

The Influence of Human Immunodeficiency Virus Coinfection on Chronic Hepatitis C in Injection Drug Users: A Long-Term Retrospective Cohort Study

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In this study we analyzed the influence of human immunodeficiency virus (HIV) infection on the course of chronic hepatitis C through multivariate analysis including age, alcohol consumption, immune status, and hepatitis C virus (HCV)-related virologic factors. Eighty HIV-positive and 80 HIV-negative injection drug users included between 1980 and 1995 were matched according to age, gender, and duration of HCV infection and followed-up during 52 months. The progression to cirrhosis was the primary outcome measure. The impact of HIV on HCV-RNA load, histologic activity index, response to interferon therapy, and liver-related death was also considered. In HIV-positive patients, chronic hepatitis C was characterized by higher serum HCV-RNA levels ($P = .012$), higher total Knodell score ($P = .011$), and poorer sustained response to interferon therapy ($P = .009$). High serum HCV-RNA level was associated with low CD4-lymphocyte count ($P = .001$). Necroinflammatory score was higher in HIV-positive patients ($P = .023$) independently of the CD4-lymphocyte count, whereas increased fibrosis was related to decreased CD4-lymphocyte count ($P = .011$). The progression to cirrhosis was accelerated in HIV-positive patients with low CD4 cell count ($RR = 4.06$, $P = .024$) and in interferon-untreated patients ($RR = 4.76$, $P = .001$), independently of age at HCV infection ($P = .001$). Cirrhosis caused death in 5 HIV-positive patients. The risk of death related to cirrhosis was increased in heavy drinkers ($RR = 10.8$, $P = .001$) and in HIV-positive patients with CD4 cell count less than $200/\text{mm}^3$ ($RR = 11.9$, $P = .007$). In this retrospective cohort study, HIV coinfection worsened the outcome of chronic hepatitis C, increasing both serum HCV-

RNA level and liver damage and decreasing sustained response to interferon therapy. Age and alcohol were cofactors associated with cirrhosis and mortality. Interferon therapy had a protective effect against HCV-related cirrhosis no matter what the patient's HIV status was. (HEPATOLOGY 2001;34:1193-1199.)

Both hepatitis C virus (HCV) and human immunodeficiency virus (HIV) are transmitted by parenteral routes, and coinfection with these 2 viruses is common, particularly among patients with a history of injection drug use or transfusion. Because of the improvement in survival due to highly active antiretroviral therapies (HAARTs),¹ HCV coinfection becomes a major preoccupation for HIV-infected patients, and whether HIV may accelerate the progression of HCV-related disease in a way that affects survival of HIV-positive patients is an important issue. However, despite the high rate of HIV-HCV coinfection, data concerning the influence of HIV on the outcome of chronic hepatitis C²⁻⁸ and the influence of HCV on the survival of HIV-infected patients⁹⁻¹³ are scanty and conflicting. None of the previously reported studies took into account simultaneously virologic and host factors that may influence the outcome of chronic hepatitis C in HIV-positive patients. The influence of virologic factors, such as HCV-genotype or viral level, that has been reported to be a prognostic factor in transplant recipients^{14,15} has not been studied in HIV-positive patients. Host factors, such as the impact of age, gender, and alcohol consumption that influences HCV-related disease progression,^{16,17} remain to be evaluated in HIV-coinfecting patients.

Therefore, the aims of this work were (1) to compare the virologic and histologic characteristics of chronic hepatitis C in HIV-positive and HIV-negative injection drug users matched with respect to age, gender, and duration of hepatitis C; (2) to compare the progression to cirrhosis and the survival in both groups; and (3) to evaluate through multivariate analyses the respective influence of HIV and HIV-related immunodepression on HCV viral level, histologic findings, progression to cirrhosis, and survival.

PATIENTS AND METHODS

Study Design

This was a retrospective cohort follow-up study conducted in Hôpital Beaujon including 80 patients with HIV-HCV coinfection and a past history of injection drug use who were consecutively admitted between 1980 and 1995 for a liver biopsy. As a control group, 80 HIV-negative patients with chronic hepatitis C and a past

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; ALT, alanine transaminase; RR, relative risk; AST, aspartate transaminase; GGT, gamma glutamyl transpeptidase.

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history of injection drug use who were admitted for a liver biopsy during the same period were included. These control patients were selected by individually matching with HIV-positive patients according to gender, age, and known duration of hepatitis C. In HIV-positive and HIV-negative patients, we compared the virologic characteristics of HCV infection, the biochemical and histologic activity of chronic hepatitis C, the progression to cirrhosis, and the survival rate. Studied patients had been seen for the first time between 1980 and 1995. The follow-up ended at death or in May 1997.

