Hepatitis C Virus/Human Immunodeficiency Virus Coinfection: Clinical Management Issues

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The use of highly active antiretroviral therapy (HAART) has extended the healthy lifespan of patients infected with human immunodeficiency virus (HIV); deaths among people with AIDS declined for the first time in 1996, after the institution of this therapeutic approach. As the life expectancy of HIV-infected patients increases, greater attention will need to be focused on the recognition and management of potentially severe concurrent illnesses that may increase their mid- to long-range morbidity and mortality. The incidence of infection by hepatitis C virus (HCV) is increased among patients with HIV disease, reflecting shared epidemiological risks. HCV not only may have an impact on the health status of HIV-infected patients but also may decrease their quality of life and increase their health care costs. Although clinicians have been reluctant to treat viral hepatitis C in the HIV-infected population, this therapeutic nihilism is unwarranted. The majority of studies have concluded that treatment of hepatitis C in HIV-infected patients results in an initial efficacy and long-term response similar to those in the HIV-seronegative population. Furthermore, treatment of HCV infection in HCV/HIV-coinfected patients may improve tolerance for antiretroviral medications. Physicians caring for patients with HIV infection require up-to-date information to make rational decisions regarding HCV coinfection to ensure that morbidity and mortality are minimized and that quality of life and medical care costs are optimized.

Infection with hepatitis C virus (HCV) is even more prevalent than that with HIV; according to the Centers for Disease Control and Prevention (CDC), the prevalence of antibodies to HCV in the general population of the United States in early 1999 was 1.8%, corresponding to an estimated 3.9 million Americans infected with HCV. In comparison, the prevalence of HIV in the United States was estimated by the CDC to be 800,000–900,000. HCV not only may have an impact on the health status of HIV-infected patients but also may decrease their quality of life and increase their health care costs. The CDC estimates that the economic burden of HCV infection in the United States is $500 million a year (see the CDC homepage [http://www.cdc.gov]). In terms of mortality, a recent European study showed that chronic liver disease, especially that due to hepatotropic viruses, was the fifth leading cause of death among HIV patients admitted to the hospital over a 4.5-year period [1]. Furthermore, data from a post–protease treatment database of ~4000 patients (CHORUS) suggest that 39-year-old HIV-infected patients with CD4 cell counts >200/mm³ have almost-matched survival rates, compared to those of age-matched HIV-uninfected patients, but that the leading cause of non-AIDS–related death among these patients was liver disease [2].

In addition to the fact that both are major health issues, there are many important similarities between HIV and HCV infection. Both viruses have a single-stranded RNA genome and result in a subclinical, chronic infection. Each of these viruses is able to evade the host’s immune system, and each is naturally resistant to eradication through use of our present therapeutic approaches. Phylogenetically, the viruses are differentiated into clades (6 in the case of HCV [with 11 genotypes] and >11 for HIV), and both viruses further evolve in the human host to form quasi species, although viral evolution and genesis of viral quasi species is greater for HIV. In addition, the replication rate of each virus is extraordinarily high, with billions of HIV virions and trillions of HCV virions being produced daily.
HCV Transmission is Predominantly Parenteral

The risk of HCV transmission is far greater for patients who acquire HIV infection through the parenteral than for those who acquire it through the sexual route. It is estimated that 50%-98% of patients who acquired HIV though injection drug use are coinfefted with HCV. The incidence of HCV infection is also quite high (60%-85%) among HIV-infected hemophiliac patients who, in the past, were treated with nonvirus-attenuated clotting products.

Only half of all patients infected with HCV admit to a history of percutaneous exposure; sexual transmission is thought to play a role in some of the remaining cases. Despite the fact that a number of studies have addressed this issue, the role of homosexual and heterosexual transmission of HCV is still controversial; it is believed to occur but with low efficiency. Sexual transmission is a common mode of HIV transmission but is not as effective for HCV. Nevertheless, the prevalence of HCV antibodies in HIV-infected homosexual males is ~4%-8%, which is different from that in HIV-uninfected homosexuals [3]. However, this is still greatly increased from the prevalence in the general population.

