Progression of Chronic Hepatitis C to Liver Fibrosis and Cirrhosis in Patients Coinfected with Hepatitis C Virus and Human Immunodeficiency Virus

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To evaluate the factors associated with the evolution of chronic hepatitis C in human immunodeficiency virus (HIV)—infected patients, a cross-sectional analysis of 41 HIV-infected patients with chronic hepatitis C (known as "HIV-HCV [hepatitis C virus]–coinfected patients") and a control group of patients with chronic hepatitis C who did not have HIV infection (known as "non–HIV-infected patients") was performed. The association of histological variables with demographic parameters, HCV load and genotype, HIV load, $CD4^+$ T cell count, and response to highly active antiretroviral therapy (HAART) was evaluated. HIV-HCV–coinfected patients showed a significantly higher HCV load, more-advanced fibrosis, and a higher liver fibrosis progression rate (FPR) than did non–HIV-infected patients. A high HCV load and a low $CD4^+$ T cell count were associated with a higher FPR. The immune response induced by HAART did not influence this progression. In conclusion, HIV-HCV–infected patients, mainly such patients with a high HCV load and an immunodepressed state, have a higher FPR. An independent effect of the immune response to HAART was not evident.

Studies of the natural history of hepatitis C virus (HCV) infection in immunocompetent patients have demonstrated that death associated with chronic hepatitis C results mainly from the development of liver fibrosis and the subsequent occurrence of cirrhosis and its complications [1, 2]. Approximately 6% of immunocompetent HCV-infected hosts can be expected to develop hepatic decompensation due to cirrhosis during a 20-year period, although the time frame in which the various stages of liver disease develop is highly variable [3]. Numerous factors have been associated with an increased risk of progression of HCV infection to cirrhosis, including male sex, older age at the time of infection, and alcohol consumption [4, 5].

The increase in the survival of HIV-infected patients, related to the use of HAART [6], has been associated with higher morbidity and mortality rates attributable to chronic HCV infection [7]. HCV-induced liver disease has an accelerated course in HIV-coinfected patients [8–11]. This accelerated progression of disease in HIV-infected patients with chronic hepatitis C (i.e. "HIV-HCV–coinfected patients") could be explained by several factors, such as the higher HCV load detected in such patients [12, 13] or the immunodeficiency state (as this factor can be related to the $CD4^+$ T cell count) [7, 8, 11, 14–18]. However, the effect of the HCV load on histopathologic liver lesions in these patients had not been previously established. Likewise, although it could be postulated that improvement of immune function associated with antiretroviral therapy might

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reduce the liver fibrosis progression rate (FPR), the influence of the effects of modifications of immune parameters induced by HAART remains controversial or unknown. The aim of the present study was to investigate the independent effects of HCV load and of immune reconstitution induced by therapy on the accelerated evolution of liver fibrosis and cirrhosis in HIV-HCV–coinfected patients.

PATIENTS AND METHODS

Patients. Forty-one HIV-HCV–coinfected patients and 147 non–HIV-infected patients with chronic hepatitis C (i.e., "non–HIV-infected patients"), all of whom were seen at the Infectious Diseases and Gastroenterology Units of the University Hospital Puerta del Mar, Cádiz, Spain, were included in this cross-sectional study performed from 1996. Criteria for inclusion in the study included an increase in serum aminotransferase levels for ⩾6 months, HCV infection (defined as a positive result of serologic analysis performed using a second- or third-generation ELISA and a positive result of PCR analysis), and a liver biopsy specimen with interpretable findings. Criteria for exclusion from the study included the presence of clinical or biochemical criteria of decompensated cirrhosis, the presence of hepatitis B surface antigen, previous therapy with IFN or ribavirin, and the presence of infectious, autoimmune, tumoral, biliary, or vascular-associated liver disease. Informed consent was obtained from each patient, and the protocol was approved by the institutional human research committee

For each patient, a specific questionnaire was completed. The questionnaire included questions about host factors (e.g., sex, age at the time of infection, route of transmission of infection, and alcohol consumption), biochemical variables (serum concentrations of alanine aminotransferase [ALT]), time-related factors (age at biopsy and the estimated duration of infection), and virological variables (genotype and HCV load at biopsy). For HIV-HCV–coinfected patients, $CD4^+$ T cell counts and HIV loads were recorded both at the time of diagnosis of HIV infection and at biopsy, as was the type of HAART received.

