Hepatitis C (HCV) infection occurs in as many as 33% of the patients with human immunodeficiency virus (HIV) infection. In view of their improved survival, liver disease will become more clinically significant in patients coinfected with HIV/HCV. Several studies in patients with hemophilia have shown that coinfected patients develop earlier and more severe liver disease, including hepatocellular carcinoma. In nonhemophilic cohorts, lower CD4 counts are associated with an increased prevalence of cirrhosis. However, HCV infection does not seem to alter the natural history of HIV infection in most cases. Human immunodeficiency virus coinfection in pregnant women increases the risk of perinatal HCV transmission 2-fold, with more than 25% of occurrences involving transmission of both viruses: cesarean delivery significantly decreases this risk. The expanded use of highly active antiretroviral therapy may lead to further improvement in morbidity and mortality from HIV infection. Thus, the management of coexistent HCV liver disease will need to be formulated. We suggest that alcohol be disallowed. Interferon and ribavirin in combination are likely to become the therapy of choice, particularly in coinfected patients with higher CD4 counts, lower HCV viremia, and non-1 genotype. During treatment, complete blood cell counts need to be closely monitored. Future controlled trials will determine the efficacy and safety of long-acting interferon preparations. Administration of highly active antiretroviral therapy, with the intent to prevent decreases in CD4 counts, seems crucial in stemming liver disease progression. However, some drugs have clear-cut hepatotoxic potential and patients with known liver disease should be closely monitored.

**BACKGROUND**

In the absence of human immunodeficiency virus (HIV) infection, the progression of hepatitis C (HCV) to cirrhosis is slow, but is accelerated by the use of more than 50 g of alcohol daily, male sex, older age at infection, longer disease duration, and coinfection with hepatitis B. These estimates are likely to represent a worst-case scenario, as the follow-up of patients with elevated transaminase levels or with more clinical symptoms formed the basis for the largest reported series. Indeed, patients with normal serum alanine aminotransferase levels have a much slower estimated progression of fibrosis.

More than 60% of the HIV-seropositive patients with a history of injection drug use, and about 4% of the HIV-positive homosexual patients are coinfected with the HCV. A Veterans Affairs Cooperative Study noted an overall anti-HCV antibody prevalence of 33%, confirming European data. In many cases, coinfection with HIV/HCV resulted in earlier instances of cirrhosis and liver failure. Because of the improved survival of patients with HIV, coinfection with HCV is likely to become a significant clinical problem in the future.

This article reviews the diagnosis and natural history of HCV infection in HIV-seropositive patients and summarizes data...
concerning sexual and perinatal transmission. It also examines the efficacy and adverse events of HCV therapy in this group of patients, and the impact of highly active antiretroviral therapy (HAART) on the course of hepatitis C.

METHODS

We searched the Ovid databases, including AIDSLINE and MEDLINE from January 1, 1993, to November 30, 1999, using the following key words: “hepatitis C,” “HCV,” “HIV,” “liver diseases,” “drug toxicity,” “antiviral therapy,” “therapy,” “interferon,” and “vaccination.” These key words were exploded and appropriate search combinations were performed. References were manually scanned for relevant articles published prior to 1993. Abstracts were included only if the complete data set was available to us. Relevant abstracts from the Seventh Conference on Retroviruses and Opportunistic Infections were also included. In this review article, patients with dual HIV/HCV infection are termed “coinfected patients” or “patients with HIV/HCV.” Articles concerning perinatal transmission were selected when they included both HCV-infected and coinfected pregnant women, to ensure uniformity of cohort definition and also because it is the most relevant to the current study. Articles concerning sexual transmission were selected only if the complete data set was available to us. Relevant abstracts from the Seventh Conference on Retroviruses and Opportunistic Infections were also included. In this review article, patients with dual HIV/HCV infection are termed “coinfected patients” or “patients with HIV/HCV.” Articles concerning perinatal transmission were selected when they included both HCV-infected and coinfected pregnant women, to ensure uniformity of cohort definition and also because it is the most relevant to the current study. Articles concerning sexual transmission were selected only if the complete data set was available to us. Relevant abstracts from the Seventh Conference on Retroviruses and Opportunistic Infections were also included.