Hepatitis C may also be transmitted, although likely less frequently, through heterosexual sex. Some studies have suggested that the presence of HIV also increases heterosexual transmission of HCV; 1 study showed male-to-female sexual transmission to be 5 times more likely in the presence of HIV [4]. Higher HCV viral loads may be responsible for this increased transmissibility, as has been noted in HIV-coinfected patients (table 1).

Vertical transmission of HCV from mother to child, which also appears to occur with low efficiency, may be facilitated by HIV coinfection [5]. In a study of 155 mothers infected with HCV, the risk of vertical transmission of HCV was 3.2 times greater for mothers coinfected with HIV than for those with HCV infection alone [6]. The risk of vertical transmission of HCV may be proportional to the maternal HCV viral load, which may be correlated with the degree of HCV viral load, which may be correlated with the degree of HIV-related immunosuppression. Some studies have not revealed an increased rate of vertical transmission among HCV/HIV-coinfected patients.

### Table 1. Proposed effects of HIV infection on hepatitis C virus (HCV) infection.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Description</th>
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<tr>
<td>Increased sexual and vertical transmission of HCV</td>
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<tr>
<td>Increased HCV viral load</td>
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<tr>
<td>Accelerated natural history of HCV disease</td>
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<td>Worsened hepatic damage due to HCV</td>
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<tr>
<td>Increased genomic activity of HCV (development of quasi species)</td>
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<tr>
<td>Increased risk of hepatotoxicity with HAART</td>
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<tr>
<td>No change in the efficacy of IFN-based therapy</td>
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**NOTE.** HAART, highly active antiretroviral therapy.

HIV Coinfection Accelerates the Natural History of HCV Disease

Despite a significant prevalence of infection, not every HIV-infected patient will invariably die of HCV-related hepatic disease. Of immunocompetent, HCV-infected patients, half develop chronic hepatitis and ~20% develop cirrhosis (figure 1), which occurs after 10–20 years of infection. In ~15% of the patients who develop HCV-related cirrhosis, hepatocellular carcinoma will increase. The immunosuppression associated with HIV significantly alters the natural history and clinical course of HCV infection. Compared with that due to hepatitis B virus infection, the hepatic damage due to HCV infection is believed to be more dependent on direct viral cytopathicity rather than predominantly due to the patient’s immune response. Still, cell-mediated immunity—specifically, expansion of Th1 clones that recognize multiple core epitopes of HCV—is also important in the elimination of HCV, but through the elimination of virally infected hepatocytes, it results in hepatic damage [7–9].

The decline in cell-mediated immunity associated with progressive HIV infection is believed to permit greater HCV replication and, consequently, greater infection and injury to hepatocytes, although there is a poor correlation between HCV plasma viral load and the degree of hepatic damage. Coinfection with HIV also probably alters the response of immune cells to HCV; when CD3⁺/CD30⁺ cells are infected with both HIV and HCV, their cytokine production is skewed toward an anti-inflammatory Th2 response rather than the protective Th1 response seen when cells are infected with HCV alone [10].

HCV is capable of escaping from immunologic control...
In a study by Thomas et al. [17], the rate of HCV replication was inversely correlated with the CD4 cell count, whereas in others there was no such correlation found that the HCV RNA load is inversely correlated with the course of chronic HCV disease [13, 14]. Some studies have shown that HCV RNA levels increased soon after patients become HIV-infected and remains higher than that seen in immunocompetent patients throughout the course of chronic HCV disease [13, 14]. Some studies have found that the HCV RNA load is inversely correlated with the CD4 cell count, whereas in others there was no such correlation [15–17]. In a study by Thomas et al. [17], the rate of HCV replication was >8 times faster in those HIV-coinfected patients, and HCV levels increased by 0.5 log each year. Eyster et al. [15] showed that HIV-coinfected patients had 10-fold higher HCV viremia levels than did HIV-uninfected patients. Moreover, in a follow-up study conducted over a 10-year period, the Eyster group [18] showed that HCV RNA levels tripled in the HIV-uninfected group but increased 58 times among HIV-infected individuals. Again, the pathogenic significance of these findings is unclear, since the correlation between HCV plasma load and histologic hepatic damage is poor.

