Coinfection with HIV and HCV: More Questions than Answers?

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Chronic infection with the hepatitis C virus (HCV) is a major public health threat in the United States and worldwide. By sharing some routes of transmission, persons infected with the human immunodeficiency virus (HIV) are at risk for coinfection with HCV. As a result, hepatic cirrhosis, end-stage liver disease, and hepatocellular carcinoma due to chronic infection with HCV are important causes of both morbidity and mortality in coinfected patients. The advent of highly active antiretroviral therapy improved the management of patients with HIV, leading to decreased morbidity and better survival. As patients infected with HIV live longer, their risk of long-term sequelae from chronic HCV increases. Coinfection with HIV may be associated with rapid progression of chronic HCV. In contrast, the effect of HCV on the natural history of HIV is less clear. Data regarding treatment of HCV in HIV-coinfected patients are limited.
(Pharmacotherapy 2000;20(12):1499–1507)

OUTLINE

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Prevalence of Coinfection

Approximately 4 million persons or 1.8% of the United States population have antibodies to hepatitis C virus (HCV), with approximately 2.7 million chronically infected with HCV RNA.[1] The prevalence of coinfection in human immunodeficiency virus (HIV)-seropositive persons was conservatively estimated to be 14.1%,[2] although rates as high as 56% were reported, depending on the cohort.[3, 4] Between 100,000 and 400,000 of the 800,000–900,000 persons infected with HIV in the U.S. potentially are coinfected with HCV. Investigators performed a retrospective, cross-sectional study of patients enrolled in two national studies in the adult AIDS clinical trials group.[5] This demographically broad cohort study revealed a coinfection rate of 35.6%. One observational open cohort study conducted at a Veterans Affairs HIV clinic determined a prevalence of 33% among 350 HIV-infected individuals.[6] Multivariate analysis identified intravenous drug use as the major predictor of HCV seropositivity. Another cohort study found a coinfection rate of 41.3% in over 1600 HIV-infected patients in an

urban HIV clinic.[7] Perhaps even more concerning is the high prevalence of coinfection in the nation's correctional facilities. A Texas Department of Corrections study reported 56% of 1862 HIV-positive inmates to be coinfected.[4] Hence, coinfection with HCV is prominent in HIV-infected patients, especially among past or current intravenous drug users.

The two viruses share several risk factors for transmission, including intravenous drug use, transfusion of contaminated blood products, and high-risk sexual behavior. The risk of coinfection depends on the route of transmission. Because HCV is spread more efficiently through blood-borne routes, HIV-seropositive hemophiliacs and intravenous drug users have a much higher risk of HCV (60% and 80% frequency, respectively).[8, 9] Hepatitis C RNA was detected in body fluids other than blood, including saliva and seminal fluid.[10] Approximately 8% of homosexual men who are HIV infected also have antibodies positive against HCV.[11] Conversely, prevalence rates are reported to be low in studies of long-term spouses of patients with chronic HCV infection. Evidence suggests that heterosexual transmission occurs, yet it is extremely inefficient.[12] Seroconversion as a result of occupational exposures of blood products through accidents with sharp items occurs at a rate of approximately 3%.[13] The risk of vertical transmission is relatively low (5%) compared with vertical transmission of hepatitis B (90%) and HIV (25%).[14, 15] However, coinfection increases the rate of vertical transmission to approximately 14%.[16, 17]

Diagnosis

Since most acute HCV and HIV infections are not recognized, screening methods are an important part of preventing long-term disease complications. Due to the high prevalence of coinfection, all persons infected with HIV should be screened for antibodies to HCV. Serum alanine aminotransferase (ALT) is a poor predictor of underlying liver disease, since progressive liver disease can occur despite persistently normal ALT levels.[18] Second- and third-generation enzyme immunoassay (EIA) tests are 95–99% sensitive for detecting antibodies to HCV in noncoinfected persons with risk factors or abnormal serum ALT, and is the initial screening test in most instances.[19] Unfortunately, EIA may produce false-negative results in recently exposed individuals and those who are immunosuppressed. In fact, it was estimated that 6–12% of HIV-positive persons who are coinfected with detectable hepatitis C viremia will not have an antibody response to EIA due to inability to mount an adequate immune response.[20–22] In high-risk or severely immunosuppressed persons, a negative EIA should be confirmed with a more sensitive qualitative or quantitative polymerase chain reaction test to detect HCV RNA directly.[22, 23]