In the present study, alcoholism was defined as ethanol ingestion of >50 g of alcohol per day for ⩾5 years. It may be assumed that HIV and HCV are simultaneously acquired after transfusion of blood derivatives, whereas injection drug users acquire HCV at the time that they first use injection drugs, with the acquisition of HIV occurring later [19]. However, for practical purposes, several authors [4, 14, 20, 21], including the authors of a recent meta-analysis [16], establish the date of HIV-HCV infection as the date of the first transfusion, the date of the first use of injection drugs, or the date of the surgery after which an elevation in ALT levels and the presence of HCV antibodies were detected, in the absence of other causes that could explain such infection. This was the date of acquisition of HCV and HIV infection used in the present study. For 50 non–HIV-infected patients, the date of acquisition of infection could not be reliably determined, and the patients were not analyzed to determine either progression of the disease to fibrosis or the risk of developing cirrhosis, both of which are time-dependent variables.

Indications for HAART were based on each individual's clinical, immunologic, and virologic status, according to the periodic recommendations of the International AIDS Society (San Francisco, CA) [22–25]. Each of the patients included in the present protocol had been treated with 2 nucleoside analogues and a protease inhibitor (nelfinavir [$n = 19$], indinavir [$n = 13$], or ritonavir plus saquinavir [$n = 9$]). Immune reconstitution in HIV-HCV–coinfected patients was defined by a $CD4^+$ T cell count that reached ⩾500 cells/μL after HAART; for comparative studies, patients whose $CD4^+$ T cell counts were >500 cells/μL at the time of diagnosis of HIV infection and whose values persisted above this level after receipt of HAART ($n = 4$) were also included in the same group of patients with immune reconstitution.

Laboratory methods. At University Hospital Puerta del Mar, patients who have risk factors for HIV infection (e.g., sexual promiscuity, injection drug use, and/or transfusion of blood derivatives) are simultaneously evaluated for HCV and HIV infection status. Likewise, if anti-HCV antibodies are demonstrated during evaluation for increased serum levels of liver enzymes, presence of anti-HIV antibodies is determined.

For each patient, presence of anti-HIV antibodies was determined by EIA (Abbott Laboratories) and was confirmed by Western blot analysis (Pasteur Institute). For HIV-infected patients, $CD4^+$ T cell counts were determined by standard flow cytofluorometry.

For serum samples obtained from all subjects, presence of anti-HCV antibodies was determined by both a second-generation EIA (EIA-2; Ortho Diagnostic Systems) and a second-generation recombinant immunoblot assay (RIBA-2; Ortho Diagnostic Systems). Serum samples were tested for HCV RNA by RT-PCR (Amplicor HCV; Roche Diagnostics). Isolates were genotyped by line probe assay (INNO-LiPA HCV; Innogenetics), as described elsewhere [26]. The HCV genotype nomenclature used was that proposed by an international panel [27].

Histological evaluation. Liver biopsy specimens, which measured >10 mm in length, were fixed, paraffin embedded, and stained with hematoxylin-eosin safranin and Masson trichrome or picrosirius red for collagen. All specimens were assessed by the same experienced pathologist (R.R.), who was not aware of the clinical or biological data. For each liver biopsy specimen, a numerical score was established, both for the grading of necroinflammatory activity (NIA) and for determining the stage of fibrosis, with use of the index of histological activity proposed by Knodell et al. [28], as modified by Scheuer [29]

Table 1. Demographic, biochemical, and virological characteristics of patients with HIV and hepatitis C virus (HCV) coinfection (HIV-HCV–coinfected patients) and of patients infected with HCV but not infected with HIV (non–HIV-infected patients).

Characteristic	All patients (n = 188)	Non–HIV-infected patients (n = 147)	HIV-HCV-coinfected patients (n = 41)
Sex, ratio of males to females	1.77:1	1.63:1	2.33:1
Age, years (95% CI)			
At liver biopsy	37.7 (34–39)	38.1 (36–40)	35.8 (34–38)
At HCV infection[a]	21.1 (19–23)	21.7 (19–24)	20.5 (18–23)
Estimated duration of HCV infection			
Years (95% CI)[a]	17.2 (16–19)	17.9 (19–24)	15.3 (13–18)
>20 Years	48.9	55.5	46.2
Risk factors for HCV infection			
Receipt of hemoderivatives	22.3	27.9	2.4[b]
Injection drug use	31.4	16.3	85.4[b]
Surgery	16.5	21.1	0.0[b]
Unknown	29.8	34.7	12.2[b]
Alcohol consumption of >50 g/day	21.2	24.1	12.8
HCV genotype, no. (%) of patients			
1	105 (55.9)	91 (61.9)	21 (51.2)
3	56 (29.8)	38 (25.9)	14 (34.1)
4	27 (14.4)	18 (12.2)	6 (14.6)
HCV load, mean $\times$ 10^6 copies/mL (95% CI)	3.65 (2.5–4.9)	2.33 (1.4–3.1)	5.70 (1.1–8.1)[b]
Serum ALT concentration, mean IU (95% CI)	108 (96–121)	113 (98–130)	94 (77–112)

NOTE. Data are % of patients, unless otherwise indicated. ALT, alanine aminotransferase.

