of treatment with ribavirin. The mean drop in hemoglobin level

is about 2.5 g/dL,¹ usually reaching nadir during the first 4 weeks. In 5% to 10% of cases, the hemoglobin level declines >4 g/dL. Ribavirin-induced anemia is usually not clinically important except that it may exacerbate significant cardiovascular disease. Therefore, ribavirin use should be carefully monitored in patients with coronary disease. Some clinicians request stress tests in patients older than 55 or 60 years of age before initiation of ribavirin. If a patient being considered for therapy is under the care of a cardiologist, early consultation with that specialist is advisable and should be documented.

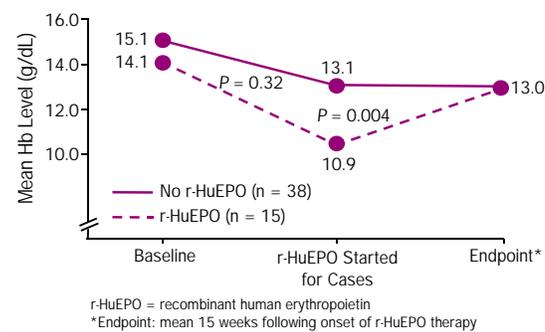
In all patients treated with ribavirin, clinicians should monitor hemoglobin level at least twice during the first month of treatment and monthly thereafter. Hemoglobin levels usually return to baseline within 4 to 8 weeks after cessation of therapy.¹ Dose reduction to 600 mg/day with a brief period off ribavirin, if necessary, is an appropriate way to manage most instances of ribavirin-induced anemia. Dose reduction is recommended for patients whose hemoglobin level drops to <10 g/dL or, if at high cardiac risk, by ≥ 2 g/dL, and does not reduce treatment efficacy.¹ Treatment discontinuation is required if hemoglobin drops to <8.5 g/dL in a patient at normal cardiac risk or to <12 g/dL in a patient at high cardiac risk.

Some clinicians have found erythropoietin to be useful in managing this complication, particularly in HIV/HCV-coinfected patients. Douglas T. Dieterich, MD, reported an average 2.1 g increase in hemoglobin level in a case-control study of 15 patients (Fig. 1).⁴

Other Adverse Effects

Other adverse effects that occur more frequently in patients treated with interferon/ribavirin combination therapy, compared with interferon monotherapy, include nausea, rash,

Fig. 1. Comparison of Hemoglobin Level Between r-HuEPO and No r-HuEPO Groups.



dry skin, pruritus, noncardiac chest pain, dry cough, and dyspnea (disproportionate to the degree of anemia). As with anemia, many of these adverse effects, if judged sufficient to alter treatment at all, can be handled by dose reduction rather than treatment discontinuation. Some, such as rash, may not reappear at the original level of intensity, even if the dose is escalated back to the initial treatment level. Rash may be improved by steroid cream, and anecdotal reports suggest possible benefits of bronchodilators for cough.

Survey Findings

Survey respondents indicated that hemolytic anemia (rating, 4.5 on a scale of 1 = least important to emphasize to 5 = most important to emphasize) and fatigue (rating, 4.0) are the adverse effects of combination therapy that they stress the most when communicating with a patient who is considering combination therapy (in this hypothetical case, a previous nonresponder to interferon monotherapy). Clinicians also mention the side effects of thyroid dysfunction (rating, 3.8) and thrombocytopenia (rating, 3.3). They put less emphasis on the side effects of cough (rating, 2.8) and rash (rating, 2.6).

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VI. Special Challenges in Coinfected Patients

There are a number of special patient populations that pose particular challenges to clinicians who treat hepatitis C virus (HCV) infection. In this section, four of these populations are briefly discussed: nonresponders to therapy, patients with cirrhosis, patients with extrahepatic manifestations of HCV infection, and HIV-infected patients with chronic HCV and hepatitis B virus (HBV) infections.