Despite advanced serologic and molecular tests, histologic examination is still the gold standard to diagnose the extent of liver damage.[23] Persons at greatest risk of progression to cirrhosis are those with extraportal fibrosis, bridging inflammation, and necrosis on biopsy.

Molecular Biology of HIV And HCV

Both HIV and HCV are RNA viruses with high rates of viral production and mutation. The HCV is a single-stranded RNA virus of the Flaviviridae family. It replicates to produce approximately 10^{12} or 1 trillion viral particles/day, with an estimated serum half-life of 2.7 hours.[24] A tremendous amount of genetic diversification exists due to a high mutation rate, which results from frequent mutations during transcription and lack of proofreading activity in HCV RNA polymerase. The large rate of viral production and high mutation rate explain the existence of a family of closely related variants or quasi species existing in a single host. Genetic diversification of HCV led to a classification system of genotypes or clades based on Arabic numerals 1–6.[25]

The HIV is a double-stranded RNA virus of the Retroviridae family. Similar to HCV, it has a great deal of genetic variability as a consequence of a high rate of viral turnover and mutation. Approximately 10^9 viral particles are produced and excreted each day, with a half-life of about 6 hours.[26] Replication of HIV also is highly prone to error, resulting in several mutations and the existence of a quasi species. The heterogeneity of both HIV and HCV could explain the persistent infection by avoidance of immune recognition and resistance to drug therapy.

Natural History of HCV Infection

Noncoinfected Patients

A large percentage of noncoinfected patients carry the hepatitis C virus for an entire lifetime without experiencing significant liver damage.[27]

Approximately 85% of those acutely infected develop chronic, persistent infection.[18, 28] Of these, 20–30% will develop liver cirrhosis within 20–30 years.[29] After developing cirrhosis, the risk of progressing to hepatocellular carcinoma or decompensated cirrhosis greatly accelerates.[30] Numerous prognostic factors, including host, virus, and environmental variables, likely determine who will progress to severe liver damage and at what rate.

Factors determining the level of hepatitis C viremia in HCV infection are poorly defined. Interpatient viral loads are highly variable, and limited data exist concerning the viral load and correlation with disease progression. Yet, serum HCV RNA levels are predictive of response to treatment in patients infected with HCV alone. A correlation was seen between low pretreatment viral loads ($< 2 \times 10^6$ copies/ml) and virologic response to treatment with interferon and ribavirin.[31, 32] Other factors associated with disease progression are age at infection above 40 years, alcohol intake of 50 or more g/day, and male gender.[33, 34]

Coinfected Patients

Coinfected patients often have higher HCV RNA concentrations than those infected with only HCV.[35] A prospective cohort study showed significantly ($p<0.001$) higher HCV RNA levels in 468 coinfected patients (7.19 $\log_{10}$ copies/ml) than in 501 HIV-negative controls (6.73 $\log_{10}$ copies/ml) regardless of $CD4^+$ cell count.[36] Immunosuppression due to HIV enhanced replication of HCV in other studies as well.[37, 38]

Research from the Centers for Disease Control and Prevention shed new light on the problem of liver disease in patients infected with HIV.[39] Investigators examined the causes of death from the U.S. National Vital Statistics System from 1987–1997 and found a 10% death rate due to associated liver disease in persons who died with HIV infection in 1997. Causes of death included sequelae of chronic liver disease, non-A, non-B hepatitis, and nonalcoholic cirrhosis. It is possible that many of these patients were coinfected with HCV. These observations led the U.S. Public Health Service–Infectious Disease Society of America to mention chronic HCV infection in guidelines for prevention of opportunistic infections.[40] The guidelines stress the importance of screening for, and prevention of, HCV and vaccination against hepatitis A and B viruses in HIV-infected persons. The importance of monitoring for hepatotoxicity in coinfected patients also is discussed, as well as the increased rate of liver fibrosis and the possibility of treating HCV. Although HCV may not be an opportunistic infection in the classic sense, it plays an important role in the morbidity and mortality of coinfected patients.