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HCV RNA CONCENTRATIONS IN PATIENTS WITH HIV

To measure peripheral HCV RNA, most investigators have used serum samples. Serum must be separated from white and red blood cells soon after clot formation, as significant increases in HCV RNA levels occur when the serum is separated after 3 to 4 hours. Consequently, interpretation of studies giving insufficient data on specimen handling is difficult.

As a whole, patients with HIV/HCV have higher serum HCV RNA levels and liver HCV RNA levels than patients with HCV alone. In patients with HCV infection, serum HCV RNA levels increase by at least 0.5 logs after HIV seroconversion. A study in coinfection patients demonstrated that HCV RNA, including the RNA-negative strand (a true marker of HCV replication), is often found in extrahepatic sites. Production of HCV RNA outside of the liver could explain the lack of correlation between liver and serum levels, as assayed by different polymerase chain reaction–based methods.

An independent inverse correlation between serum HCV RNA levels and CD4 lymphocyte counts was predicted and, indeed, documented in 2 groups of coinfected patients. However, other studies demonstrated either a weak inverse correlation or no correlation between HCV RNA levels and CD4 counts.

The biological behavior of HCV appears to be different in the setting of immunosuppression. Significantly fewer HCV genome variations (quasi species) occur in patients with HIV infection than in immunocompetent patients. However, in coinfectected patients, more variability occurs in the HCV hypervariable region, resulting in more changes in the envelope amino acid sequence. Three groups found that coinfected patients with hemophilia may frequently undergo changes in the predominant genotype over time, even after heat-treated clotting factors were administered.

Thus, HIV coinfection is associated with increased HCV viral titers, possibly because of increased viral replication in a setting of immunosuppression. The absence of a convincing inverse correlation between HCV RNA levels and CD4 counts may be explained by the fact that peripheral CD4 counts do not reflect intrahepatic immunity. The significance of HCV sequence variations in coinfected patients remains to be determined.

NATURAL HISTORY IN PATIENTS WITH HEMOPHILIA

The use of liver failure as an end point in the natural history of HCV is unsatisfactory because of difficulties in defining failure. Elevations in the serum bilirubin level may be associated with opportunistic infections and with numerous medications used in HIV disease, independent of liver function. Patients with compensated cirrhosis should not be included in the definition of liver failure, as HCV-associated cirrhosis may follow an indolent course for years.

Some studies have not clearly ruled out concurrent hepatitis B infection or have even included patients with circulating hepatitis B surface antigen. Perhaps the major drawback is that very few studies attempted to quantify the patient’s alcohol consumption. This is a crucial piece of information since alcohol consumption is a major cofactor in the progression of liver disease in patients with HCV.

With few exceptions, articles presented no histologic data because of the sample population. The advantage of studying patients with hemophilia is the frequent availability of a known HCV-exposure date.
major studies included 165 coinfected patients: the coinfected patients developed hepatic decompensation or failure more frequently (8% and 14%, respectively) than HCV-infected controls without HIV (0% and 1%, respectively). The median follow-up was approximately 15 years in both studies. While it is tempting to conclude that HIV infection accelerated the progression of liver disease, it is difficult to discount possible cofactors, particularly alcohol use.

A recent study used the United Kingdom National Haemophilia Register data to assess the risk of death from liver disease and hepatocellular cancer in patients with hemophilia. Liver disease deaths constituted 5% of all deaths. The study cohort suffered mortality rates from liver disease and liver carcinoma (assumed to be due to HCV infection) that were higher than expected in the general population. In addition, coinfected patients who were contaminated between the ages of 25 and 44 years had a much higher likelihood of dying of chronic liver disease or cancer (17.1%) than patients with HCV infection only (2.2%). The difference was less marked in older patients, 18.7% in coinfected patients vs 14.3% in patients with HCV.