Nonresponders

Until new therapies become available, many physicians who treat HCV infection are considering long-term maintenance therapy with interferon for patients who do not achieve a sustained response to initial treatment. The goals of maintenance therapy are to:

- Improve hepatic histology
- Delay progression to cirrhosis
- Decrease the risk of hepatocellular carcinoma (HCC)
- Avoid the need for liver transplantation
- Improve life expectancy

Improvement or stabilization in hepatic histology after treatment occurs in about 60% of patients in studies of interferon, even among patients who fail to achieve a sustained virologic response.^{1,2} For example, in a comparison of 185 interferon-treated patients with 102 untreated controls, a statistically significant percentage of treated patients experienced decreased or stable fibrosis compared with controls, and a significantly smaller percentage of treated patients versus controls experienced worsening of fibrosis (Table 1).

Table 1. The Effects of Treatment With Interferon on Fibrosis

	Treated	Controls	P Value
Increased fibrosis	22%	56%	<0.0001
Decreased fibrosis	23%	8%	0.002
Stable fibrosis	55%	36%	0.003
Rate of fibrosis (before F/U)	0.103 U/year	0.213 U/yr	<0.001
Rate of fibrosis (after F/U)	0.000 U/year	0.133 U/yr	NS

F/U = follow-up, NS = not significant

Reprinted from Sobesky R, Mathurin P, Charlotte F, et al. Modeling the impact of interferon alpha treatment on liver fibrosis progression in chronic hepatitis C: a dynamic view. *Gastroenterology*. 1999;116:378-386. © 1999 and 1998 by American Gastroenterological Association.

In the single published study examining long-term maintenance therapy, Shiffman et al³ randomized 53 virologic nonresponders who demonstrated histologic improvement posttreatment to 30 months of interferon maintenance therapy (n = 26) or observation (n = 27). Maintenance

Fig. 1A. Maintenance Therapy: Fibrosis.

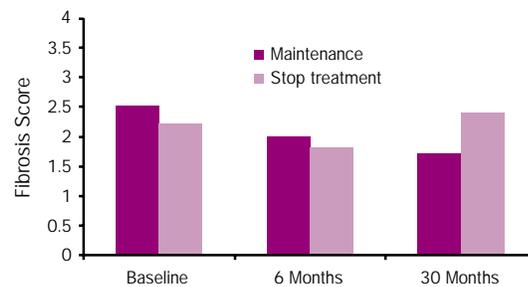
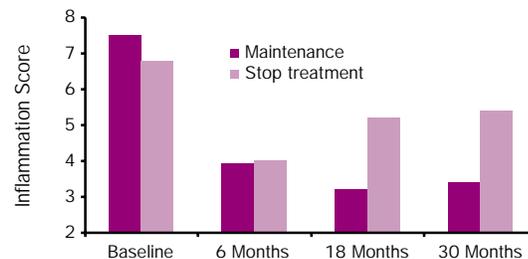


Fig. 1B. Maintenance Therapy: Inflammation.



Reprinted from Shiffman ML, Hofmann CM, Contos MJ, et al. A randomized, controlled trial of maintenance interferon therapy for patients with chronic hepatitis C virus and persistent viremia. *Gastroenterology*. 1999;117:1164-1172. © 1999 and 1998 by American Gastroenterological Association.

therapy had a beneficial effect on histology. In the maintenance therapy group, fibrosis score remained stable, whereas in the observation group, fibrosis score increased, ultimately reaching pretreatment levels (Fig. 1A). A similar phenomenon was observed with inflammation scores (Fig. 1B).

The decision to continue interferon in nonresponders must be individualized and should take into consideration how well the patient has tolerated treatment, pretreatment degree of inflammation and fibrosis, and the patient's risk factors for disease progression.

Survey Findings

Survey respondents believe that maintenance therapy has been shown to improve fibrosis score (rating, 4.4 on a scale of 1 = strongly disagree to 5 = strongly agree) and inflammation score (rating, 4.3), but not necessarily survival (rating, 2.9).

Patients With Cirrhosis

A presumptive diagnosis of cirrhosis is made in the presence of abnormal liver enzyme levels, evidence of liver insufficiency, clinical evidence of portal hypertension, and a known etiology for liver disease (eg, HCV infection). A liver biopsy is the only way to make a definitive diagnosis. In certain patients with signs and biochemical features of advanced cirrhosis, liver biopsy may not be necessary.

The most important determinant of outcome in patients with cirrhosis is Child-Pugh class, which is based on clinical parameters (Table 2). All patients should have this class determined routinely at each clinical visit.

