Hepatitis C Virus Infection–Related Morbidity and Mortality among Patients with Human Immunodeficiency Virus Infection

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Hepatitis C virus (HCV) has emerged as a major pathogen among patients with human immunodeficiency virus (HIV). Morbidity and mortality were compared among 263 patients with HIV alone, 166 patients with HIV and HCV, and 60 patients with HCV alone (mean duration of follow-up, 2 years and 10 months). No differences in HIV loads and CD4 cells counts were observed between the HIV and HIV/HCV groups. Alanine aminotransferase levels were higher (52 U/L versus 35 U/L; $P < .05$) and albumin levels were lower (3.5 g/dL versus 3.8 g/dL; $P < .02$) among coinfected patients than they were among patients with HIV alone. Liver decompensation developed in 10% of patients with HIV/HCV coinfection. In contrast, no liver-related deaths or decompensation occurred in patients without coinfection ($P < .05$). Of the patients with HIV alone, 7% died, compared with 11% of the coinfected patients ($P < .02$); 47% of the deaths in the latter group were due to liver-related causes. In summary, HCV infection causes increased morbidity and mortality in patients with HIV infection.

Hepatitis C virus (HCV) infection, an emerging disease, has reached epidemic proportions. In the United States alone, 4 million people are infected with this disease, and 170 million people are estimated to be infected worldwide. Each year, 30,000 new infections are observed in the United States. Approximately 75% of the people who contract the virus will carry it for life; 20% of these persons will develop cirrhosis of the liver [1–3]. Recent studies have demonstrated a dramatic reduction in rates of mortality and morbidity among patients with HIV infection: mortality rates decreased from 29.8 deaths per 100 person-years in 1995 to 8.8 deaths per 100 person-years in the second half of 1997 [4]. With this increased lifespan, HCV is now emerging as a major pathogen in these patients. Given the shared epidemiological risks in the past of injection drug abuse, sexual contact, and use of blood products, 30%–40% of HIV-infected patients are also infected with HCV. However, only a few studies, each with a limited number of patients, have attempted to assess HCV infection–related morbidity and mortality in patients with HIV infection [4–7]. Eyster et al. [6] observed increased frequency of liver failure in patients with hemophilia who had coinfection with HIV/HCV. Although some studies have suggested that HIV infection hastens the progression of HCV infection–related diseases [4–7], others have failed to confirm these observations [8–11].

In this study, we characterized the impact of HCV infection in a large cohort of HIV-infected patients and assessed the factors that might promote progression of HCV-related chronic liver disease in patients with HIV infection. Results were compared with control groups of patients who had either HIV infection alone or HCV infection alone. In addition, we analyzed the effect of

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hepatitis B virus (HBV) and treatment with protease inhibitors (PIs) on patients with HCV-related liver dysfunction.

METHODS

Study population and design. The study population was drawn from the Veterans Affairs Medical Center (VAMC), Houston, which serves ~500 HIV-infected patients. Study groups consisted of patients followed at the AIDS unit from January 1994 through May 1998 (mean duration of follow-up, 2 years and 10 months). The group of coinfected patients consisted of HIV- and HCV-positive patients; the 2 groups of control patients consisted of HIV-positive patients who were HCV seronegative and HCV-positive patients who were HIV seronegative. The latter control group was drawn from patients who had been followed since 1994 at the VAMC Substance Dependence Clinic.

Medical records for all patients were identified and retrieved by use of coding software (MUMPS language) to search the database for all patients who were coded as positive for HIV infection. Patients whose HCV infection status was not known were excluded from the study. The chart reviews were performed after approval was given by the institutional review board. The data were collected by means of a comprehensive review of patient medical records and the HIV-AIDS registry, which was maintained by the hospital's AIDS coordinator. Patient data included the following: age, sex, race, risk factors for HIV and HCV infection, presence of AIDS (according to the 1993 revised criteria of the Centers for Disease Control and Prevention, Atlanta), and clinical data. Only patients who completed 6 months of follow-up with at least 2 visits were included in the study. Dates of death were confirmed via the National Veterans Affairs Immunology Case registry and the Social Security Death Index, and by review of computerized clinical records. Information regarding alcohol intake was drawn from the hospital charts retrospectively. Laboratory data included CD4 cell count, serological markers, and biochemical values, such as alanine aminotransferase levels (ALT; normal level, 15–37 U/L) and aspartate aminotransferase levels (AST; normal level, 30–65 U/L).