A number of studies have suggested that the presence of HIV infection accelerates the course of HCV-related liver disease in HCV/HIV-coinfected patients. Bierhoff et al. [19] showed that histologic evidence of liver damage due to HCV is worsened in the presence of HIV; HCV/HIV-coinfected patients had a greater degree of fibrosis, which is the most important prognostic factor for development of cirrhosis and ultimately survival. Garcia-Samaniego et al. [20] also showed that HIV coinfection was associated with a higher histologic-activity score (piecemeal necrosis, portal inflammation, and fibrosis), compared with that for HIV-negative patients.

These pathologic findings appear to have clinical significance. Martin et al. [21] described 3 HCV/HIV-coinfected patients, all of whom rapidly developed cirrhosis within 3 years of acquiring HCV infection. Another study comparing HCV-infected with HCV/HIV-coinfected hemophiliacs showed a greater risk of liver failure in the HCV/HIV-coinfected patients (9% vs. 0%) [22]. The risk of liver failure in this study was inversely correlated with CD4 cell counts.

In a second study of 225 hemophiliacs with HCV, the HIV-coinfected patients had a 21-fold higher risk of hepatic decompensation than did the HIV-uninfected hemophiliacs, again correlating with declining CD4 cell counts [23]. Sanchez-Quijano et al. [24] showed that after 15 years of HCV infection, 25% of HIV-infected patients developed cirrhosis, compared with 6.5% of HIV-uninfected control subjects. Soto et al. [25], in a cross-sectional article that examined the effects of HIV on Spanish HCV-infected injection drug users, showed that 14.9% of HCV/HIV-coinfected patients developed cirrhosis after a mean of 6.9 years, compared with 2.6% (after 23.2 years) of the HIV-uninfected, HCV-infected patients.

Explanations other than higher HCV RNA levels have been suggested for the worsened natural history of HCV disease, including a higher incidence of infection with HCV genotypes 1a and 1b, which are resistant to treatment, and a greater incidence of infection with mixed HCV genotypes. The significance of different infecting genotypes is unclear, since this factor has not been found to correlate with the worsened histologic damage associated with HCV disease. Another possibility reflects the fact that HIV-infected patients use greater amounts of hepatotoxic medications, which may exacerbate the HCV-related hepatic disease. For instance, nucleoside analogues may result in severe hepatocyte-mitochondrial toxicity and have been implicated in lactic acidosis, steatohepatitis, and death due to liver failure [26].

Other factors that have been found to influence hepatic fibrosis in HCV/HIV-coinfected patients include the length of time infected with HCV and the ingestion of >50 g of alcohol per day [27]. Some studies have suggested that HIV infection does not effect progression of HCV infection [28]. All of these natural history studies are limited by the inability to precisely pinpoint the onset of HCV infection.

Although HIV appears to alter the natural history of HCV, it is less clear what effect HCV infection has on the natural history of HIV infection. HCV RNA has been identified in peripheral blood mononuclear cells; therefore, CD4 cells may represent an important reservoir of HCV, as well as of HIV. HCV-induced CD4 cell stimulation may therefore induce HIV replication. In an in vitro study, mononuclear cells coinfected with HCV and a murine retrovirus replicated hepatitis virus more rapidly and vigorously than they did in the absence of retrovirus [29].

Despite this theoretical and experimental evidence of an effect of HCV on HIV, most cross-sectional and longitudinal studies have not concluded that HCV infection accelerates the progression of HIV disease or shortens survival of these patients. Still, other studies have shown contradictory results. A study showed that the progression to AIDS, wasting, and death was accelerated among HCV/HIV-coinfected patients with CD4 cell counts >500/mm³ [30]. Other studies have revealed that progression to both AIDS and death was faster in patients infected with HCV genotype 1 than in patients infected with other genotypes [31].