[a] Age at the time of HCV infection and, logically, estimated duration of HCV infection were evaluated for 138 patients (97 non–HIV-infected patients and 41 HCV-HIV–coinfected patients).

[b] $P < .001$, for comparison of non–HIV-infected patients with HIV-HCV–coinfected patients.

and Desmet et al. [30]. NIA was graded according to 3 components: periportal inflammation with or without bridging necrosis (scale, 0–10), intralobular degeneration and focal necrosis (scale, 0–4), and portal inflammation (scale, 0–4). In accordance with the previously cited studies, the intensity of NIA was scaled as follows: A0 denoted no histological activity; A1, minimal activity (scale units, 1–3); A2, mild activity (scale units, 4–8); A3, moderate activity (scale units, 9–12); and A4, severe activity (scale units, >12). The stage of liver fibrosis was determined using a scale of F0–F4 (F0 denoted no fibrosis; F1, periportal fibrosis without septa; F2, few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis).

We have calculated the FPR as the ratio of the fibrosis stage to the duration of infection [31]. A validation method was made by comparing the estimated FPRs with the FPR observed for paired liver biopsy specimens obtained from 12 patients who had never received treatment. For these patients, the FPR was calculated as the difference between the scores for specimens obtained from 2 consecutive biopsies, divided by the time (in years) elapsed between performance of the 2 biopsies.

Statistical analysis. Sex, consumption of alcohol ($\leq$50 or >50 g/day), HCV genotype (1, 4, or other), age at the time of HCV infection ($\leq$20 or >20 years), virus load ($\leq$2 or $>2 \times 10^6$ copies/mL), $CD4^+$ T cell count ($\leq$200 or >200 cells/μL; $\leq$500 or >500 cells/μL), and immune response to HAART were compared using the χ^2 test. NIA (minimal, mild, moderate, or severe), fibrosis and the FPR, serum concentrations of ALT, and virus load were compared using Student's t test. The association between quantitative variables was determined by means of Pearson's coefficient of correlation.

The variables with statistically significant influence on the FPR in the univariate analysis were included in a multivariate analysis by use of multiple linear regression. The Kaplan-Meier method was used to analyze the significance of the different variables associated with cirrhosis. Finally, the variables with a possible prognostic value were evaluated by regression of proportional

Table 2. Histological findings for patients with HIV and hepatitis C virus (HCV) coinfection (HIV-HCV–coinfected patients) and for patients infected with HCV but not infected with HIV (non–HIV-infected patients).

Histological finding	All patients (n = 188)	Non–HIV-infected patients (n = 147)	HIV-HCV–coinfected patients (n = 41)
NIA score, mean (95% CI)	5.7 (5–6)	6.0 (5–7)	4.7 (3–6)
Knodell histological activity index			
Minimal	41 (22)	24 (16)	17 (42)
Mild	116 (62)	97 (66)	19 (46)
Moderate	31 (16)	26 (18)	5 (12)
Severe	0	0	0
Liver fibrosis score, mean (95% CI)	1.32 (1.1–1.5)	1.18 (0.9–2.4)	1.80 (0.4–3)[a]
Liver fibrosis stage			
F0	59 (32)	51 (35)	8 (20)
F1	66 (35)	51 (35)	15 (37)
F2	22 (12)	18 (12)	4 (10)
F3	23 (12)	18 (12)	5 (12)
F4	18 (9)	9 (6)	9 (22)[a]
FPR, mean (95% CI)	0.121 (0.103–0.140)	0.106 (0.081–0.129)	0.144 (0.113–0.174)[a]

NOTE. Data are no. (%) of patients, unless otherwise indicated. FPR, fibrosis progression rate; NIA, necroinflammatory activity.

[a] $P = .04$, for comparison of HIV-HCV–infected patients with non–HIV-infected patients.

risks for dependent variables of time, according to use of the Cox model with the stepwise method. $P < .05$ was considered to be statistically significant. The statistical analysis was done with the use of SSPS software (InstallShield), version 10.0.

RESULTS

The demographic characteristics of the patients studied are shown in table 1. The groups of HIV-HCV–coinfected patients and non–HIV-infected patients were comparable with respect to sex, age at infection, age at biopsy, mean duration of HCV infection, and alcohol consumption, but their risk factors for HIV infection were different, mainly because there were more injection drug users in the group of HIV-HCV–coinfected patients.