Patients classified as Child-Pugh class A (compensated cirrhosis) have a good prognosis and, unless there is a major contraindication, should be treated with pharmacologic therapy. Treatment with interferon/ribavirin produces sustained

Table 2. Child-Pugh Classification of Severity of Liver Disease

Points Assigned per Parameter	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	≤2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.3	<2.8
Prothrombin time (seconds over control)	1–3	4–6	>6
INR	<1.7	1.8–2.3	>2.3
Encephalopathy	None	Grades 1–2	Grades 3–4
Modified Child-Pugh score*	5–6	7–9	10–15
Grade	A	B	C
Degree of disease	Well-compensated	Significant functional compromise	Decompensated
Patient survival			
1-year rate (%)	100	80	45
2-year rate (%)	85	60	35

*Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy.

response rates in up to 38% of patients with stage 3/4 fibrosis.^{4,5} As discussed above, patients who do not respond to treatment may be candidates for maintenance therapy, as interferon has been shown to significantly reduce the risk of HCC and decompensation and to improve survival (Table 3).⁶ For example, Nishiguchi et al⁷ randomized 90 HCV-infected patients with compensated cirrhosis to interferon (6 MU t.i.w. for 12–24 weeks) or symptomatic treatment. Over 2 to 7 years of follow-up, HCC was detected in 4% of interferon-treated patients versus 38% of controls ($P = 0.002$).

Table 3. Effect of Interferon on Cirrhosis

	Cumulative Probability at 4 Years		P Value
	IFN	No IFN	
HCC	4.4%	23%	<0.001
Decompensation	11%	38%	<0.001
Survival	92%	63%	<0.0001

Predictors of survival: IFN therapy, albumin <3.4 g/dL

HCC = hepatocellular carcinoma, IFN = interferon

Reprinted from Serfaty L, Aumaitre H, Chazouilleres O, et al. Determination of outcome of compensated hepatitis C virus-related cirrhosis. *Hepatology*. 1998;27:1435-1440. © 1999 and 1998 by American Gastroenterological Association.

Patients with Child-Pugh class B (7–9 points) or C (≥10 points) are rarely candidates for pharmacologic therapy but may be appropriate candidates for transplant evaluation. The role of liver transplantation in patients with end-stage liver disease has not been evaluated in HIV-infected patients but is currently being considered at some medical centers.

Regardless of Child-Pugh class, routine clinical care of patients with cirrhosis is essential. Such patients should be vaccinated against hepatitis A and B, as well as pneumococcus and

influenza. The patient's current medications should be reviewed, keeping in mind that antihypertensive agents may no longer be needed and that therapies with hepatotoxic potential should be avoided. Education is an important component of care. Points to emphasize include:

- Total abstinence from alcohol
 - Use no more than 2 g/day of acetaminophen; do not use at all in alcoholics
 - Avoid using nonsteroidal anti-inflammatory drugs, especially if ascites are present
 - Avoid raw seafood, which is a risk factor for a potentially lethal *Vibrio vulnificus* infection and hepatitis A virus
 - Avoid iron and vitamin A supplements, which accumulate in the liver
- Nezam H. Afdhal, MD, endorses an aggressive approach to screening patients with cirrhosis:
- Perform endoscopy every 2 years to check for varices
 - Prescribe nonselective β blockers, such as nadolol or propranolol, for all patients with varices
 - Screen for hepatoma using ultrasound (every 6 months) and serum markers, such as alpha-fetoprotein (every 3 months)

Survey Findings

Survey respondents rated HCV infection (rating, 4.4 on a scale of 1 = not likely to 5 = very likely) as one of the most likely causes of liver injury in patients with cirrhosis, followed by HBV infection (rating, 4.2) and hepatotoxic medications (rating, 4.2). They considered hepatic iron (rating, 3.8) and hepatic fat (rating, 3.4) to be other possible but less likely causes.

Patients With Extrahepatic Manifestations of HCV Infection

HCV replicates efficiently only in hepatocytes. Yet, more than 27 extrahepatic manifestations of HCV infection have been described. Most of these remain unconfirmed, but HCV does have demonstrated pathogenic involvement in mixed cryoglobulinemia (MC). Although it is plausible that immunologic features of HCV infection may be responsible for other disease manifestations (eg, autoimmune thyroiditis, rheumatoid arthritis), most studies on these diseases are small and are limited by patient selection biases; thus, correlations between HCV infection and most extrahepatic manifestations other than MC are currently tenuous.