A smaller investigation showed that 4% of all deaths occurring in HIV-positive patients with hemophilia were due to liver disease. Although there was no convincing overall association between HCV positivity and mortality, patients with an indeterminate HCV antibody and more advanced immunosuppression experienced higher liver mortality. Two studies found no excess liver mortality in coinfected patients with hemophilia who had CD4 counts higher than 0.35 × 10^9/L. However, in patients with acquired immunodeficiency syndrome, 50% of deaths were due to liver disease. Since hepatic decompensation was clinically evident in patients with CD4 counts lower than 0.20 × 10^9/L, it may be inferred that liver fibrosis had progressed before marked immunosuppression occurred. In 2 studies, patients with hemophilia and HCV infection alone did not develop liver decompensation. On average, the time course from first HCV exposure to the onset of clinical liver disease has been calculated to be 15 to 20 years in coinfected patients with hemophilia. Historically, that outcome would be twice as likely and at least 10 years earlier than in patients with HCV only.

Interestingly, HCV genotype 1 is more common in coinfected patients compared with HCV-infected patients in Europe and in the United States. This fact has been used to explain, in part, the presumably worse prognosis in patients with HIV/HCV.

NATURAL HISTORY IN PATIENTS WITHOUT HEMOPHILIA

Hepatic tissue is more easily detected in patients without hemophilia. Coinfected patients with CD4 counts lower than 0.40 × 10^9/L display less piecemeal necrosis and portal inflammation. This finding corroborates the idea that HCV-induced liver disease is immune mediated. A recent report evaluated the factors associated with histologic severity in 59 HCV-infected patients, 48 patients (81%) being HIV coinfected who had CD4 counts higher than 0.20 × 10^9/L at the time of liver biopsy. Both HIV positivity and genotype 1b were significantly associated with hepatic fibrosis and piecemeal necrosis.

A Spanish study evaluating 547 liver biopsy specimens found that cirrhosis was present in similar percentages of HCV-infected patients (13%) and coinfected patients (12%). However, cirrhosis was found earlier, within 5 years of presumed HCV infection, in 4% of the coinfected group; thereafter, more patients in the HCV-infected group (21%) developed cirrhosis. Considering that the evaluation of alcohol use was unclear and that firm evidence has emerged that alcohol is strongly and independently associated with fibrosis in coinfected patients, interpretation of the study data must be cautious.

In an attempt to clarify the relationship between HIV and HCV, 2 groups used a simple mathematical formula to estimate the rate of hepatic fibrosis progression in patients with HCV. One study compared liver biopsy specimens from 84 patients with HIV/HCV with those of 120 patients with HCV infection alone. The 2 groups had comparable risk factors, age, sex, alcohol use, estimated duration of HCV infection, and laboratory values. The median estimated rate of fibrosis progression was similar to prior estimates, and was no higher in coinfected patients compared with the HCV-infected cohort. The second study evaluated 122 patients with HIV/HCV and 122 controls with HCV and found that coinfected patients had a significantly higher estimated progression of fibrosis. The crucial difference between these 2 studies resides in CD4 counts, which were higher in the first (mean, 0.48 × 10^9/L) as opposed to the second cohort (median, 0.30 × 10^9/L). Six articles, listed in Table 1, have shown an inverse correlation between CD4 counts and the prevalence of cirrhosis. This fact may well explain the above discrepant results. Additionally, a Th2 type of cytokine response, which is often found in patients with HIV, has been linked in mice, with more severe liver fibrosis after experimental injury. A Th2 response promotes antibody production and limits Th1 or a cytotoxic response.

### Table 1. Correlation Between CD4 Cell Counts and Prevalence of Cirrhosis

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Mean CD4+ Cell Counts, × 10^9/L</th>
<th>No. of Patients With Cirrhosis/Total No. of Sampling (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbaro et al, 1996</td>
<td>530</td>
<td>4/55 (7.3)</td>
</tr>
<tr>
<td>Puoti et al, 1998</td>
<td>482</td>
<td>10/84 (11.9)</td>
</tr>
<tr>
<td>Benhamou et al, 1999</td>
<td>305</td>
<td>19/122 (15.6)</td>
</tr>
<tr>
<td>Pol et al, 1998</td>
<td>300</td>
<td>10/52 (19.2)</td>
</tr>
<tr>
<td>Toyota et al, 1997</td>
<td>194</td>
<td>5/27 (18.5)</td>
</tr>
<tr>
<td>Bierhoff et al, 1997</td>
<td>99</td>
<td>4/22 (18.2)</td>
</tr>
</tbody>
</table>

*Indicates the studies where the median, rather than mean, was used for analyses.*
In humans, it could be hypothesized that declines in CD4 counts and a shift of helper lymphocytes toward a Th2 response lead to increased hepatic fibrogenesis.