HIV-infected patients had received their diagnosis a mean (±SD) of 8.1 ± 3.8 years (range, 3–14 years) before the present study. At diagnosis, the mean $CD4^+$ T cell count was 334 cells/μL (95% CI, 244–424 cells/μL), with 81% of HIV-infected patients having <500 $CD4^+$ T cells/μL and 31% having <200 cells/μL. All patients had been receiving HAART for a median of 36 months (95% CI, 27–43 months); 32 of the patients had an undetectable HIV load. The median increase in the number of $CD4^+$ T cells was 225 cells/μL (range, −27 to 431 cells/μL). At liver biopsy, the mean $CD4^+$ T cell count (±SD) was 577 ± 280 cells/μL (range, 245–1496 cells/μL), with 56% of the patients having >500 $CD4^+$ T cells/μL.

The distribution of HCV genotypes was similar between groups. HIV-HCV–coinfected patients had significantly higher HCV loads. Likewise, the percentage of patients with an HCV load of $>2 \times 10^6$ copies/mL was significantly higher among coinfected patients than among non–HIV-infected patients (71% vs. 37%; $P < .005$). Serum ALT levels were similar for groups (table 1). In the HIV-HCV–coinfected group, the HCV load had a significantly negative correlation with the $CD4^+$ T cell count ($r = -.34$; $P = .032$) and a positive correlation with age at HCV infection ($r = .35$; $P = .032$).

NIA. The NIA score was similar for both groups (table 2). For HIV-HCV–coinfected patients, a similar NIA score was detected in groups of subjects classified according to their degree of immunodeficiency (the NIA score was 4.89 [95% CI, 3.35–6.42] for patients with $CD4^+$ T cell counts of ≤200 cells/μL vs. 4.22 [95% CI, 3.10–5.34] for patients with $CD4^+$ T cell counts of >200 cells/μL; $P = .45$). The NIA score showed a significant correlation with serum ALT concentrations in both groups (for HIV-HCV–coinfected patients, $r = .48$ [$P < .005$]; for non–HIV-infected patients, $r = .28$ [$P < .05$]). Only in the non–HIV-infected group did the correlation between the NIA score and the HCV load approach statistical significance (for HIV-HCV–coinfected patients, $r = .00$ [$P > .05$]; for non–HIV-

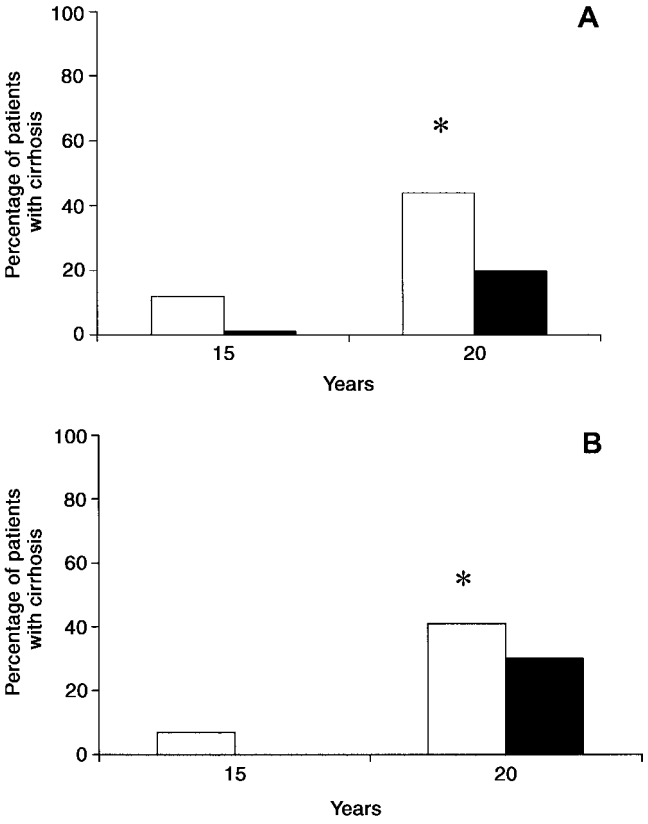

Figure 1. Percentages of patients coinfected with HIV and hepatitis C virus who had cirrhosis after 15 or 20 years of evolution of HCV infection. *A,* Patients with ≤200 *(open bars)* or >200 *(solid bars)* $CD4^+$ T cells/μL at the time of diagnosis of HIV infection. *B,* Patients without *(open bars)* or with *(solid bars)* immune reconstitution. *$P < .05$.

infected patients, $r = .24$ [$P = .05$]). For both groups, the variables of sex, age at infection or age at biopsy, estimated duration of infection, alcohol consumption, and genotype were not correlated with either the NIA score or the serum ALT concentrations (data not shown).

Fibrosis and cirrhosis. The fibrosis score was significantly higher for HIV-HCV–coinfected patients than for non–HIV-infected patients (table 2). The fibrosis score showed a positive and significant correlation with the estimated duration of infection in both groups (for HIV-HCV–coinfected patients, $r = .49$ [$P = .001$]; for non–HIV-infected patients, $r = .255$ [$P = .01$]).