### Hepatitis C Infection Limits Our Ability to Treat against HIV

Anecdotal evidence suggests that the presence of HCV infection increases the risk of hepatotoxicity to a number of antiretroviral drugs. Despite this, few studies have addressed whether the presence of HCV affects the development of hepatic damage due to antiviral agents.
HIV protease inhibitors have not been found to inhibit HCV replication [32]. In addition, the control of HIV to <400 copies of HIV-RNA per milliliter of plasma by anti-HIV medications has no effect on the HCV viral load. Instead, initiation of HAART has been noted to transiently increase the level of transaminases, as well as the HCV viral load, for the first 3–4 months, but these typically return to baseline over the ensuing 3–8 months [33]. Few studies have addressed whether HCV infection increases the liver toxicity associated with HAART. Until results of such trials are available, clinicians may be reluctant to treat HIV-infected patients with certain antiretroviral medications, for fear of inducing severe hepatic damage (table 2).

Many antiretroviral drugs are hepatotoxic; according to data found in the Physicians’ Desk Reference (PDR), hepatotoxicity due to antiretroviral drugs occurs at a frequency of 3%–12%, depending on the therapeutic agent. Zidovudine may be the most likely nucleoside analogue to cause severe steatohepatitis, but it is likely that the whole class of medications might be implicated. According to the PDR, indinavir appears to be the worst offender in the protease class, with saquinavir and nelfinavir seemingly relatively benign. Of the nonnucleoside reverse-transcriptase inhibitors, nevirapine seems to be the most hepatotoxic, followed by efavirenz and then delavirdine.

Each antiviral agent has a different potential to cause liver toxicity in the presence or absence of HCV. HCV infection may increase trough levels of protease inhibitors, especially ritonavir. In a study that examined the factors associated with hepatotoxicity in HIV-infected patients receiving nucleoside analogue therapy, Hernandez et al. [34] found that coexisting HCV infection, older age, and a lower CD4 cell count were contributory. Similarly, Rodriguez-Rosado et al. [35] found that HCV infection increased the hepatotoxicity due to HAART by 2.8-fold.

In the largest study to date, Sulkowski et al. [36] studied ~300 patients who were prescribed new antiretroviral therapies from 1996 through 1998. During therapy, transaminase levels increased in all patients, although severe hepatotoxicity (transaminase levels >5 times the upper limit of normal) was present in only 10% of patients, with the highest incidence among patients given ritonavir (30%). The incidence of hepatotoxicity of any grade was greater among patients infected with HCV (54% vs. 39%). Overall, among patients receiving antiretrovirals, excluding ritonavir, severe hepatotoxicity was seen in 9.4% of patients with chronic viral hepatitis, compared with 2.7% of those without viral hepatitis. However, most patients with chronic hepatitis did not have hepatotoxicity (88%).

Multivariate logistic analysis suggests that only ritonavir and a CD4 cell count increase >0.05 × 10^3 cells were associated with severe hepatotoxicity. In this study, 60% of instances of severe hyperbilirubinemia were due to indinavir use. Again, the incidence of severe hyperbilirubinemia was higher among patients with HCV coinfection than among patients with HIV

### Table 2. Interrelationships between highly active antiretroviral therapy (HAART) and hepatitis C virus (HCV) infection.

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<tr>
<th>HAART has no effect on HCV replication</th>
<th>All antiretrovirals may elevate liver-associated enzyme levels</th>
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<tr>
<td>The presence of HCV-associated elevations in liver-associated enzyme levels</td>
<td>May lead to hesitancy to treat with HAART</td>
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<tr>
<td>HCV/HIV coinfection increases risk of hepatotoxicity due to HAART</td>
<td>Ritonavir use is associated with severe transaminitis</td>
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<tr>
<td>Indinavir use is associated with severe hyperbilirubinemia</td>
<td>Mitochondrial toxicity due to nucleoside analogues may be exacerbated by HCV</td>
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infection only (5.1% vs. 1.4%). It may be surmised that the increased incidence of hepatotoxicity in HCV-infected patients receiving HAART may be due to enhanced CD8 cell activity with CD4 cell reconstitution; studies have not shown that the increase in hepatotoxicity is due to increased HCV replication [8, 37].