Several case reports have illustrated that, after simultaneous infection with HIV and HCV, liver failure and death may occur within 5 years. However, there is no denominator to establish an incidence rate, and at least 1 case of simultaneous HIV/HCV coinfection did not lead to rapidly progressive liver disease.

In summary, a minority of patients with HIV/HCV coinfection develop accelerated liver disease early in the course of their HIV disease, particularly when hemophilia and/or excessive alcohol use is present. In patients without hemophilia, when alcohol use is controlled for, hepatic fibrosis seems not to accelerate, at least not in patients with CD4 counts higher than 0.20 × 10^9/L. However, cirrhosis and hepatic decompensation are increasingly found in patients with lower CD4 counts. Therefore, in patients with HIV/HCV coinfection, maintenance of CD4 lymphocyte levels must be viewed as an absolute priority.

### INFLUENCE OF HCV ON HIV INFECTION

Two early studies evaluated the possible effect of HCV infection on the natural history of HIV infection. The other study specifically considered immune parameters and found that HCV infection did not affect progression to acquired immunodeficiency syndrome. Three subsequent studies, from Scotland, Spain, and the United States, detected no difference in the time course of immunity markers and progression to acquired immunodeficiency syndrome in HIV-infected patients, whether HCV-positive or HCV-negative. Two articles described an accelerated clinical progression (including death) in coinfected patients, but declines in CD4 counts were similar in the 2 groups. Recent investigations found that HIV/HCV coinfection, under specific circumstances, may lead to faster progression to acquired immunodeficiency syndrome; these are infection with genotype 1, increases in HCV RNA greater than 1 log compared with baseline, and the development of advanced liver disease. In aggregate, however, the bulk of evidence suggests that HCV coinfection does not directly alter the course of HIV infection (Table 2).

### SEXUAL AND PERINATAL TRANSMISSION OF HCV IN COINFECTED PATIENTS

It is known that stable partners of HCV-infected patients—in the absence of injection drug use—have a higher risk of HCV infection than partners of HCV-negative index cases. Human immunodeficiency virus coinfection in the index case was initially thought to enhance sexual transmission. However, other studies did not confirm this initial impression. Table 3 summarizes available studies illustrating that HIV coinfection does not increase the low risk of HCV sexual transmission.

Pooled data from studies comparing rates of perinatal HCV transmission in both singly and coinfected pregnant women using HCV antibody or HCV RNA are given in Table 4.
in at least 25% of these cases, HCV and HIV were transmitted together. Factors associated with HCV transmission from coinfected women included the following: lower maternal CD4 percentages, higher maternal HCV viremia (transmission being negligible in mothers with \(<5\log_{10}\) copies per milliliter), and infant HIV coinfection. Using anti-HCV as the end point and including both singly and dually infected mothers, transmission of HCV was rarer in infants born by cesarean delivery (5/79 [6%]) as opposed to vaginal delivery (34/146 [23%]; \(P<.01\). Similar results were found when HCV RNA was used as an end point.

Conversely, a study of 487 HIV-infected pregnant women demonstrated increased HCV transmission to the child (26% vs 16%) in the HCV coinfected subgroup. Moreover, women transmitting HIV had higher HCV RNA levels than those who did not.

**THERAPY OF HCV IN COINFECTED PATIENTS**

Coinfected patients were excluded from placebo-controlled trials with interferon alfa treatment for chronic hepatitis C. Six studies, none placebo-controlled, are available on interferon treatment in patients with HIV/HCV. Both interferon alfa-2a and interferon alfa-2b were used at doses ranging from 1 million units thrice weekly to 9 million units daily as induction therapy for 4 to 12 months. When results are pooled (Table 5), 83 (42%) of 198 treated patients (all with CD4 counts \(>0.15 \times 10^9/L\)) had alanine aminotransferase level normalization at the end of treatment. A sustained response occurred in 35 (24%) of 144 patients in studies investigating HCV RNA, virological response rates paralleled biochemical response. All responders did so within 3 months of treatment and escalating dosages in nonresponders were not effective. Response rates were lower in HIV-infected vs non-HIV-infected patients, but these differences were not statistically significant. Tolerability was reasonable considering that more than 90% of patients completed therapy.