Liver biopsy showed the presence of cirrhosis in 18 patients. Sex, age at infection, alcohol consumption, HCV load, and HCV genotype were similar for patients with and without cirrhosis. In contrast, 22% of HIV-HCV–coinfected patients had cirrhosis at liver biopsy, whereas, for the non–HIV-infected group, this percentage was 6% ($P = .03$). In addition, HIV-HCV–coinfected patients developed cirrhosis earlier than did non–HIV-infected patients. Of the HIV-HCV–coinfected patients, 19% had cirrhosis 15 years after HCV infection, and 35% had cirrhosis 20 years after HCV infection. Of the non–HIV-infected patients, 2% of patients had cirrhosis 15 years after HCV infection, and 3% of patients had cirrhosis 20 years of infection. For the HIV-HCV–coinfected group, the immunodeficiency state was significantly associated with the presence of cirrhosis. Patients with $CD4^+$ T cell counts of ≤200 cells/μL at the time of diagnosis of HIV infection or with a $CD4^+$ T cell count of ≤500 cells/μL at liver biopsy (after receipt of HAART), had a higher percentage of cirrhosis than did patients with >200 cells/μL at the time of diagnosis of HIV infection or patients with >500 cells/μL at liver biopsy (figure 1).

FPR. The HIV-HCV–coinfected group showed a significantly higher FPR than did the non–HIV-infected group (table 2). The FPR correlated with the HCV load in both groups of patients (for the HIV-HCV–coinfected group, $r = .51$ [$P = .003$]; for the non–HIV-infected group, $r = .39$ [$P = .03$]).

The accelerated progression of fibrosis was more significant among patients who were more immunosuppressed. Persons with a $CD4^+$ T cell count of ≤200 cells/μL at the time of diagnosis of HIV infection had a statistically higher FPR than did patients with a $CD4^+$ T cell count of >200 cells/μL (0.212 [95% CI, 0.150–0.271] vs. 0.127 [95% CI, 0.092–0.151]; $P = .007$). Moreover, differences in the FPR between HIV-HCV–coinfected patients with >200 $CD4^+$ T cells/μL and non–HIV-infected patients were not statistically significant (0.127 [95% CI, 0.089–0.152] vs. 0.106 [95% CI, 0.081–0.129]; $P = .3$).

A HAART-induced increase in the $CD4^+$ T cell count to >500 cells/μL was detected in 56% of HIV-infected patients at the time of liver biopsy. The difference in the FPR between those patients with an increase of ≤225 or >225 $CD4^+$ T cells/μL (the median increase in this series) continued to be nonsignificant (0.167 [95% CI, 0.122–0.212] vs. 0.145 [95% CI, 0.123–0.191]; $P = .5$). Although FPR was more accelerated in HIV-HCV–coinfected patients with either no response or a poor immune response to HAART (<500 $CD4^+$ T cells/μL at biopsy) ($n = 18$), compared with patients with a good response to these drugs (>500 $CD4^+$ T cells/μL) ($n = 23$), differences did not reach statistical significance (0.168 [95% CI, 0.111–0.212] vs. 0.139 [95% CI, 0.094–0.177]; $P = .45$).

The effect of the putative variables associated with the FPR was evaluated. As shown in table 3, alcohol consumption and age of >20 years at the time of infection, together with the NIA score, were associated with a more accelerated FPR among non–HIV-infected patients. In the HIV-HCV–coinfected group, age of >20 years at the time of infection and a $CD4^+$ T cell count of ≤200 cells/μL at the time of diagnosis were associated with a rapid FPR. Multivariate analysis showed that alcohol consumption and age at infection were independent factors that influenced the FPR in non–HIV-infected patients, whereas age at infection, HCV load, and an immunodepressed state at the time of diagnosis of HIV infection ($CD4^+$ T cell count,

Table 3. Univariate analysis of variables putatively associated with the liver fibrosis progression rate (FPR) among patients with HIV and hepatitis C virus (HCV) coinfection (HIV-HCV–coinfected patients) and among patients infected with HCV but not infected with HIV (non–HIV-infected patients).