According to retrospective studies on the effect of HIV on clinical progression of chronic HCV, HIV modifies the natural history of HCV infection.[41–43] In a case-control study, 122 coinfected patients were matched according to age, gender, daily alcohol use, age at HCV infection, and duration and route of HCV infection, with a control group of 122 HCV-positive, HIV-negative patients.[41] The rate of fibrosis progression was determined by dividing the fibrosis stage (determined by biopsy) by duration of HCV infection (years). Investigators found a significantly faster rate to liver fibrosis in coinfected patients (26 yrs) compared with patients infected with only HCV (38 yrs). Risk factors independently associated with more rapid progression were HIV seropositivity, alcohol consumption of more than 50 g/day, age at HCV infection above 25 years, and immunosuppression ($CD4^+ \leq 200$ cells/mm^3). The trend was toward a slower rate of fibrosis progression in patients receiving highly active antiretroviral therapy (HAART). Unfortunately, only 12% of coinfected patients were receiving HAART, and a statistically significant difference could not be determined. Other findings included the combined effect of alcohol use and immunosuppression on rate of fibrosis. The median time to fibrosis was 16 years in coinfected patients with $CD4^+$ counts of 200 cells/mm^3 or less who consumed more than 50 g/day of alcohol, compared with 36 years for those with counts above 200 cells/mm^3 who drank less than 50 g/day of alcohol.

Natural History of HIV in Coinfection

The effect of HCV on the course of HIV is disputed due to differences in study design and lack of data in patients receiving HAART. Studies reported both an increased risk of progression of HIV and no effect of HCV on HIV.[6, 44–47] In a large Veterans Affairs cohort, HCV had little influence on the progression of HIV to acquired imunodeficiency syndrome (AIDS) or death.[6] This study included more than 1800 HIV-infected patients from a large urban population who were part of a continuing cohort study. Investigators sought to determine the effect of HCV infection

on length of survival in patients with HIV infection. A subset of 350 subjects of the entire population was tested for antibody to HCV, resulting in a coinfection rate of 33%. The 115 coinfected patients were matched with noncoinfected patients according to age, gender, antiretroviral therapy, baseline viral load, and $CD4^+$ cell count. Using Kaplan-Meier survival curves, no differences were seen between groups for end points of time to AIDS and death from diagnosis of HIV. These results suggest that HCV infection had little influence on the severity or progression of HIV disease in this cohort. Unfortunately, only 20% of participants were receiving HAART and had received protease inhibitors for less than 1 year. Hence, the effects of HAART on the survival of coinfected patients could not be assessed. Another prospective cohort study found similar rates of HIV progression in coinfected compared with noncoinfected patients before the HAART era.[47]

A case-control study evaluated the effect of HCV infection on immunologic and clinical progression of HIV.[44] Retrospectively, 119 coinfected patients were matched according to age, gender, and $CD4^+$ count with 119 HIV-infected, HCV-negative controls. Clinical progression was defined as developing one of the following: 30% decrease in Karnofsky score, 20% loss of body weight, AIDS-defining illness, or death. Immunologic progression was defined as a decline in baseline $CD4^+$ cell count by at least half. The results were somewhat contradictory. Immunologically, no difference was seen between coinfected and noncoinfected patients. However, 23.1% of coinfected patients met criteria for clinical progression, compared with 13.4% of the HCV-negative group ($p<0.002$). The authors did not provide data concerning viral load that would help confirm clinical progression. Other limitations of this study were retrospective design and the fact that patients were followed from the first clinic visit, not from the time of HIV diagnosis.