The following variables were associated with interferon response: higher CD4 cell counts, lower HCV viremia, and genotype 3a. Histologic improvement 1 year after the end of therapy was observed not only in responders but also in relapsers and nonresponders, a finding noted in patients with HCV alone. A non-concurrent prospective study performed in coinfected patients with chronic hepatitis (60% due to HCV infection) showed an association between interferon treatment and a reduced incidence of liver failure at 3 years.

During interferon therapy for chronic hepatitis C, 5 patients experienced greater than 5% declines in CD4 counts, resulting in the occurrence of de novo opportunistic infections in 4 patients. Such impressive CD4 cell count depletions are observed in only 5% of interferon-treated patients in the largest published study, occurring within 2 to 10 weeks of starting interferon therapy, and may be irreversible in up to 50% of cases. Their frequency is lower in patients treated with zidovudine. In patients with HIV and hepatitis delta coinfec- tion, treatment with high interferon doses (up to 10 million units thrice weekly) did not result in significant changes in CD4 cell counts, HIV viremia, or the occurrence of opportunistic infections. While interferon does not affect HIV RNA levels in patients with HIV/HCV concerns have been raised about its effect on tolerability of concurrent HAART. Weekly injections of pegylated interferon preparations may help alleviate this problem.

There are no published articles on the long-term effect of interferon alfa and ribavirin combination therapy in coinfected patients. In HIV-negative patients, this combination is associated with a 40% sustained virological response. Recent abstracts suggest that approximately 50% of the patients with HIV/
HCV become HCV RNA–negative at the end of therapy.\textsuperscript{101,102} Although encouraging, these results must be tempered with concerns about the safety and tolerability of ribavirin therapy in coinfection patients.\textsuperscript{102} Anemia associated with ribavirin therapy can be successfully countered with the use of subcutaneous erythropoietin.\textsuperscript{103} Ribavirin was studied as an antiretroviral treatment and was found to be ineffective.\textsuperscript{103-108} Most studies used 600 to 800 mg/d\textsuperscript{103,108} because severe depletions of CD4 cell counts were observed with doses of 1200 to 1600 mg.\textsuperscript{103,104} This has been attributed to a direct lymphotoxic effect of ribavirin therapy.\textsuperscript{105} Finally, ribavirin may interfere with the antiretroviral effect of zidovudine, and potentiate the effect of didanosine.\textsuperscript{109}

In the future, protease or helicase inhibitors, as well as antisense molecules, may prove useful as antiviral therapies.\textsuperscript{12} Ultimately, liver transplantation may be considered in selected patients; however, preliminary results show that HIV–positive patients with hemophilia have much lower survival rates (16%) than their HIV–negative counterparts (75%, $P = .02$).\textsuperscript{110}

\section*{EFFECT OF ANTIRETROVIRAL TREATMENT ON HEPATITIS C}

The use of HAART has reduced the occurrence of opportunistic infections and increased survival in patients with HIV.\textsuperscript{111} The effect of HAART on HCV coinfection has been described in a few patients.\textsuperscript{112-115} Two studies showed no significant alterations in serum transaminase levels and HCV viremia during HAART.\textsuperscript{114,115} Two other studies found significant increases in HCV viremia and serum transaminase levels, peaking after 4 to 6 weeks and returning to baseline between 4\textsuperscript{115} and 9 months.\textsuperscript{112} Levels of HIV RNA decreased and CD4 cell counts increased in both studies. One group\textsuperscript{115} hypothesized that a decrease in endogenous interferon activity\textsuperscript{116} occurs secondary to HIV suppression by HAART. It would follow that reduced interferon levels lead to enhanced HCV replication. Ultimately, the increase in peripheral CD4 cell counts may help restore intrahepatic immunity against hepatocyte–expressed HCV antigens, leading to higher alanine aminotransferase levels.\textsuperscript{113} Supporting this hypothesis, it was observed that hepatic necroinflammation worsened in biopsy specimens performed 1 to 2 months after starting HAART.\textsuperscript{112} In addition, 14% (7/51) of patients treated with protease inhibitors developed hepatic decompensation compared with only 3% (4/148) of patients who were not treated with protease inhibitors.\textsuperscript{112} In another study of 187 patients, 2% developed liver failure after 1 month of HAART.\textsuperscript{117} Several additional reports of liver injury occurring during HAART have been published recently, not exclusively in patients with HCV.\textsuperscript{118-125} A recent prospective study found that regimens containing ritonavir were much more likely to induce severe (ie, alanine aminotransferase levels $> 5$ times above the upper limit of normal) hepatotoxicity than regimens with nucleoside analogs.\textsuperscript{123} Two cases of severe hepatotoxicity occurred every 100 patient-months while receiving the latter regimens, compared with 3.3 episodes per 100 patient-months with any protease inhibitor–containing regimen.\textsuperscript{123} Ritonavir–containing combinations were associated with 6 episodes per 100 patient-months.