	All patients		HIV-HCV–coinfected patients		Non–HIVinfected patients	
Parameter	Mean FPR (95% CI)	*P*	Mean FPR (95% CI)	*P*	Mean FPR (95% CI)	*P*
Sex						
Male	0.133 (0.11–0.15)	.6	0.154 (0.11–0.19)	.8	0.140 (0.07–0.15)	.5
Female	0.122 (0.09–0.14)		0.136 (0.08–0.18)		0.109 (0.07–0.14)	
Age at infection						
≤20 years	0.111 (0.09–0.12)	.01	0.135 (0.10–0.17)	.01	0.082 (0.06–0.10)	.01
>20 years	0.153 (0.12–0.18)		0.165 (0.11–0.21)		0.139 (0.10–0.18)	
Duration of infection						
≤20 years	0.086 (0.06–0.09)	.000	0.102 (0.05–0.15)	.03	0.079 (0.06–0.10)	.000
>20 years	0.154 (0.13–0.17)		0.158 (0.10–0.20)		0.151 (0.12–0.17)	
Alcohol consumption						
≤50 g/day	0.120 (0.10–0.13)	.03	0.143 (0.11–0.17)	.1	0.090 (0.06–0.11)	.03
>50 g/day	0.168 (0.11–0.21)		0.218 (−0.11 to 0.55)		0.149 (0.09–0.20)	
NIA score						
Minimal-mild	0.122 (0.10–0.14)	.09	0.149 (0.12–0.18)	.9	0.089 (0.07–0.11)	.009
Moderate-severe	0.151 (0.11–0.19)		0.146 (0.06–0.23)		0.155 (0.10–0.21)	
HCV load, copies/mL						
$\leq 2 \times 10^6$	0.132 (0.10–0.16)	.8	0.129 (0.06–0.19)	.4	0.124 (0.07–0.17)	.1
$>2 \times 10^6$	0.135 (0.10–0.16)		0.156 (0.12–0.19)		0.080 (0.04–0.11)	
HCV genotype						.1
Either 1 or 4	0.135 (0.11–0.16)	.4	0.151 (0.11–0.19)	.8	0.172 (0.06–0.28)	
Other	0.153 (0.10–0.20)		0.142 (0.08–0.20)		0.110 (0.06–0.16)	
HIV infection						
No	0.116 (0.09–0.14)	.02	—		—	
Yes	0.152 (0.13–0.20)		—		—	
$CD4^+$ T cell count						
At diagnosis of HIV infection						
>200 cells/μL	0.112 (0.09–0.13)[a]	.001	0.130 (0.10–0.16)	.009	—	
≤200 cells/μL	0.212 (0.15–0.27)		0.210 (0.15–0.27)		—	
At liver biopsy						
>500 cells/μL	0.122 (0.10–0.14)[a]	.06	0.139 (0.09–0.18)	.45	—	
≤500 cells/μL	0.159 (0.11–0.20)		0.160 (0.11–0.21)		—	

NOTE. *P* values are for the comparison of the 2 groups listed for each parameter. NIA, necroinflammatory index.

[a] Patients without HIV coinfection were considered to have >500 $CD4^+$ T cells/μL, both at the time of diagnosis of HIV and at the time of liver biopsy.

≤200 cells/μL) were the independent factors associated with the FPR in HIV-HCV–coinfected patients (table 4).

DISCUSSION

HIV infection modifies the natural history of chronic hepatitis C, with rapid progression of fibrosis and cirrhosis [9, 11, 14, 18, 32]. In fact, the prevalence of cirrhosis was significantly higher at each of the stages of evolution of HIV disease in HIV-HCV–coinfected patients analyzed in our study. Those patients with a $CD4^+$ T cell count of <200 cells/μL had a higher prevalence of cirrhosis, a finding that supports the importance of immune surveillance for the development of liver lesions.

We have identified 2 different patterns of evolution of chronic HCV infection as a function of the presence or absence of HIV coinfection. In non–HIV-infected patients, the FPR was associated with older age at the time of infection and with alcohol consumption. These parameters previously have been related to this accelerated evolution [11, 14]. In the HIV-HCV–coinfected group, an accelerated FPR was associated with the $CD4^+$ T cell count and with the HCV load. The decrease in cell-mediated immunity associated with HIV infection is

Table 4. Multivariate analysis of variables associated with the rate of fibrosis progression among patients with HIV and hepatitis C virus (HCV) coinfection (HIV-HCV–coinfected patients) and among patients infected with HCV but not infected with HIV (non–HIV-infected patients).

Group, parameter	β	95% CI	P
All patients[a]			
Age >20 years at HCV infection	.003	0.001–0.005	.003
Daily consumption of >50 g of alcohol	.006	0.005–0.0.93	.02
HIV infection	.030	−0.012 to 0.072	.1
$CD4^+$ T cell count of ⩽200 cells/μL at diagnosis of HIV infection	.06	0.001–0.129	.04
Non–HIV-infected patients[b]			
Age >20 years at HCV infection	.06	0.004–0.12	.03
Daily consumption of >50 g of alcohol	.08	0.01–0.15	.02
HIV-HCV–coinfected patients[c]			
Age >20 years at HCV infection	.004	0.002–0.011	.145
HCV load $>2 \times 10^6$ copies/mL	.005	0.001–0.008	.008
$CD4^+$ T cell count of ⩽200 cells/μL at diagnosis of HIV infection	.07	0.014–0.12	.01

NOTE. β, partial regression coefficient; F, F statistic.