To assess the impact of HCV infection on morbidity, liver-related and non–liver-related clinical events were analyzed individually. Liver-related clinical end events included development of decompensated liver disease (e.g., ascites, gastrointestinal bleeding from varices, jaundice due to hepatocellular injury, encephalopathy, and hepatorenal syndrome), hepatocellular carcinoma, and death due to either of the 2 aforementioned causes. Decreases in albumin levels to <3.0 g/dL and changes in ALT levels of >25% were considered to be biochemical events. In addition to total number of deaths, we also analyzed non–liver-related end events, such as nephropathy, diabetes mellitus, non-Hodgkin's B cell lymphoma; the presence of autoimmune phenomena, such as vasculitis (proven by biopsy), idiopathic thrombocytopenic purpura, mixed cryoglobulinemia, and Sjögren's syndrome; and the presence of skin abnormalities, such as lichen planus. In the intergroup analysis, the study groups were further stratified on the basis of treatment with PIs, HBV infection status, and CD4 cell count.

Statistical analysis. Student's unpaired *t* test was used to compare the study groups with regard to variables with normal distributions (such as age), and the χ^2 test was used for variables with nonnormal distributions (such as serum albumin level). For the analysis of qualitative data, the χ^2 test was used to test for group differences when there were >2 possible values (such as ethnic distribution). Data are presented as mean values; *P* values (2-tailed) of <.05 were considered statistically significant.

RESULTS

Demographic characteristics, seroprevalence, and baseline assessment. Four hundred ninety-three patients had documented HIV infection and were tested for HCV infection during the study period. Sixty-four patients were excluded from the study because of insufficient information about their clinical status, because of short duration of follow-up, or because their HCV infection status was not confirmed; this left 429 patients who were considered for further study. Of the 429 patients, 166 (39%) were coinfected with both HIV and HCV (known as the "coinfected group"), and 263 (61%) were HIV positive but HCV negative (known as the "HIV-only group" or first control group). The "HCV-only group," or second control group, was drawn from a total of 129 subjects who had been followed at the VAMC substance dependence clinic during the past 4 years. Of these 129 patients, HCV infection status was available for 84 (65%). Seventy-eight (93%) of 84 patients were positive for HCV antibody, and 60 (77%) of these patients had durations of follow-up of at least 6 months. All 3 groups were comparable with regard to age, with mean ages (±SD) of 46 ± 0.5 years, 46 ± 1.2 years, and 50 ± 1.2 years reported for patients in the coinfected group, the HIV-only group, and the HCV-only group, respectively. Of the patients in the coinfected group, 53% were African American and 18% were white; in the HIV-only group, 38% were African American and 27% were white; and in the HCV-only group, 17% were African American and 45% were white (table 1). African American patients were significantly more prevalent in the coinfected group. Injection drug abuse was significantly more common among patients in the coinfected group and in the HCV-only group than it was among patients in the HIV-only group.

Comparative analysis of baseline information was performed for all groups by use of values recorded during the first encounter with the patient at the hospital (table 2). HIV loads

and CD4 cell counts were comparable for coinfected patients and patients with HIV alone (58,168 RNA copies/mL and 73,964 RNA copies/mL and 312 cells/μL and 325 cells/μL, respectively), which suggests, at least by these parameters, that no direct effect of HCV on HIV replication and immune status was observed. There were statistically significant differences between coinfected patients and patients with HIV infection alone with regard to levels of ALT (52 U/L vs. 35 U/L, respectively) and AST (52 U/L vs. 77 U/L, respectively; $P < .005$). Coinfected patients and patients with HCV alone had similar levels of ALT and AST, regardless of the patients HIV infection status, which suggests that HIV infection did not affect transaminase levels. The levels of albumin were significantly lower among coinfected patients than they were among patients with HIV infection alone or with HCV infection alone, which suggests more advanced liver injury among patients in the coinfected group ($P < .001$).