A prospective study evaluated the effect of HCV and progressive liver disease on the natural history of HIV infection in hemophiliacs.[46] Progressive liver disease was defined as developing one or more of the following: sustained elevation in serum bilirubin, ascites, hepatic encephalopathy, esophageal or gastric varices, or histologic evidence of cirrhosis or hepatocellular carcinoma. Coinfected patients with progressive liver disease had a faster progression to AIDS and death than those without progressive liver disease. Again, limitations of this study were absence of viral load data and lack of HAART in the cohort. Nevertheless, coinfected patients were 3.6 times (95% confidence interval [CI] 1.3–10) more likely to have progressive liver disease than HCV-negative, HIV-positive patients. The most convincing evidence to date reveals little influence of HCV on progression of HIV disease. This deserves further study.

Observational studies reported an increased mortality rate in coinfected patients.[48, 49] One report characterized all deaths in a Bronx, New York, HIV clinic from April 1996–September 1997.[48] Thirty-five coinfected patients and 38 noncoinfected patients were matched based on age at death, alcohol use, duration of follow-up at clinic, therapy with antiretrovirals, and therapy with protease inhibitors. Even with small numbers, a significantly greater number of HCV-positive patients died (12/38) with $CD4^+$ counts greater than 200 cells/mm^3 than did HCV-negative patients (1/35, $p<0.002$). Causes of mortality were diverse and not directly due to HIV infection. Five of 12 patients died of advanced liver disease due to chronic HCV infection. Another report from an urban clinic consisting of 1100 patients listed 40 deaths occurring in 1998 and the first 9 months of 1999.[49] Patients who died in 1999 were more likely to have lower viral loads, higher $CD4^+$ cell counts, better adherence to therapy, and a response to HAART compared with those dying in 1998. The three most common causes of death in both years were AIDS-associated wasting, mycobacterial disease, and complications from HCV. Based on these data, mortality due to chronic HCV infection continues to be a leading cause of death in coinfected patients despite access to HAART.

The Impact of HAART in Coinfection

Combination regimens for HIV have vastly improved survival, with a reported 64% decrease in AIDS-related deaths in 1996 and 1997.[50] With improved survival, a number of acute and chronic toxicities are recognized as a result of HAART. For example, hepatotoxicity is a significant concern, especially in coinfected patients who are predisposed to liver disease.[51, 52] Liver toxicity with antiretrovirals has been known for several years and is not limited to one class of agents, although most reports implicate protease inhibitors.[53] A prospective study in an

urban HIV clinic sought to determine the frequency of severe hepatotoxicity associated with HAART and how it relates to hepatitis B or C infection.[54] Of 298 HIV-positive patients, 52% were coinfected and 71% were receiving protease inhibitors. Severe hepatotoxicity was defined as grade 3 (serum ALT 5–10 times upper limit of normal) or grade 4 (serum ALT > 10 times upper limit of normal). Regimens containing ritonavir were responsible for half of all cases of severe hepatotoxicity and had a 5-fold higher risk for severe hepatotoxicity than other regimens. Although hepatotoxicity of any grade was more common in coinfected than noncoinfected patients (54% vs 39%, p=0.009), coinfected patients were not more likely to have severe toxicity with ritonavir, suggesting that there is no indication to withhold protease inhibitors based solely on HCV status. Another important finding was that patients with increases in $CD4^+$ counts above 50 cells/mm^3 from baseline were most likely to have severe hepatotoxicity. This would suggest that immune reconstitution of cytotoxic T cell activity as a result of HAART may play a role in hepatotoxicity. Others noted similar occurrences in coinfected patients, with increases in HCV RNA and development of acute hepatitis with elevated serum ALT after responding to HAART.[55]

On the other hand, HAART may have beneficial effects on histologic progression of HCV. A group of 172 coinfected patients was examined to determine the impact of protease inhibitors on the rate of liver fibrosis progression.[56] At the time of histologic examination, 58 patients had received protease inhibitors for a mean of 14 months. The rate of fibrosis progression was determined by dividing fibrosis stage by duration of HCV infection. A high fibrosis progression rate was defined as less than 20 years. Based on logistic regression, $CD4^+$ counts below 200 cells/mm^3, alcohol consumption above 50 g/day, and no previous treatment with a protease inhibitor were all independently associated with a high fibrosis progression rate. Thus not only are protease inhibitors not more hepatotoxic in coinfected patients, they in fact may be beneficial in the long term.