Some of the reported cases of drug-induced hepatotoxicity revealed histologic features of drug toxicity (eosinophilic infiltration, microvesicular steatosis), but some also showed evidence of chronic viral hepatitis with or without fibrosis.\textsuperscript{118-124} In summary, HAART must be administered cautiously, and liver function should be monitored in all patients, in particular those with chronic liver disease due to hepatitis C.

\section*{OTHER MANAGEMENT ISSUES}

Patients with HCV, particularly those with advanced disease, may be more susceptible to liver damage caused by hepatitis A.\textsuperscript{126} However, this is still controversial, as other groups have not confirmed this finding.\textsuperscript{127} Hepatitis A vaccination in HIV–positive patients yields an 88% antibody response rate, has no adverse effects on immunological parameters,\textsuperscript{128} and may be indicated in patients with hepatic fibrosis or cirrhosis, regardless of origin.

Similarly, hepatitis B is associated with more advanced liver disease in patients with chronic hepatitis C.\textsuperscript{3-5} Patients with HIV/HCV coinfection and a negative anti–hepatitis B core antibody should be considered for hepatitis B vaccination, although a serological response is substantially less frequent (about 50%) than in immunocompetent hosts.\textsuperscript{43} Hepatitis B vaccination in patients with HIV has been associated with a small increase in HIV load and a decrease in CD4 cell counts—both transient.\textsuperscript{129} Since alcohol intake accelerates the course of hepatitis C,\textsuperscript{2,5,36,61} alcohol and withdrawal results in increased CD4 cell counts.\textsuperscript{130} Patients with HIV infection and chronic hepatitis C should be advised to completely abstain from it.

\section*{CONCLUSIONS}

We believe that liver disease associated with HCV will become more clinically significant in patients with HIV. Coinfection leads to earlier and more severe liver disease, including hepatocellular carcinoma. In most instances, HCV infection does not seem to markedly alter the natural history of HIV disease. The HIV/HCV coinfection in pregnant women increases the risk of perinatal HCV transmission 2-fold, with more than 25% of occurrences involving transmission of both viruses; cesarean delivery significantly decreases this risk.

The management of patients with HIV/HCV includes the elimination of alcohol. Therapy with combined interferon and ribavirin should be considered, particularly in patients with higher CD4 cell counts, lower HCV viremia, and non-1 genotype. During treatment, complete blood cell counts need to be closely followed up. Future controlled trials will determine the efficacy and safety of long-acting interferon preparations alone or combined with ribavirin. The administration of HAART, with the intent to prevent declines in CD4 cell counts, seems crucial in stemming liver disease progression. However, some drugs have clear-cut hepatotoxic poten-
tial and patients with known liver disease should be closely monitored.

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Call for Papers

Call for Papers: Genetic Theme Issue

The November 2001 issue of the Archives of Internal Medicine will join JAMA and the family of Archives journals in publishing a theme issue on human genomics and genetics. This is a critical topic that includes diagnosis of genetic diseases, gene therapy, genetic screening and counseling, ethical issues, confidentiality, and the care of patients and families with inherited diseases.

We welcome manuscripts for consideration in this issue. Papers received by March 1, 2001, will have the best chance of inclusion.

James E. Dalen, MD, MPH
Editor