Clinical end events. Clinical end points and deaths are shown in table 3. During follow-up, 14 (8.4%) of 166 coinfected patients developed decompensated liver disease, and 2 other patients (1.2%) developed hepatocellular carcinoma; no patients with HIV infection alone or HCV infection alone developed either condition ($P < .05$ for both). Nineteen (11.4%) of 166 coinfected patients, 18 (6.8%) of 263 patients with HIV infection alone ($P < .05$), and no patients with HCV infection alone died during the study period. All of the subjects who died of liver-related diseases belonged to the coinfected group. In addition to liver disease, which caused 9 deaths, other causes of death included sepsis (in 4 patients), pneumonia (in 1), and cardiac arrest (in 1). The cause of death in the 4 remaining coinfected patients could not be determined. Therefore, 9 (47%) of 19 deaths in the coinfected group were due to liver disease. In contrast, all 18 deaths in the HIV-only group were due to complications related to HIV infection, and no liver-related deaths were observed in the HCV-only group.

Relationship of CD4 cell counts and end events. To assess whether increased rates of morbidity or mortality were directly related to the degree of immunodeficiency, we compared the CD4 cell counts of coinfected patients with those of patients with HIV alone (table 4). Overall, there were no differences in the 2 groups with regard to the proportion of subjects who had CD4 cell counts of <50 cells/μL. Among patients in the coinfected group, 26 (16%) of 166 had CD4 cell counts of <50 cells/μL, whereas 60 (23%) of the patients with HIV infection alone had CD4 cell counts of <50 cells/μL. Furthermore, no differences in mortality rates were observed among the coinfected patients and those with HIV infection alone, all of whom had low CD4 cell counts. Five (19%) of 26 coinfected patients and 10 (17%) of 60 patients with HIV infection alone died. In contrast, significant increases in rates of mortality ($P = .02$) and morbidity ($P < .001$) were observed in coinfected patients who had CD4 cell counts of >50 cells/μL, compared with patients with HIV infection alone who had CD4 cell counts of >50 cells/μL. Fourteen (10%) of the 140 coinfected patients who had CD4 cell counts of >50 cells/μL died, compared with 8 (4%) of the 203 patients with HIV infection alone who had

Table 1. Demographic characteristics of 489 patients who were infected with HIV, hepatitis C virus (HCV), or both.

	Patients with			*P* value	
Characteristic	HIV/HCV coinfection ($n = 166$)	HIV infection alone ($n = 263$)	HCV infection alone ($n = 60$)	1[a]	2[b]
Age, mean years ± SD	46 ± 0.5	46 ± 1.2	50 ± 1.2		
Race or ethnic group					
African American	87 (53)	99 (38)	10 (17)	<.003	<.001
Hispanic	11 (7)	18 (7)	5 (8)	NS	NS
White	31 (18)	71 (27)	27 (45)	.05	<.001
Unknown	37 (22)	75 (28)	18 (30)	NS	NS
Risk factors					
Injection drug abuse	87 (53)	40 (15)	45 (75)	<.001	.002
Heterosexual contact	5 (3)	42 (16)	0	<.001	NS
Homosexual contact	8 (5)	65 (25)	0	<.001	NS
Needlestick	2 (1)	0	0	NS	NS
Unknown	64 (38)	116 (44)	15 (25)	NS	NS

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] For patients with HIV infection alone and patients coinfected with HIV and HCV.

[b] For patients with HCV infection alone and patients coinfected with HIV and HCV.

Table 2. Mean laboratory values for 489 patients who were infected with HIV, hepatitis C virus (HCV), or both.

Characteristic	Patients with HIV/HCV coinfection	Patients with HIV infection alone	Patients with HCV infection alone
HIV load, mean RNA copies/mL	58,168[a]	73,964[a]	NA
CD4 cell count, mean cells/μL	312	325	NA
Alanine aminotransferase level, mean U/L	52	35[b]	52
Aspartate aminotransferase level, mean U/L	77	42[b]	52
Alkaline phosphatase level, mean U/L	111	97	90
Albumin level, mean g/dL	3.5[c]	3.8	3.9
Total protein level, mean g/L	74	75	76
Bilirubin level, mean mg/dL	0.8	1.15	0.7

[a] Determination of virus loads was initiated at the Veterans Affairs Medical Center, Houston, in December 1996.
[b] Statistically significant differences were observed between coinfected patients and patients with HIV infection alone ($P < .005$).
[c] Significant differences were observed between coinfected patients and patients with HIV infection alone as well as coinfected patients and patients with HCV infection alone ($P < .001$).