Treatment of Chronic HCV Infection

Noncoinfected Patients

Interferon α (IFN-α) has been evaluated for the treatment of chronic HCV since the late 1980s.[57] Its success was limited, with virologic sustained response (SR) rates achieved in only 19% of those treated for 24 weeks at a dosage of 3 MU 3 times/week.[58] The rate of response is more disappointing in patients infected with genotype 1. It is estimated that up to 70–80% of infections in the U.S. are caused by genotype 1a or 1b[59] Duration of therapy from 48–96 weeks was associated with significant improvements in biochemical SR from 14–27% ($p<0.001$) by meta-analysis.[58, 60] Increasing the dosage of IFN-α to 5–10 MU 3 times/week resulted in higher initial clearance of HCV RNA, yet when dosages were decreased or stopped, relapse rates were similar to those with previous regimens.[61]

Standard dosages of IFN-α combined with ribavirin resulted in improved SRs in HCV-positive, HIV-negative patients, leading to combination therapy becoming the standard of care.[23, 31, 32] The SR rates were significantly greater (31–43%) with standard dosages of IFN-α combined with ribavirin 1000–1200 mg/day compared with standard-dosage IFN-α alone for both 24 and 48 weeks. As with IFN-α monotherapy, response rates are lowest in patients with genotype 1, high baseline viral loads ($> 2 \times 10^6$ copies/ml), and liver cirrhosis.[31, 32] Long-term data concerning the effect of treatment on morbidity and mortality are lacking. However, patients who achieve a biochemical and virologic SR at 6 months after therapy appear to have eradication of HCV and cure of disease.[62] Combination therapy with IFN-α and ribavirin in noncoinfected patients may delay liver disease progression even in the absence of a complete virologic response.[31, 32]

Adverse effects of treatments for HCV are diverse, ranging from cytopenias and influenza-like symptoms to frank neuropsychiatric disturbances, including suicidal ideation due to IFN-α. These adverse effects are well characterized in noncoinfected individuals.[63] Flu-like symptoms are the most common and predictable, and typically occur early in the course of therapy. Tolerance to these effects usually develops with subsequent doses during the first week of therapy. Hemolytic anemia is the major dose-limiting toxicity of ribavirin. It is characterized by a decrease in hemoglobin of 2–3 g/dl over the first 2 weeks, with stabilization by the fourth week in noncoinfected patients.[31]

Coinfected Patients

There has been reluctance to treat HCV in coinfected persons because of the long natural

history of HCV and early progression of HIV before the era of HAART. Limited data exist concerning the treatment of HCV in these patients. In a few small trials, treatment of HCV with IFN-α in standard or slightly higher dosages and durations (3–5 MU 3 times/wk for 24–48 wks) in coinfected patients led to similar rates of response as in HIV-negative, HCV-positive patients.[64–69] Unfortunately, these trials were conducted before the HAART era, and most patients were receiving zidovudine (ZDV) monotherapy for HIV infection. Patients tolerated IFN-α well, with the most common laboratory abnormality being a decrease in $CD4^+$ cell count. Coinfected patients with high $CD4^+$ counts (> 200 cells/mm^3) were most likely to have virologic or biochemical SR to therapy.

Published data concerning treatment with IFN-α plus ribavirin in coinfected individuals are not available; however, several trials are under way. An abstract reported 12-month follow-up results of combination therapy in 10 patients randomized to receive IFN-α 3 MU 3 times/week monotherapy and 11 to receive IFN-α plus ribavirin 800–1000 mg/day.[70] Median baseline HCV RNA was 5.0×10^6 and 3.25×10^5 copies/ml, respectively. Patients in the IFN-α arm were allowed to cross over to the combination arm after 12 weeks of therapy if HCV RNA was still detectable. After 12 weeks of treatment, the median HCV RNA in that group had decreased to 4.35×10^6 copies/ml (0/8 undetectable), whereas the combination therapy group had a decrease to 600 copies/ml (4/8 undetectable). After 12 months of therapy, the original combination group had an undetectable median HCV RNA value. The median value for the original IFN-α monotherapy group had 98,300 copies/ml after switching to combination therapy. The most common adverse effect was anemia, occurring in nearly 50% of patients receiving combination therapy.