The synergistic hepatocellular damage between HCV and antiretrovirals may relate to the ability of each to cause mitochondrial damage [38]. Since the literature suggests that HCV coinfection increases the risk of hepatotoxicity from HAART, the presence of HCV infection limits our ability to care for HIV-infected patients. It is logical to infer that normalizing alanine aminotransferase levels and reducing HCV titer through anti-HCV treatment might increase the tolerance of HCV/HIV-coinfected patients to antiretroviral therapy, although this remains untested.

### The Presence of HIV Does Not Alter the Efficacy of Anti-HCV Therapy

Because of the effect of HIV on the natural history of HCV disease, infection with HCV should be treated as any other opportunistic disease, as has been suggested in the US Public Health Service Infectious Diseases Society of America 1999 guidelines [39]. Until recently, the only US Food and Drug Administration–approved treatment for chronic hepatitis C was IFN-α monotherapy. A standard dosing regimen of 3 million units (MU) thrice weekly for 6 months induces normalization of transaminase levels and histologic improvement in up to 50% of treated patients. However, of these initial responders, more than one-half relapse within 6 months after termination of treatment.

In all, IFN-α therapy induces a sustained response, with eradication of the virus and stable improvement of liver histologic findings in <20% of treated patients. The rate is even lower among patients infected with HCV genotype 1b, who constitute the majority of infected patients in the United States. Few study reports have described long-term results for so-called sustained responders, thus raising the question of how IFN-α affects the future development of sequelae of hepatitis C (e.g., cirrhosis and end-stage liver disease). The incidence of hepatocellular carcinoma may be reduced even if treatment fails [40, 41]. Patients whose HCV RNA clears after 6 months of treat-
ment with IFN-α and whose HCV is genotype 1a or 1b should be treated for at least 12 (and perhaps 18) months. Several factors may help predict which patients will respond to IFN-α: low pretreatment levels of HCV RNA, low genomic diversity, infection with a non-HCV 1b genotype, and low-grade pretreatment hepatic fibrosis. The latest explanation advanced for the low treatment success rate in the HCV genotype 1–infected patients is the observation that the E2 protein of the genotype 1 HCV envelope has sequence homology with the protein kinase PKR. This enzyme is responsible for the actions of IFN. The E2 protein of genotype 1 is a blocker of the action of IFN [42].

Another theory postulates that patients who fail to respond to IFN are genetically predisposed to a Th2 cytokine response to HCV, which is ineffective in inhibiting HCV replication [43]. A much simpler epidemiological explanation for the lack of response would be an increased incidence of occult hepatitis B virus coinfection, as shown by Cacciola [44]. It is unknown whether the newly described transfusion-transmitted virus, found with an increased prevalence in HIV-infected patients and those infected with HCV, also increases hepatic toxicity in these patients [45]. It appears likely that transfusion-transmitted virus–like hepatitis G virus does not influence the severity of liver disease, although this remains to be determined.

It is widely believed that HIV-coinfected patients respond poorly to IFN-α monotherapy, because of the higher HCV viral titers in these patients. Several studies, however, have shown that the biologic and histologic benefit of IFN-α therapy in HCV/HIV-coinfected patients (i.e., normalization of transaminase levels in 50% of treated patients) is not significantly different from that noted in HIV-uninfected patients. Most of the patients in these studies were parenteral injection drug users with high CD4 lymphocyte counts and without diagnosed AIDS.

A study showed an initial complete response in ~45% of HCV/HIV-coinfected patients treated with IFN-α therapy, which was sustained in 80% [46]. The majority of studies have not been as encouraging. In a study of 12 patients who had high CD4 lymphocyte counts and were treated with IFN-α therapy, only 1 patient (8.3%) had a sustained complete response after a 12-month follow-up [47]. Another prospective, controlled trial, which included 78 patients, showed a complete response after 8 months of therapy in 38% of HCV/HIV-coinfected patients, compared with a 47% response rate among HIV-negative patients [48]. This study, in addition to others, demonstrated a positive correlation between CD4 cell count and response to therapy.

Alternatively, a comparative study that examined treatment of HCV-infected, HIV-seropositive patients (IFN dose, 5 MU thrice weekly) and HIV-seronegative patients (IFN dose, 5 MU thrice weekly) for 6 months showed that complete response (44.1% vs. 47.4%) was similar immediately after completion, as was complete biologic response 12 months after cessation of treatment (23.2% vs. 24.3%) [49]. However, a sustained virologic response was observed in only 50% of HIV responders and 89.5% of HIV-uninfected responders.