CD4 cell counts of >50 cells/μL. Liver-related morbidity in the coinfected group was independent of CD4 cell count; 2 (7.7%) of 26 patients who had CD4 cell counts of <50 cells/μL and 14 (10%) of 140 patients who had CD4 cell counts of >50 cells/μL developed liver failure during follow-up. Also, of the patients who had CD4 cell counts of <50 cells/μL, the proportion of those who died was higher in the HIV-only group than it was in the coinfected group (10 [17%] of 60 patients vs. 8 [4%] of 203 patients, respectively; $P < .05$). These observations suggest that HCV infection is responsible for significant liver-related morbidity, irrespective of CD4 cell count, and that it is responsible for most of the deaths that were observed in patients with preserved CD4 cell counts.

Relationship of liver function tests and end events. To assess whether ALT levels may serve as a predictive marker, the coinfected group was divided into 2 subgroups: patients with ALT levels of >50 U/L (65 patients) and those with ALT levels of <50 U/L (101 patients). No differences in mortality rates were observed among patients with ALT levels of <50 U/L and those with ALT levels of >50 U/L; 9 (14%) of 65 patients in the former group and 10 (10%) of 101 patients in the latter group died during the course of the study. This finding suggests that ALT levels are not a useful marker of more severe disease and that they do not forecast mortality rates for these patients. In contrast, albumin levels appeared to be a predictor of morbidity and mortality in coinfected patients (table 5). Overall, no statistically significant difference was observed between the coinfected and HIV-only groups with respect to the number of patients with albumin levels of <3 g/dL, although a higher number of coinfected patients had albumin levels of <3 g/dL, compared with patients in the HIV-only group ($P < .17$). In the coinfected group, significant differences with regard to the development of liver disease were observed in a comparison of patients with low albumin levels (11 patients [20%]) and those with normal levels (5 patients [4%]; $P < .02$). Because no cases of liver decompensation were observed among patients in the HIV-only and HCV-only groups, intergroup analysis could not be performed for these groups.

There were significant differences in mortality rates for patients with albumin levels of <3 g/dL, compared with those for patients with albumin levels of >3 g/dL, in both the coinfected group and the HIV-only group ($P < .05$). In the coinfected group, 54 (32%) of 166 patients had albumin levels of <3.0 g/dL and 8 (15%) of these 54 patients died. Of the remaining

Table 3. Distribution of clinical end events among patients who were infected with HIV, hepatitis C virus (HCV), or both.

End events	Patients with HIV/HCV coinfection ($n = 166$)	Patients with HIV infection alone ($n = 263$)	Patients with HCV infection alone ($n = 60$)
Decompensated liver disease[a]	14 (8.4)	0 (0)	0
Hepatocellular carcinoma	2 (1.2)	0 (0)	0
Total number of deaths[b]	19 (11)	18 (7)	0
Liver disease–related deaths, *n/N* (%)[a]	9/19 (47)	0/18 (0)	0

NOTE. Data are no. (%) of patients, unless otherwise indicated.
[a] Differences are statistically significant between the patients with HIV/HCV coinfection and those with HIV infection alone ($P < .05$).
[b] Statistically significant differences were observed only between patients with HIV/HCV coinfection and those with HIV infection alone ($P \leq .02$).

Table 4. Interrelationship of CD4 cell counts and clinical end events for patients with HIV infection and for patients coinfected with HIV and hepatitis C virus (HCV).

	No. (%) of patients with			
	HIV/HCV coinfection (n = 166)		HIV infection alone (n = 263)	
Clinical end event[a]	CD4 cell count, <50 cells/μL	CD4 cell count, >50 cells/μL	CD4 cell count, <50 cells/μL	CD4 cell count, >50 cells/μL
All	26 (16)	140 (84)	60 (23)	203 (77)
Death	5 (19)	14 (10)	10 (17)	8 (4)
Decompensated liver disease	2 (7.7)	14 (10)	0 (0)	0 (0)

[a] Significant increases in rates of mortality (P = .024) and morbidity (P < .001) were observed among patients with HIV/HCV coinfection who had CD4 cells counts of >50 cells/μL, compared with patients who had HIV infection alone and CD4 cell counts of >50 cells/μL.

112 patients with albumin levels of >3 g/dL, only 11 patients died (10%; P < .05). This relationship between albumin level and subsequent death was also seen among patients in the HIV-only group: 68 (26%) of 263 patients had albumin levels of <3 g/dL and 9 (13%) of these patients died, whereas only 9 (5%) of the 195 patients who had albumin levels of >3 g/dL died. Such a relationship could not be studied in the HCV-only group because only 3 patients had albumin levels of <3g/dL and because there were no deaths in this group. Furthermore, during 48 months of follow-up, the decrease in albumin levels was seen predominately in the coinfected patients, which suggests that HCV infection plays a contributory role in liver dysfunction in these patients (data not shown).