A noncomparative, observational study reported a 45% SR after 24 weeks of combination therapy in patients who had either relapsed or had not responded to IFN-α monotherapy.[71] This was similar to the SR in patients who were not coinfected after 24 weeks of retreatment with the addition of ribavirin to IFN-α.[72]

In a study of the effect of IFN-α-ribavirin on HIV RNA and $CD4^+$ counts, baseline HIV RNA was 1500 copies/ml for the IFN-α group and fewer than 400 copies/ml for the combination group.[70] All patients in both groups achieved or maintained undetectable HIV RNA (< 400 copies/ml) after 12 months of therapy. Nineteen of 21 patients were treated with HAART; all regimens contained either ZDV or d4T. Based on data presented, there is little clinical relevance of the reported in vitro antagonism by ribavirin of thymidine analogs ZDV and d4T phosphorylation.[73] Unfortunately, randomization of this trial created bias in baseline characteristics of the two treatment groups. Other limitations were the large disparity between baseline HCV viral loads and $CD4^+$ counts of the two groups and lack of information concerning specific HCV genotypes and length of therapy in the 19 patients receiving HAART.

Table 1. Percentage of Patients HCV RNA Negative[70]

Drug and Dosage	No. of Patients	Week 12	Week 48	Week 72
IFN-α_{2a} 3 MU	21	17	19	5
PEG-IFN 45 µg	20	20	30	10
PEG-IFN 90 µg	20	55	40	30
PEG-IFN 180 µg	45	76	62	36
PEG-IFN 270 µg	40	60	60	30

The baseline $CD4^+$ count for the combination group was 544 cells/mm^3, compared with 190 cells/mm^3 for the IFN-α group. Also, the results presented were preliminary or end-of-treatment responses and not SRs 6 months after treatment. Finally, combination treatment for HCV caused a decrease in $CD4^+$ cell counts similar to reports with IFN-α monotherapy. Baseline $CD4^+$ counts dropped from a median of 544 to 237 after 3 months of therapy in the combination group and returned to 311 after 12 months of therapy. The monotherapy group had median $CD4^+$ cell counts drop from 186 to 139 after switching to combination therapy. This smaller absolute reduction may be due to the shorter duration of combination therapy in the original monotherapy group.

New Treatment Options

One strategy to increase the activity IFN-α is to attach IFN-α to polyethylene glycol (PEG). Attachment of the 40-kilodalton strand of PEG leads to a marked increase in half-life (100 hrs), permitting prolonged IFN-α activity while decreasing the dosing frequency to once/week. A randomized, multicenter, phase II study in 155 noncirrhotic, noncoinfected patients evaluated the safety and efficacy of pegylated INF-α_{2a} (PEG-IFN) 45, 90, 180, or 270 µg once/week compared with standard IFN-α_{2a} 3 MU 3 times/week in HCV-infected, HIV-negative

patients.[74] Patients were randomized according to genotype and HCV RNA. Sustained response rates 24 weeks after therapy with PEG-IFN 180 µg approached those of combination therapy with ribavirin (Table 1). Other factors leading to improved response were Caucasian race (34% vs 18%), HCV RNA less than 2 million copies/ml (44% vs 14%), and non-1 genotype (61% vs 21%). Tolerability of PEG-IFN was similar to that of standard IFN. Preliminary results of PEG-IFN are promising, with greater efficacy and equivalent safety compared with standard IFN monotherapy. Additional studies involving a different PEG-IFN and the combination of PEG-IFN with ribavirin in both noncoinfected and coinfected patients are in progress.