In the majority of these studies, the side effect profile and tolerance of treatment were found to be no different between the HCV/HIV-coinfected patients and the HIV-uninfected patients. Use of IFN-α may result in a decrease in the CD4 cell count of HIV-infected patients. However, this decline is transient and reversible upon discontinuation of treatment, reflecting neutropenia, and does not appear to increase the risk of opportunistic infection.

Given the low sustained-response rate, use of IFN-α monotherapy has been largely abandoned in favor of combination therapy with ribavirin (table 3). Ribavirin, a guanosine analogue, is a broad-spectrum antiviral agent that targets both DNA and RNA viruses. When used alone, ribavirin will reduce alanine aminotransferase levels without significantly changing viral HCV RNA levels, a circumstance that suggests it does not affect viral replication. However, when used in combination with IFN-α, ribavirin reduces the rate of hepatitis relapse, which indicates enhancement of the antiviral activity of IFN-α.

Ribavirin may act on IFN-α–resistant subpopulations of virus or on intracellular reservoirs of HCV that are not accessible to IFN-α. Other postulated mechanisms include inhibition of viral-dependent RNA polymerase, inhibition of the 5′-CAP structure of viral messenger RNA, and inhibition of inosine monophosphate dehydrogenase. The most likely mechanism of action is that ribavirin increases production of Th1 cytokines and decreases production of Th2 cytokines. Combination therapy appears to be safe and more efficacious than IFN-α monotherapy when given to immunocompetent patients.

A recent large, randomized study demonstrated a superior sustained response in naive, HIV-seronegative patients to combination therapy for either 24 or 48 weeks, compared with the response in those patients receiving extended-duration IFN-α monotherapy [50]. Combination of ribavirin with IFN may
increase the sustained response rate to closer to 50%. This superior response has been demonstrated in all subgroups, including those infected with genotype 1, with high baseline viral load, or with pretreatment cirrhosis or bridging fibrosis.

The effect of IFN/ribavirin combination therapy has been encouraging in a small series of HIV-infected patients. In a recent report, Dieterich et al. [51] described 24 patients who were treated with combined IFN and ribavirin. They showed that after only 3 months, patients receiving combination therapy had decreased HCV RNA levels, from a median of 350,000 copies/mL to 600 copies/mL. After 6 months, the median HCV viral load remained at 600 copies/mL and had become undetectable in 5 (62.5%) of 8 combination-treated patients. Anemia was seen in 21% of combination-treated patients but was successfully treated with erythropoietin.

In a report presented at the same conference, Landau et al. [52] noted that combination IFN/ribavirin rendered HCV RNA undetectable in 10 (50%) of 20 patients after 6 months. In the majority of these patients, HCV RNA was undetectable at 3 months of treatment. In a Spanish study, Sauleda et al. [53] also showed a complete virologic response in 50% of HIV-infected patients treated with combination therapy. In each of these studies, combination therapy did not have a significant effect on the HIV viral load or CD4 cell count.

In the initiation of IFN-based therapy against HCV, the high incidence of adverse events is an important consideration. In a large percentage of patients, therapy is associated with mild to moderate adverse effects. Before treatment is begun, patients should be prepared for a decrease in their quality of life. The majority of patients receiving the drug will experience a self-limited, dose-dependent, flu-like illness that usually begins 2-4 h after the IFN dosing. The syndrome consists of mild fever, chills, headache, lethargy, arthralgias, and myalgias. These symptoms usually respond to treatment with acetaminophen and/or prednisone, and the severity appears to decrease after repeated dosing. These early side effects rarely limit the use of IFN.

Less common adverse events represent later manifestations of IFN therapy, appearing 2-6 weeks after initiation of treatment. They occur more commonly with high-dose therapy and include irritability, fatigue, depression, headaches, anorexia, nausea, rashes, and alopecia. Thrombocytopenia and leukopenia associated with this medication necessitate monitoring of blood cell counts but are generally reversible, and granulocyte colony-stimulating factor may be used as prophylaxis for neutropenia.