[a] Adjusted $r = .268$; $F = 7.7$; $P = .000$.

[b] Adjusted $r = .37$; $F = 5.04$; $P = .01$.

[c] Adjusted $r = .442$; $F = 5.7$; $P = .003$.

believed to permit greater replication of HCV and, consequently, greater infection of and injury to hepatocytes [32]. Also, coinfection with HIV probably alters the response of immune cells to HCV. Whereas patients with >200 $CD4^+$ T cells/μL had an FPR similar to that of non–HIV-infected patients, patients with $CD4^+$ T cell counts of ⩽200/μL had the highest FPR. The other parameter associated with a rapid FPR was HCV load. It previously had been demonstrated that the HCV load was higher in HIV-HCV–coinfected patients with low CD4+ T cell counts than in patients with high $CD4^+$ T cell counts [11, 14, 32, 33]; this was also detected in our study. However, the effect of HCV load on histopathologic liver lesions in these patients, which is demonstrated in the present study, had not been previously established.

Neither sex, risk factors for HCV infection, nor HCV genotypes were associated with an accelerated FPR. It previously has been demonstrated that risk factors for HCV infection have no effect on the stage of histopathologic lesions of the liver [4]. Also, although infection by genotypes 1 or 4 has been associated with a higher HCV load [34] and worse evolution [35], we and other investigators [14] did not detect worse evolution in those patients infected by genotypes 1 or 4 than in those infected by other genotypes.

It has been hypothesized that immune restoration induced by HAART may lead to better control of HCV replication [32]. Benhamou et al. [18] have analyzed the role of HAART in the progression of liver fibrosis due to HCV. They have demonstrated a lower FPR for patients who have been receiving HAART for a median period of 14 months, although some methodological variables are doubtful; thus, patients who did not receive HAART had significantly lower $CD4^+$ T cell counts and higher HIV loads than did patients who received HAART. Likewise, the effect of HAART on $CD4^+$ T cell count or HIV load was unknown. Hence, our work could be considered the first study in which, after a median period of 36 months of treatment, the effects of the immune response to HAART on liver lesions were evaluated. Patients with immune reconstitution induced by HAART had a lower prevalence of liver cirrhosis; however, on the basis of the results of multiple linear regression, an independent effect of immune reconstitution can be discounted. This supports, in contrast, the $CD4^+$ T cell count before receipt of treatment as the factor more clearly implicated in the FPR. The results for the effect of HAART are similar to those observed with HCV load. No differences were seen between those with and those without immunologic response [36–39]. It could be stated that anti-HIV regimens and improvement of immunologic parameters are not sufficient to control HCV infection.

In conclusion, a higher HCV load and a lower immunocompetence level influence the natural history of chronic hepatitis C, with rapid progression of fibrosis and cirrhosis occurring in HIV-HCV–coinfected patients. Immune reconstitution induced by HAART did not modify the progression of liver fibrosis. The accelerated progression of liver fibrosis and cirrhosis support a more aggressive approach to the treatment of HCV infection in these patients.