Impact of PIs on HCV infection. Recent studies have suggested that PIs possibly have an effect on HCV replication and that they may cause liver toxicity in some instances [12–14]. The coinfected group and the HIV-only group were divided into 2 subgroups according to whether the patients received treatment with PIs. Forty-five of 166 coinfected patients were treated with PIs for at least 6 weeks, and 135 of 263 patients with HIV infection alone were treated with PIs. Although PIs were given regardless of HCV infection status and without provider bias, patients with HIV infection alone were treated significantly more often than were patients with coinfection (P < .02). Of importance, there were no differences between treated and nontreated patients in the coinfected group with regard to mean ALT levels (61 U/L and 62 U/L, respectively) or albumin levels (3.8 g/dL and 3.7 g/dL, respectively). Similar observations were made in patients in the HIV-only group, who had normal levels of liver enzymes regardless of whether they received treatment with PIs. These findings suggest that PIs have no immediate impact on HCV infection–related liver dysfunction.

Impact of HBV on coinfection. The clinical manifestations of HBV infection can include fulminant hepatitis, severe chronic liver disease, and cirrhosis [15]. Because many HIV-infected patients may also be infected with HBV, we assessed the role of HBV infection in the liver dysfunction seen in our cohort of patients. Overall, there were no statistically significant differences in ALT levels among hepatitis B surface antibody (HB_sAg)–positive and HB_sAg-negative patients. Thirty-two (19%), 45 (17%), and 20 (33%) patients were found to be HB_sAg positive in the coinfected, HIV-only, and HCV-only groups, respectively. Elevated ALT levels were observed in coinfected patients and patients with HCV infection alone, but not in patients with HIV infection alone. Lower albumin levels were observed among patients in the coinfected group only, regardless of HB_sAg status. These observations were also confirmed after all HB_sAg-positive subjects were excluded from analysis. In summary, these results suggest that HBV infection, unlike HCV infection, does not play a major contributory role in the development of liver dysfunction in HIV-infected patients.

Extrahepatic manifestations of HCV infection. In addition to liver injury, a significant number of patients with chronic HCV infection may also develop extrahepatic involvement, including mixed cryoglobulinemia, vasculitis, diabetes mellitus, glomerulonephritis, and non-Hodgkin's B cell lymphoma [16–24]. Because HIV infection also has well-documented systemic manifestations that can overlap with those of HCV infection, we assessed extrahepatic manifestations in the patients we studied (table 6). Sixteen (10%) of 166 patients in the coinfected group, 11 (4%) of 263 in the HIV-only group, and 3 (5%) of 60 in the HCV-only group had conditions with autoimmune manifestations (e.g., vasculitis, idiopathic thrombocytopenic purpura, and Sjögren's syndrome). These values reached statistical significance when coinfected patients were compared with patients who had HIV infection alone (P = .02). The prevalence of diabetes mellitus was observed to be more pronounced in coinfected patients (12%) and in patients with HIV infection alone (9.5%), and statistically significant values were observed for the coinfected group and the HCV-only group (P = .05). This observation is consistent with a recent report that linked HCV infection and diabetes mellitus [19]. Certain nephropathic conditions, such as proteinuria and hematuria, were also significantly more common among pa-

Table 5. Interrelationship of albumin levels and clinical end events among patients who were infected with HIV, hepatitis C virus (HCV), or both.

	No. (%) of patients with					
	HIV/HCV coinfection (n = 166)		HIV infection alone (n = 263)		HCV infection alone (n = 60)	
Clinical end event	Albumin level, <3 g/dL	Albumin level, >3 g/dL	Albumin level, <3 g/dL	Albumin level, >3 g/dL	Albumin level, <3 g/dL	Albumin level, >3 g/dL
All	54 (32)	112 (67)	68 (26)	195 (74)	3 (5)	57 (95)
Development of liver disease[a]	11 (20)	5 (4)	0	0	0	0
Death[b]	8 (15)	11 (10)	9 (13)	9 (5)	0	0

[a] In coinfected patients, significant differences in the development of liver disease were observed between those patients with albumin levels of <3 g/dL and those with albumin levels of >3 g/dL ($P < .02$).