About 90% of type II cryoglobulins are secondary to HCV infection, and about 80% have restricted monoclonal rheumatoid factor (mRF).⁸ In the United States, cryoglobulins are found in <5% of all HCV-infected persons, 70% of those with palpable purpura, and 30% of those with liver disease.⁸ Palpable purpura are the hallmark of MC, occurring in 82% of cases.⁸ These lesions appear to be due to complexes of HCV, mRF, and IgG formed in situ. In contrast, HCV has not been detected in glomerular or nerve lesions. Other clinical manifestations of MC are shown in Table 4.

There is no standard therapy for mixed cryoglobulinemia secondary to HCV infection. Vincent Agnello, MD, uses an open-ended adaptation of an interferon alfa-2b monotherapy

Table 4. Clinical Manifestations of Mixed Cryoglobulinemia

Manifestations	Patients (%)
Purpura	82
Arthralgia	42
Weakness	45
Liver involvement	42
Renal involvement	34
Peripheral neuropathy	26
Raynaud's phenomenon	22
Sicca syndrome	6
Female gender	66
Mean age (years)	52.5

Table from "mixed cryoglobulinemia and other extrahepatic manifestations of hepatitis C" by Liang TJ, Hoofnagle JH in *Hepatitis C*, copyright © 2000 by Academic Press, reproduced by permission of the publisher.

regimen proposed by Casato et al⁹ consisting of 3 MU q.d. for 3 months, then 3 MU t.i.w. until serum HCV RNA and cryoglobulins are undetectable. In this regimen, immunosuppressive therapy is used only for malignant transformation. There are no data on interferon/ribavirin combination therapy in these patients. However, because the goal of retreatment is eradication of underlying virus, it is likely that combination therapy will be more effective than interferon alone.

Survey Findings

Survey respondents rated therapy of MC secondary to HCV infection on a scale of 1 = strongly disagree to 5 = strongly agree. Survey respondents thought the efficacy of interferon monotherapy and interferon/ribavirin would be similar to that in patients without MC (rating, 3.7). They also believe that elevated cryoglobulin levels in virologic responders to interferon alfa may be indicative of a malignant transformation in an mRF-producing B cell (rating, 3.5). Some believe that interferon alfa monotherapy regimens are the same as those used for HCV without MC (rating, 3.2), while fewer believed that immunosuppressive therapy should never be used (rating, 2.7).

Chronic HBV and HCV Infections in HIV-Infected Persons

Another important issue among HIV/HCV-coinfected patients is the concurrent management of HBV infection. In one study of HCV+ patients who were HBsAg-, HBV DNA was detected by PCR in 33%.¹⁰ Furthermore, HBV was detected in 47% of those who failed interferon therapy versus only 25% of those who responded,¹⁰ suggesting that HBV coinfection reduces the likelihood of a sustained response to treatment for HCV infection. In HIV-infected patients, immune reconstitution has been associated with severe flares of previously inactive HBV.¹¹

Interferon alfa is widely used for the treatment of patients with HBV infection and has been shown to be equivalent to lamivudine in terms of efficacy in patients without HIV infection. Few data on treatment of HBV infection with interferon in HIV-infected patients are available. Advantages of interferon include:

- Short duration of therapy (4 months)
- $\geq 30\%$ HBeAg loss in patients without HIV infection¹² (data

are lacking in HIV+ patients; two very small pilot studies suggest HBeAg loss in 20%¹³ and seroconversion in 60%¹⁴)

- Higher response in patients with high ALT and low HBV DNA levels
- 10% HBsAg loss in patients without HIV infection¹²
- No mutations
- Documented long-term improvement in natural history¹²

Disadvantages of interferon as first-line therapy for HBV infection include the inconvenience of injection, side effects, and limited efficacy in select populations (eg, Asians, those with precore mutations, patients with decompensation, and immunosuppressed patients).