Bacterial infection associated with the immunosuppression induced by IFN therapy is among one of the most worrisome effects of therapy. Urinary tract infections, sinusitis, and bronchitis are seen with increased frequency in patients receiving this drug. More serious infections have also been noted; thus any sign of fever should be promptly evaluated. Despite the high incidence of adverse effects associated with the use of this agent, there does not seem to be an increase in the incidence of intolerance among HIV-infected patients.

One area of concern regarding the use of combination therapy for HIV-infected individuals is tolerance of the potential side effects of anemia and decreasing leukocyte count in this immunosuppressed population. The most serious side effect of combination therapy is hemolytic (ribavirin-related) anemia, which can be managed by ribavirin-dose reduction. A decline in leukocyte and platelet counts is also noted. Erythropoietin may prevent or reverse the anemia associated with this regimen [54].

There has been some concern about administering ribavirin to HIV-infected individuals because of potential inhibition of the phosphorylation of zidovudine and stavudine [55], although phosphorylation of dideoxynosine increases [56]. In studies published thus far, the HIV RNA levels have not changed when ribavirin was combined with either zidovudine or stavudine. However, the incidence of anemia was much higher than among HIV-uninfected individuals.

Other modalities may replace typical IFN-α-based therapy. IFN-α monotherapy may be replaced with longer-acting pegylated IFN (PEG-IFN). This IFN has been modified by attachment of a 43-kDa branched polyethylene glycol (PEG) moiety, resulting in sustained delivery but reduced clearance. PEG-IFN therefore has a half-life of ~54 h, compared with 8 h for routine IFN-α, and may be administered once weekly [57]. An initial study [57] suggested that for HIV-seronegative patients, the safety profile of PEG-IFN was similar to that of routine IFN, and PEG-IFN appears to have an efficacy equivalent or slightly superior to that of routine IFN monotherapy. Further controlled studies of this antiviral agent will be needed before further conclusions can be drawn; but with regard to HIV, the potential inhibition of zidovudine and stavudine phosphorylation by ribavirin makes use of PEG-IFN monotherapy very appealing.

Although studies of PEG-IFN have not been completed with an HIV-infected population, research is currently under way in the form of a phase III prospective multicenter trial examining PEG-IFN alone versus PEG-IFN plus ribavirin and IFN plus ribavirin.

Despite the advances in IFN-based therapy, other unique therapeutic modalities are sorely needed. In an interesting recent study, Schlaak et al. [58] showed that when 2 (28.6%) of 7 HCV/HIV-coinfected patients were treated with IL-2, the HCV RNA cleared (for 6 months in 1 patient and 11 months in the other). Although the proinflammatory effects of IL-2 therapy may theoretically have upregulated anti-HCV immune responses in these patients, large studies will be necessary to determine whether other immunomodulatory agents, in addition to IFN, should be considered in the treatment of HCV infection. Other new approaches that will soon be tested include the use of antisense technology, ribozymes, HCV-specific protease inhibitors, and helicase inhibitors. It is likely that future anti-HCV therapy will entail multiple combinations of medications with IFN-α.
Conclusions

In the preprotease era, the presence of hepatitis virus infection was not viewed with concern, but now that the healthy lifespan of these patients has increased substantially, many patients with concurrent hepatitis C will die of liver disease before succumbing to the effects of HIV. Realistic expectations of long-term survival with HIV disease, especially with early diagnosis and combination antiretroviral therapy, demand consideration of therapy for concurrent chronic viral hepatitis. Not only does HCV infection affect the health status of HIV-infected patients, leading to enhanced risk of mortality and mortality, but also the accompanying elevation of liver-associated enzyme levels limits our use of many medications effective in the treatment of HIV disease, because of the threat of worsened liver disease.

Research in the past 5 years has yielded new agents with greater efficacy, greater ease of use, and fewer adverse effects for patients with hepatitis C. The next several years are likely to be just as fruitful, with the development of many more agents. This opens the possibility of dramatically more effective combination therapy for HCV infection in the near future.

References