References

1. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med **2001**; 345:41–52.
2. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology **1996**; 24:289–93.
3. Di Bisceglie AM. Natural history of hepatitis C: its impact on clinical management. Hepatology **2000**; 31:1014–8.
4. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet **1997**; 349(9055):825–32.
5. Martin P. Hepatitis C genotypes: the key to pathogenicity? Ann Intern Med **1995**; 122:227–8.
6. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med **1998**; 338:853–60.
7. Soriano V, Sulkowsk M, Bergin C, et al. Care of patients with chronic hepatitis C and HIV co-infection: recommendations from the HIV-HCV International Panel. AIDS **2002**; 16:813–28.
8. Eyster ME, Diamondstone LS, Lien JM, Ehmann WC, Quan S, Goedert JJ. Natural history of the hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immunodeficiency virus. The Multicenter Hemophilia Cohort Study. J Acquir Immune Defic Syndr **1993**; 6:602–10.
9. 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.
10. Soto B, Sánchez-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.
11. Di Martino V, Rufat P, Boyer N, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. Hepatology **2001**; 34:1193–9.
12. Eyster ME, Fried MW, Di Bisceglie AM, Goedert JJ. Increasing hepatitis C virus RNA levels in hemophiliacs: relationship to human immunodeficiency virus infection and liver disease. Multicenter Hemophilia Cohort Study. Blood **1994**; 84:1020–3.
13. Lau JYN, Davis GL, Brunson ME, et al. Hepatitis C virus infection in kidney transplant recipients. Hepatology **1993**; 18:1027–31.
14. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Mutivirc Group. Hepatology **1999**; 30:1054–8.
15. Cribier B, Rey D, Schmitt C, Lang JM, Kirn A, Stoll-Keller F. High hepatitis C viraemia and impaired antibody response in patients co-infected with HIV. AIDS **1995**; 9:1131–6.
16. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis **2001**; 33:562–9.
17. Allory Y, Charlotte F, Benhamou Y, Opolon P, Le Charpentier Y, Poynard T. Impact of human immunodeficiency virus infection on the histological features of chronic hepatitis C: a case-control study. The MULTIVIRC Group. Hum Pathol **2000**; 31:69–74.
18. Benhamou Y, di Martino V, Bochet M, et al. Factors affecting liver fibrosis in human immunodeficiency virus– and hepatitis C virus–coinfected patients: impact of protease inhibitor therapy. Hepatology **2001**; 34:283–7.
19. Garfein RS, Vlahov D, Galai N, Doherty MC, Nelson KE. Viral infections in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. Am J Public Health **1996**; 86:655–61.
20. Gordon SC, Elloway RS, Long JC, Dmuchowski CF. The pathology of hepatitis C as a function of mode of transmission: blood transfusion vs intravenous drug use. Hepatology **1993**; 18:1338–43.
21. Pérez-García T, Galán F, Fernández-Gutiérrez C, Girón JA, Rodríguez-Iglesias M. Relationship of hepatitis C viremia to HIV state and to infection by specific hepatitis C genotypes. Liver **1999**; 19:288–93.
22. Carpenter CC, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1996: recommendations of an international panel. International AIDS Society–USA Panel. JAMA **1996**; 276:146–54.
23. Carpenter CC, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1997: updated recommendations of the International AIDS Society–USA Panel. JAMA **1997**; 277:1962–9.
24. Carpenter CC, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1998: updated recommendations of the International AIDS Society-USA Panel. JAMA **1998**; 280:78–86.
25. Carpenter CC, Cooper DA, Fischl MA, et al. Antiretroviral therapy in adults: updated recommendations of the International AIDS Society–USA Panel. JAMA **2000**; 283:381–90.
26. Prati D, Capelli C, Zanella A, et al. Influence of different hepatitis C virus genotypes on the course of asymptomatic hepatitis C virus infection. Gastroenterology **1996**; 110:178–83.
27. Simmonds P, Alberti A, Alter HJ, et al. A proposed system for the nomenclature of hepatitis C viral genotypes. Hepatology **1994**; 19: 1321–4.
28. Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology **1981**; 1:431–5.
29. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. J Hepatol **1991**; 13:372–4.
30. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology **1994**; 19:1513–20.
31. French METAVIR Cooperative Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. Hepatology **1994**; 20:15–20.
32. Thomas DL, Shih JW, Alter HJ, et al. Effect of human immunodeficiency virus on hepatitis C virus infection among injecting drug users. J Infect Dis **1996**; 174:690–5.
33. Torre D, Tambini R, Cadario F, Barbarini G, Moroni M, Basilico C. Evolution of coinfection with human immunodeficiency virus and hepatitis C virus in patients treated with highly active antiretroviral therapy. Clin Infect Dis **2001**; 33:1579–85.
34. Poles MA, Dieterich DT. Hepatitis C virus/human immunodeficiency virus coinfection: clinical management issues. Clin Infect Dis **2000**; 31: 154–61.
35. García-Samaniego J, Soriano V, Castilla J, et al. Influence of hepatitis C virus genotypes and HIV infection on histological severity of chronic hepatitis C. The Hepatitis/HIV Spanish Study Group. Am J Gastroenterol **1997**; 92:1130–4.
36. 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 coinfected with HIV. J Infect Dis **1998**; 177:783–5.
37. Macías J, Sanchez-Quijano A, Rey C, Lissen E. Antiretroviral treatment with nucleoside analogs does not decrease the viremia of the hepatitis C virus in patients with HIV-1 infection 9 [in Spanish]. Med Clin (Barc) **1998**; 11:118–9.
38. Rockstroh JK, Theisen A, Kaiser R, Sauerbruch T, Spengler U. Antiretroviral triple therapy decreases HIV viral load but does not alter hepatitis C virus (HCV) serum levels in HIV-HCV–coinfected haemophiliacs. AIDS **1998**; 12:829–30.
39. Pérez-Cano R, Fernández-Gutiérrez C, López-Suárez A, Mira J, Girón-González JA. Factors related to the chronicity and evolution of hepatitis C infection in patients co-infected by the human immunodeficiency virus. Clin Microbiol Infect **2002**; 8:589–97.