Lamivudine, a reverse transcriptase (RT) inhibitor developed for the treatment of HIV infection, is also effective for treatment of HBV infection. Lamivudine prevents replication of HBV because, like HIV, HBV replicates by means of an RNA intermediate using an RT. Advantages of lamivudine as first-line therapy are:

- Convenient administration
- Few adverse effects
- $\geq 30\%$ HBeAg loss; 16% to 18% HBeAg seroconversion in patients without HIV infection¹⁵; approximately 22% HBeAg loss in HIV-infected patients¹⁶
- Histologic response in majority¹⁵
- Effectiveness in subpopulations that fail to respond to interferon

Unfortunately, although lamivudine has the advantage of treating both HBV and HIV infections in coinfecting patients, its use as a single anti-HIV agent is not recommended because it leads to rapid, high-grade resistance by HIV. This resistance is conferred by a mutation of the YMDD motif (which is analogous to the HIV RT M184V mutation). Other disadvantages of lamivudine include a longer duration of treatment versus interferon and the fact that it does not produce HBsAg loss.¹⁵

Adefovir, an investigational nucleoside that inhibits RT, has also been found to be highly active against HBV infection. Cross-resistance between lamivudine and adefovir has not been demonstrated at this time.

Conclusions

Initial results on maintenance therapy are promising, and additional studies are under way. Many clinicians currently consider maintenance therapy for patients who fail to sustain a virologic response to treatment, especially in patients with stage II or greater fibrosis. Halting fibrosis prior to the onset of cirrhosis should decrease the rates of HCC, death, and liver transplantation. In patients who already have cirrhosis, sustained response to therapy is still possible, and maintenance therapy may have even greater value in those who do not respond. Most patients with asymptomatic cirrhosis will live more than 15 years, so general medical care and preventive medical strategies are crucial.

Although many extrahepatic manifestations have been reported, MC is one of the few that has a clearly demonstrated correlation with HCV infection. No standard therapy exists for MC, and data on interferon/ribavirin in this population are lacking. Some experts consider interferon monotherapy regimens to be appropriate.

HBV infection should also be considered in patients with HIV/HCV infections. The presence of HBV may reduce the likelihood of response to therapy. However, chronic HBV infection is treatable with either interferon or lamivudine.

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Overall Conclusions

Coinfection with HCV and HIV is a serious problem in the United States. The impact of HCV infection among patients who are infected with HIV is expected to increase as advances in antiretroviral therapy extend the lifespan of these patients. Infectious disease specialists can help to counter this trend by identifying HIV patients coinfecting with HCV, evaluating liver disease, treating patients who are appropriate candidates for interferon α -2b and ribavirin combination therapy, and referring patients who need neuropsychiatric management.

Management of HIV infection in coinfecting patients generally is carried out in the same way as for patients with HIV alone; HCV infection is not a contraindication to HAART therapy. Although there is some increased risk of hepatotoxicity associated with antiretroviral medications, coinfecting patients can usually tolerate these medications. HAART should not be withheld from most coinfecting patients, although other potentially hepatotoxic drugs should be used with care, and patients must be counseled against the use of alcohol. Treatment of HIV

usually begins first, although in some cases it may be necessary to begin by treating the HCV infection (eg, patients with advanced hepatitis but in the early stages of HIV infection).

Coinfecting patients must receive adequate treatment for their HCV infection. Patients should be screened for psychiatric disorders, especially depression, before initiating interferon α -2b/ribavirin combination therapy. The goal of HCV treatment is defined by the patient's immunologic status. For patients with stable HIV disease, the goal is HCV eradication, and these patients should be treated in the same way as patients not infected with HIV. For patients with low CD4 counts, the treatment goal is to improve the immune status using antiretroviral medications while reducing the progression of liver disease and improving quality of life.

The management of coinfecting patients has undergone rapid evolution in recent years as effective combination therapies have emerged for both HCV and HIV infection. As a result, coinfecting patients are living longer and in better health than in the past. Infectious disease specialists can make a valuable contribution by taking a leadership role in addressing HCV infection in coinfecting patients.