Comparing and Contrasting Treatment of HIV and HCV

Several important differences exist in treatment of HIV and HCV. Whereas HIV replicates through a DNA-intermediate, incorporating itself into the host genome, HCV does not use host DNA as an intermediate. Thus eradication of HCV infection is possible. In fact, for unknown reasons HCV may spontaneously become undetectable after acute infection in approximately 15% of patients.[18] Direct antiretroviral agents are an integral part of treatment of HIV. Hepatitis C virus contains many similar enzymes responsible for viral replication, including protease, helicase, and polymerase enzymes, that are potential targets for new drugs. Investigators have been hampered in their efforts to develop these agents due to absence of a cell culture system, although a system that relies on replication of HCV RNA in hepatoma cell lines recently was developed.[75] Although funding for HCV research is increasing, it is a mere 1/50 of the $1.8 billion slated to be spent on HIV in the year 2000.[2]

Several barriers to compliance exist with antiretroviral therapy, including intolerance, high pill burdens, storage issues, drug interactions, and cost. An important implication of nonadherence to anti-HIV therapy is drug failure leading to viral rebound and possible disease progression. Similar to HAART regimens, adherence to anti-HCV therapy is extremely important. Interferon-α-based therapy also has barriers that may limit adherence, including adverse effects such as flu-like symptoms, fatigue, neutropenia, and depression, and the necessity for parenteral administration.[62] The addition of IFN-α-ribavirin only adds to the high cost of HAART. Average wholesale price ranges from $6400–17,280, based on body weight and length of therapy.[76] This creates a dilemma for both health care systems and patients who cannot afford to treat both HIV and HCV.

Conclusion

Several questions remain unanswered regarding the efficacy and safety of treatment of coinfected persons. Ribavirin, a guanosine derivative, may enhance the anemia frequently seen in HIV disease due to the virus or specific antiretrovirals (ZDV). To complicate matters, $CD4^+$ counts may decrease dramatically after therapy with IFN-α and ribavirin. The reason for this is not known, but it is hypothesized that ribavirin may have more of an immunomodulatory effect as opposed to a direct antiviral effect in the treatment of HCV.[77] What will be the long-term immunologic implications of this drop in $CD4^+$ counts? Will $CD4^+$ counts return to baseline after completion of therapy? Typically, HIV-negative patients with genotype 1 and higher baseline HCV RNA respond better to 48 weeks of combination therapy than to 24 weeks.[31, 32] The combination of a higher viral burden and the high prevalence of genotype 1 in the U.S. may necessitate longer treatment durations in coinfected patients.

Clearly, HCV-related liver disease will continue to increase as patients continue to live longer with HIV infection. This is magnified by the fact that as the population of patients with HCV ages, HCV-related deaths are expected to triple to 38,000/year by 2010.[78] Based on shared risk factors for transmission, the HIV-infected population likely will be a large part of the increasing mortality due to chronic HCV. Treatment of HCV should be reserved for those at the greatest risk for progression to cirrhosis.[23] This includes patients with detectable HCV RNA, persistently abnormal serum ALT, and histologically moderate hepatic fibrosis. Coinfected patients seem to have a higher risk for hepatic fibrosis due to more rapid clinical progression of chronic HCV.[41–43] One goal of therapy against HCV is to eradicate serum HCV, thus slowing or possibly stopping the progression to cirrhosis and end-stage liver disease and carcinoma. Limited data indicate that the combination of IFN and ribavirin may improve the response to IFN in coinfected patients.

The future of treatment for HCV includes

agents with direct antiviral activity against HCV similar to antiretroviral therapy for HIV.[79] It is estimated that such a drug will be available within the next 10 years. Until then, agents such as PEG-IFN-α alone and in combination with ribavirin are expected to improve existing treatments. Whether or not HCV accelerates HIV progression is not clear. As patients survive longer with HIV disease, interactions among HCV disease, host-mediated immunity, and hepatotoxicity due to HAART will continue to be important issues in coinfected patients. It appears that patients with stable or slowly progressive HIV disease are the most likely to benefit from treatment of HCV due to potential enhancement of liver disease by HIV and higher probability of response to therapy for HCV.

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