[b] In both coinfected patients and patients with HIV infection alone, significant differences in mortality rates were observed between patients with albumin levels of <3 g/dL and those with albumin levels of >3 g/dL ($P < .05$).

tients in the coinfected group than they were among patients in the HIV-only and HCV-only group ($P < .03$). Cases of B cell lymphoma were observed more frequently in coinfected patients than they were in patients in either the HIV-only group or the HCV-only group, but these values did not reach statistical significance.

DISCUSSION

In the past, because of the rapidly advancing nature of HIV disease, slowly progressing chronic infections, such as HCV infection, have largely been ignored. Recently, because of advances in antiretroviral therapy, the life expectancy of HIV-infected patients has increased dramatically. Because up to 50% of HIV-positive patients may be coinfected with HCV, it has become critically important to understand the impact of chronic HCV infection in HIV-infected patients. Limited studies have suggested that HCV infection may cause significant hepatic and extrahepatic morbidity in these patients. These observations are supported by our data from a large cohort of patients; these data demonstrate a significant increase in morbidity and mortality rates among in HIV-infected patients with HCV coinfection. Decompensated liver disease and hepatocellular carcinoma developed in 10% of coinfected patients. In contrast, during the evaluation period, no patients in the HIV-only and HCV-only groups developed liver-related decompensation or died. Eleven percent of the coinfected patients died, compared with only 6.8% of the patients with HIV infection alone. Of importance, 47% of the deaths in the coinfected group were due to liver-related causes, such as cirrhosis, ascites, variceal bleeding, and encephalopathy. This finding is consistent with recent observations that the progression of liver fibrosis is accelerated in coinfected patients [25].

The increased morbidity and mortality rates among coinfected patients were not likely to have been caused by more advanced HIV disease. Indeed, a comparison of coinfected patients and patients with HIV infection alone revealed no differences between the 2 groups with regard to mean CD4 cell counts, and similar proportions of subjects who had CD4 cell counts of <50 cells/μL were observed in the 2 groups. Furthermore, no differences in mortality rates were observed among the patients with low CD4 cell counts in either in the coinfected group or the HIV-only group. In contrast, significant increases in rates of mortality ($P = .02$) and morbidity ($P < .001$) were observed among patients in the coinfected group who had CD4 cell counts of >50 cells/μL, compared with patients in the HIV-only group who had CD4 cell counts of >50 cells/μL. In the coinfected group, liver-related morbidity was independent of CD4 cell count; 7.7% of the patients who had CD4 cell counts of <50 cells/μL and 10% of those who had CD4 cell counts of >50 cells/μL developed liver failure during follow-up. Taken together, these observations indicate that HCV infection results in significant liver-related morbidity irrespective of CD4 cell count and is responsible for most of the deaths that were observed in coinfected patients who had CD4 cell counts of >50 cells/μL.

Because of the possible direct and indirect effect of PIs on immunological parameters and virologic loads as well as liver toxicity [12–14], the influence of PIs on HCV infection–related liver dysfunction was studied in these patients. In our study, levels of ALT and albumin did not differ among patients who received PIs and patients who did not receive treatment with PIs, which suggests that this new class of drugs had little or no impact on HCV infection–related liver dysfunction in this group of coinfected patients.

HBV replication inversely correlates with inflammatory response, and a large number of studies in the past have clearly demonstrated increased prevalence of HBV infection and reactivation of HBV replication in subjects with advanced HIV infection [15, 26, 27]. Concurrently, with progression of immunosupression, very few cases of liver dysfunction were observed in these patients. Because molecular markers of HBV

Table 6. Extrahepatic manifestations of hepatitis C virus (HCV) infection in 489 patients who were infected with HIV, HCV, or both.

Extrahepatic manifestation	Patients with			*P* values	
	HIV/HCV coinfection (n = 166)	HIV infection alone (n = 263)	HCV infection alone (n = 60)	1[a]	2[b]
B cell lymphoma	4 (2.4)	2 (0.77)	0 (0)	NS	NS
Autoimmune conditions	16 (10)	11 (4)	3 (5)	.02	NS
Diabetes mellitus	20 (12)	25 (9.5)	2 (3)	NS	.05
Proteinuria	59 (35)	67 (25)	0 (0)	.03	<.001
Hematuria	40 (24)	39 (15)	0 (0)	.02	<.001
Nephrotic syndrome or glomerulonephritis	2 (1.2)	1 (0.3)	0 (0)	NS	NS

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] A comparison of patients with HIV/HCV coinfection and those with HIV infection alone.