Expert Perspectives: Strategies for the Management of HIV/HCV Coinfection

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CME Posttest

1. The high prevalence of coinfections with HIV and hepatitis C virus (HCV) is attributed largely to transmission via:
 - a. Intravenous drug use
 - b. Heterosexual sex
 - c. Mother-to-infant transmission
 - d. Homosexual sex among men
2. HIV-infected patients coinfecting with HCV:
 - a. Account for only about 6% of HIV-infected patients
 - b. Have the same mortality rate as patients infected with HIV alone, because AIDS is almost always the cause of death
 - c. Have a more rapid rate of progression to fibrosis/cirrhosis compared with patients infected only with HCV
 - d. All of the above
3. With reference to the viral characteristics of HIV and HCV, which of the following is **true**?
 - a. HIV and HCV are both single-stranded RNA viruses
 - b. HIV replicates faster than HCV
 - c. In the absence of treatment, HIV and HCV viral loads progressively rise in persons with chronic infections
 - d. All of the above
4. Which of the following is **false** regarding the effects of treatment in HIV/HCV coinfecting patients?
 - a. Interferon commonly produces an increase in absolute number of CD4 cells
 - b. Ribavirin inhibits the intracellular phosphorylation of zidovudine in vitro
 - c. Initiation of highly active antiretroviral therapy (HAART) may increase the HCV viral load for the first 3 to 4 months
 - d. Mitochondrial toxicity is most common with stavudine
5. Which of the following is **false** regarding HAART-related hepatotoxicity?
 - a. Only a minority of HCV/HIV coinfecting patients experience severe (grade 3/4) hepatotoxicity
 - b. It occurs with increased frequency in patients coinfecting with HCV
 - c. It tends to be more severe in patients coinfecting with HCV
 - d. It is most commonly associated with indinavir

(continued on next page)

CME Posttest (*continued*)

6. Interferon/ribavirin produces sustained virologic response (ie, viral eradication) in approximately what percentage of treatment-naive patients with HCV infection (HIV negative)?
 - a. 10%
 - b. 25%
 - c. 40%
 - d. 60%

7. Which of the following best describes the effects of anti-HCV treatment on hepatic histology?
 - a. Successful treatment results, at best, in stabilization of fibrosis
 - b. Histologic improvement is seen only in patients who achieve a sustained virologic response
 - c. Interferon/ribavirin, but not interferon monotherapy, is associated with histologic improvement
 - d. Histologic improvement has been observed in both responders and nonresponders to interferon therapy

8. The most powerful predictor of response to interferon/ribavirin therapy is:
 - a. Viral genotype
 - b. Viral load
 - c. Duration of infection
 - d. Stage of fibrosis

9. In a patient with HCV genotype 2 and low viral load, interferon/ribavirin:
 - a. Is not recommended
 - b. Should be given for 24 weeks
 - c. Should be given for 48 weeks
 - d. Should be given for 60 weeks

10. Response to interferon/ribavirin therapy should be assessed at:
 - a. 1 month
 - b. 3 months
 - c. 4 months
 - d. 6 months

11. If hemoglobin level decreases from 12 g/dL to 9 g/dL in a patient with average cardiac risk who is receiving interferon/ribavirin for treatment of HCV infection, the most appropriate strategy would be to:
 - a. Decrease the ribavirin dose to 900 mg/day
 - b. Decrease the ribavirin dose to 600 mg/day
 - c. Discontinue ribavirin
 - d. Discontinue both interferon and ribavirin

12. Patients with compensated cirrhosis:
 - a. Should receive regular screening (ie, ultrasound and alpha-fetoprotein measurement) for hepatocellular carcinoma
 - b. May achieve benefit in most cases from vitamin A supplements
 - c. Should be prescribed nonsteroidal anti-inflammatory drugs to decrease inflammatory activity
 - d. None of the above

Name _____

Expert Perspectives: Strategies for the Management of HIV/HCV Coinfection CME Evaluation

Release Date: July 12, 2000

Instructions

Please complete this Evaluation survey, along with the CME Posttest, and either mail or fax to
Projects In Knowledge, One Harmon Plaza, 6th Floor, Secaucus, NJ 07094; fax: **1-201-617-7333**.

1. Please rate the extent to which you achieved the learning objectives:
- | | <i>Excellent</i> | <i>Very Good</i> | <i>Good</i> | <i>Satisfactory</i> | <i>Poor</i> |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| • Recognize the magnitude of the problems of hepatitis C virus (HCV) infection and HIV/HCV coinfection | <input type="checkbox"/> |
| • Compare and contrast disease paradigms in HIV and HCV infection extrapolating lessons learned in HIV to the care of patients with HCV infection or HIV/HCV coinfections | <input type="checkbox"/> |
| • Identify appropriate candidates for treatment | <input type="checkbox"/> |
| • Develop strategies for managing HIV infection in coinfecting patients using highly active antiretroviral therapy (HAART) | <input type="checkbox"/> |
| • Describe current standards for treatment of HCV infection and ongoing management | <input type="checkbox"/> |
| • Develop strategies for managing HCV infection in coinfecting patients using interferon/ribavirin | <input type="checkbox"/> |
| • Manage adverse effects of interferon and ribavirin to allow optimum treatment outcomes | <input type="checkbox"/> |
| • Develop strategies for managing special challenges in HIV/HCV coinfections, including nonresponders to interferon/ribavirin, cirrhosis, extrahepatic manifestations, and hepatitis B virus coinfection | <input type="checkbox"/> |
2. Please rate the overall value of this print-based CME activity. Excellent Very Good Good Satisfactory Poor
3. Is this activity free of commercial bias? Yes No
4. Do you anticipate making any changes to your practice as a result of this activity? Yes No Maybe
If "yes" or "maybe," please describe: _____
5. Please indicate how long it took you to read the entire monograph and complete the posttest, and evaluation:

6. Please rate the level of the material presented: Just Right Too Advanced Too Basic
7. For each section in *Expert Perspectives: Strategies for the Management of HIV/HCV Coinfection*, please indicate your level of agreement:
(4 = Strongly Agree; 3 = Agree; 2 = Disagree; 1 = Strongly Disagree)
- | | The material was interesting | The material helps me manage patients with HCV/HIV |
|---|------------------------------|--|
| I. HIV/HCV Coinfections: Magnitude of the Problem | _____ | _____ |
| II. HCV Virology: Important Lessons Learned from HIV | _____ | _____ |
| III. Management of HIV Infection in HCV-Infected Patients | _____ | _____ |
| IV. Management of HCV Infection in HIV-Infected Patients | _____ | _____ |
| V. Managing Side Effects of Interferon and Ribavirin | _____ | _____ |
| VI. Special Challenges in Coinfecting Patients | _____ | _____ |
8. Which educational formats do you prefer?
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9. Do you currently use the Internet? If "yes," indicate how you most often use it:
- | | | |
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CME INFORMATION AND INSTRUCTIONS

Accreditation

Projects In Knowledge is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education (CME) for physicians.

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Release Date: July 12, 2000. This monograph has been planned, produced, and approved as a CME activity. This enduring activity will be reviewed within 3 years of this date and rereleased, or its designation for CME credit will become invalid.

Target Audience and Learning Objectives

This CME activity is designed for clinicians who treat HIV-infected patients and have an interest in the assessment, treatment, and ongoing management of patients with HIV/HCV coinfection.

After completing this activity, the physician should be able to:

- Recognize the magnitude of the problems of HCV infection and HIV/HCV coinfection
- Compare and contrast disease paradigms in HIV and HCV infection, extrapolating lessons learned in HIV to the care of patients with HCV infection or HIV/HCV coinfection
- Identify appropriate candidates for treatment
- Develop strategies for managing HIV infection in coinfecting patients using highly active antiretroviral therapy
- Describe current standards for treatment of HCV infection and ongoing management
- Develop strategies for managing HCV infection in coinfecting patients using interferon/ribavirin
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- Develop strategies for managing special challenges in HIV/HCV coinfections, including nonresponders to interferon/ribavirin, cirrhosis, extrahepatic manifestations, and hepatitis B virus coinfection

Estimated Time for Completion: 2 hours

For CME Credit

To receive documentation of your participation, complete the following steps:

1. Read this publication carefully.
2. Complete the CME Posttest, selecting the most appropriate choice for each statement.
3. Complete the CME Evaluation.
4. Send photocopies of the Posttest and Evaluation to Projects In Knowledge, One Harmon Plaza, Secaucus, NJ 07094, or fax to (201) 617-7333 before July 12, 2003.

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