[b] A comparison of patients with HIV/HCV coinfection and those with HCV infection alone.

replication were not routinely evaluated in the patients we studied, the analysis was performed on the basis of the presence or absence of HB_sAg. Our results demonstrated that HBV infection did not play a contributory role in the development of liver dysfunction either in the coinfected patients or in patients with HIV infection alone, and no statistically significant differences in ALT and albumin levels were observed among HB_sAg-positive and HB_sAg-negative patients. These results are in agreement with previous observations that were made regarding HIV-infected homosexual men [19].

In addition to liver injury, a significant number of patients with chronic HCV infection may develop extrahepatic involvement, such as mixed cryoglobulinemia, vasculitis, glomerulonephritis, diabetes mellitus lesions, and non-Hodgkin's B cell lymphoma [16–24]. HIV infection also has well-documented systemic manifestations, including mixed cryoglobulinemia [18], that can overlap with those of HCV infection. Therefore, it is conceivable that some extrahepatic clinical manifestations of HCV infection, which are currently attributed to HIV infection, are indeed induced by HCV infection. In our study, autoimmune conditions, proteinuria, and hematuria were significantly more common in coinfected patients, which suggests that HCV infection plays a role in the etiology of these conditions. Also, we observed increased prevalence of diabetes mellitus in coinfected patients, compared with patients with HIV infection alone, and diabetes mellitus was statistically more prevalent in coinfected patients than it was in patients with HCV infection alone. There are controversial reports regarding a link between HCV infection and non-Hodgkin's B cell lymphoma [20–24]. Our data demonstrated a moderate increase in the incidence of non-Hodgkin's B cell lymphoma in coinfected patients. Long-term studies with a larger number of patients will be required to explore the role of HCV infection in the development of B cell lymphoma in patients with HIV infection.

The validity of our data is supported by the following. All the HCV and HIV serological assessments were performed at the same laboratory, preventing bias due to interlaboratory variations. There are a number of limitations, however, with regard to the interpretation of the results of this study. First, we did not know the dates of HIV and HCV seroconversion in patients who had HIV alone, and the different duration of HIV and HCV infections could affect the estimates of progression to the study end points. Second, because HCV loads and genotypes were not routinely determined for our patients, their role in liver dysfunction and progression of liver disease could not be analyzed. However, these factors are only associated with response to treatment, and not to the progression of disease. Also, the proportion of African American patients was statistically higher in the coinfected group than it was in the other 2 groups. Reports have indicated that ~90% of African American persons are infected with HCV genotype 1, and although these patients are equally compliant and do not appear to have more advanced disease, their response to treatment for HCV infection is diminished [28]. However, there are no data to indicate accelerated progression of HCV infection in African American persons who did not have additional risk factors, such as alcohol abuse. Additional studies will clearly be required to clarify racial differences in progression of HCV infection in patients with HIV infection. Finally, histories of alcohol intake were available for only a limited number of patients. In the coinfected and HIV-only groups, information regarding alcohol intake was available for only 35 and 17 patients, respectively, and no statistical differences were observed among these 2 groups.

Our study provides evidence that HIV infection plays an important role in the acceleration of HCV infection. The benefit

of active intervention and increased surveillance against HCV infection in patients with HIV infection remains unclear because no data are currently available to demonstrate the effect of active intervention against HCV. Long-term prospective studies are needed to document the effect of treatment of HCV infection in HIV-infected patients and to assess the benefit of active intervention. Such an approach may ultimately decrease rates of morbidity and mortality that result from decompensated chronic liver disease and hepatocellular carcinoma in coinfected patients.

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References

1. National Institutes of Health. Consensus Development Conference Panel statement: management of hepatitis C. Hepatology **1997**; 26(Suppl 1): 2S–10S.
2. Alter MJ, Margolis HS, Krawczynski K, et al. The natural history of community acquired hepatitis C in the United States. N Engl J Med **1992**; 327:1899–905.
3. Kenny WE. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. N Engl J Med **1999**; 340:1228–33.
4. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. Outpatient Study Investigators. N Engl J Med **1998**; 338:853–60.
5. Martin P, Di Bisceglie AM, Kassianides C, Lisker-Melman M, Hoofnagle JH. Rapidly progressive non-A, non-B hepatitis in patients with human immunodeficiency virus infection. Gastroenterology **1989**; 97:1559–61.
6. Eyster ME, Diamondstone LS, Lien JM, Ehmann WC, Quan S, Goedert JJ. Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immunodeficiency virus. J Acquir Immune Defic Syndr **1993**; 6:602–10.
7. Soto B, Sanchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol **1997**; 26:1–5.
8. Sanchez-Quijano A, Andreu J, Gavilan F, et al. Influence of human immunodeficiency virus type 1 infection on the natural course of chronic parenterally acquired hepatitis C. Eur J Clin Microbiol Infect Dis **1995**; 14:949–53.
9. Berger A, von Depka Prondzinski M, Doerr HW, Rabenau H, Weber B. Hepatitis C plasma viral load is associated with HCV genotype but not with HIV coinfection. J Med Virol **1996**; 48:339–43.
10. Cribier B, Rey D, Schmitt C, et al. High hepatitis C viremia and impaired antibody response in patients co-infected with HIV. AIDS **1995**; 9:1131–6.
11. Wright TL, Hollander H, Pu X, et al. Hepatitis C in HIV-infected patients with and without AIDS: prevalence and relationship to patient survival. Hepatology **1994**; 20:1152–5.
12. Beld M, Penning M, Lukashov V, et al. Evidence that both HIV and HIV-induced immunodeficiency enhance HCV replication among HCV seroconvertors. Virology **1998**; 244:504–12.
13. Rutschmann OT, Negro F, Hirschel B, Hadengue A, Anwar D, Perrin LH. Impact of treatment with human immunodeficiency virus (HIV) protease inhibitors on hepatitis C viremia in patients co-infected with HIV. J Infect Dis **1998**; 177:783–5.
14. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adult infected with human immunodeficiency virus and the role of hepatitis C and B virus infection. JAMA **2000**; 283:74–80.
15. Yoffe B, Noonan CA. Progress and perspectives in human hepatitis B virus research. Prog Med Virol **1993**; 40:107–40.
16. Gumber SC, Chopra S. Hepatitis C: a multifaceted disease. Review of extrahepatic manifestations. Ann Intern Med **1995**; 123:615–20.
17. Hadzuyannis SJ. The spectrum of extrahepatic manifestations in hepatitis C virus infection. J Viral Hepat **1997**; 4:9–28.
18. Dimitrakopoulos A, Kordossis T, Hatzakis A, Moutsopoulos HM. Mixed cryoglobulinemia in HIV-1 infection: the role of HIV-1. Ann Intern Med **1999**; 130:226–30.
19. Mason AL, Lau JY, Hoang N, et al. Association of diabetes mellitus and chronic hepatitis C infection. Hepatology **1999**; 29:328–33.
20. Vallisa D, Berta R, Rocca A, et al. Association between hepatitis C virus and non-Hodgkin's lymphoma, and effects of viral infection on histologic subtype and clinical course. Am J Med **1999**; 106:556–60.
21. Zuckerman E, Zuckerman T, Levine AM, et al. Hepatitis C virus infection in patients with B-cell non-Hodgkin lymphoma. Ann Intern Med **1997**; 127:423–8.
22. Ferri C, La Civita L, Monti M, et al. Chronic hepatitis C and B cell non-Hodgkin's lymphoma. QJM **1996**; 89:117–22.
23. Collier JD, Zanke B, Moore M, et al. No association between hepatitis C and B cell lymphoma. Hepatology **1999**; 29:1259–61.
24. Levine AM, Nelson R, Zuckerman E, et al. Lack of association between hepatitis C and development of AIDS-related lymphoma. J Acquir Immune Defic Syndr Hum Retrovirol **1999**; 20:255–8.
25. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus co-infected patients. Hepatology **1999**; 30:1054–8.
26. Mai AL, Yim C, O'Rourke K, Heathcote EJ. The interaction of human immunodeficiency virus infection and hepatitis B virus infection in infected homosexual men. J Clin Gastroenterol **1996**; 22:299–304.
27. Perrillo RP, Campbell CR, Sanders GE, et al. Spontaneous clearance and reactivation of hepatitis B virus infection among male homosexuals with chronic type B hepatitis. Ann Intern Med **1984**; 100:43–6.
28. McHutchison JG, Poynard T, Gordon SC, et al. The impact of race on response to anti-viral therapy in patients with chronic hepatitis C [abstract]. Hepatology **1999**; 30:302A.