HIV-Positive Patients

Ninety-two HIV-HCV coinfecting injection drug users were admitted during the study period. Among them, 3 were excluded because of hepatitis B virus coinfection and 9 were excluded because of hepatitis delta virus coinfection. Hepatitis B and delta virus coinfection were assessed by the presence of hepatitis B surface antigen, delta antigen, or anti-delta antibodies. The patients were referred from different departments of infectious diseases to evaluate the progression of liver disease and the opportunity for interferon therapy. Epidemiologic data were recorded (*i.e.*, age, gender, onset of injection drug use, and alcohol consumption). The quantitative evaluation of alcohol consumption was obtained from the anamnesis and expressed in grams per day of average consumption. This evaluation was performed at baseline considering the self-reported alcohol consumption of the past 5 years and every year during follow-up. HIV infection was assessed by the positivity of 2 serologic tests including 1 determination of anti-HIV antibodies by Western blotting. HIV status was evaluated every 3 months by a physical examination, and the determination of the CD4 lymphocyte count in the peripheral blood. Antiretroviral therapy (Zidovudine or didanosine) was given when the CD4 lymphocyte count was less than 300/mm³. Fifty-two patients received zidovudine, 21 before the first evaluation of the study and 31 during follow-up. Only 5 patients received didanosine and none received protease inhibitor, non-nucleoside analogue, or other nucleoside analogues of HIV reverse transcriptase during the follow-up period. HCV infection was assessed for all patients by the positivity of 2 serologic second-generation or third generation tests (EIA-2.0 and EIA 3.0; Ortho Diagnostics, Raritan, NJ; RIBA 2.0 and RIBA 3.0; Chiron, Emeryville, CA). For the patients seen before 1992, the serology was performed by third generation tests from stored sera. Liver biochemical tests were performed and recorded monthly. The activity of transaminases at the first evaluation could be either normal (less than 40 UI/L) or increased. A liver biopsy was systematically performed during the first 3 months after the first clinic. It was performed percutaneously in 75 patients, or, in 5 patients, by transjugular catheterism because of ascites, elevated prothrombin time, severe thrombopenia, or elevated bleeding time.

HIV-Negative Patients

One HIV-negative control patient was sought for each HIV-positive injection drug user. The controls were injection drug users followed for more than 12 months for chronic hepatitis C. They were randomly selected among a series of 243 consecutive patients seen during the same period by the same practitioner as the patient with HIV-HCV coinfection. The controls were individually matched to the HIV-positive patients with respect to age (within 5 years), gender, and the previous known duration of chronic hepatitis C (within 5 years), estimated by the delay between the onset of injection drug use and the first clinic in Hôpital Beaujon. The same criteria for inclusion and exclusion were used in selecting HIV-negative and HIV-positive patients. The same data were recorded, except for the follow-up of HIV infection.

Interferon Therapy

A single 6-month course of interferon alfa 2b therapy, 3 MU 3 times weekly, was given when the following conditions were present: (1) no contraindication for interferon therapy, (2) histologically proven chronic active hepatitis with a Knodell activity index of more

than 6, (3) a CD4 lymphocyte count of more than 200/mm³ in HIV-positive patients, and (4) patient's consent. Forty-seven HIV-positive and 61 HIV-negative patients were thus treated ($P = .041$). Treated and untreated patients were similar with respect to age, gender, previous duration of chronic hepatitis C, serum alanine transaminase (ALT) level, and HCV genotype. Untreated patients were more often alcohol consumers (63% vs. 42%, $P = .018$), had higher serum HCV-RNA level (18.0 ± 11.7 vs. $3.8 \pm 6.0 \times 10^6$ Eq/mL, $P = .008$) and lower Knodell score (6.3 ± 3.1 vs. 7.3 ± 2.4 , $P = .029$) comparatively with treated patients. The CD4 cell count was not significantly different in HIV-positive treated and HIV-positive untreated patients. The response to interferon therapy (biochemical response) was defined by the normalization of serum ALT at the end of therapy (end of treatment biochemical response) and at 6 months after the end of therapy (sustained biochemical response). Only biochemical responses to interferon therapy were analyzed, because numerous well-stored serum samples were missing for retrospective polymerase chain reaction analysis.

Virology

HCV genotype was retrospectively determined in 76 well-stored available serum samples by using a commercial probe hybridization assay (InnoLipa HCV; Innogenetics, Ghent, Belgium), which accurately identifies HCV genotypes 1 through 6, according to the Simmonds' classification.

Quantification of serum HCV RNA was performed with a commercial branched DNA signal amplification assay (Quantiplex HCV; Chiron, Emeryville, CA) from sera harvested before interferon therapy in treated patients and stored in optimal condition at -80°C . Only 62 sera (31 from HIV-positive patients, 31 from HIV-negative patients) were available for this analysis.

Histology

At least one liver biopsy, performed at the beginning of the follow-up, was available for each patient. Histologic examination was performed without knowledge of the patient's clinical history and HIV status. All biopsies were formalin-fixed and paraffin-embedded. Sections 5 μm thick were stained for observation with hematoxylin and eosin. The following elementary lesions were scored according to the Knodell scoring system: portal inflammation, piecemeal necrosis, lobular inflammation, and fibrosis. A specific necroinflammatory score was obtained by subtracting the fibrosis score from the total score. During the follow-up, 92 patients had a second liver biopsy. It was performed systematically either after treatment, or when the patient developed jaundice, unexplained fever, or signs of portal hypertension.

Statistical Analysis

All the statistical analyses were performed with the SAS package for WINDOWS. Quantitative results were expressed by mean \pm SD. The Kaplan-Meier method was used to calculate the actuarial rate of cirrhosis and the survival rate. Univariate analyses were performed by using χ^2 , Fisher, Student *t*, Mann Whitney, linear regression, and log-rank tests. A *P* value less than .05 was considered statistically significant. Variables included in all the multivariate models were those considered as significant with a *P* value less than .10 in univariate analysis. Multivariate analyses were performed with stepwise method for multiple linear regression and time-dependent proportional hazard Cox's model. The multiple linear regression models were performed with caution to the reported validation procedures¹⁸: the normal distribution of the response variable was checked for each value of each explanatory variable, all potential explanatory variables were assessed for collinearity, and outliers were identified with their specific influence on the estimated and predicted values. The time-dependent Cox's model was performed with caution to the log-linearity of predicted values during follow-up.

RESULTS

The characteristics of the 80 HIV-positive and the 80 matched HIV-negative injection drug users are indicated in Table 1. They were followed-up during 52 ± 30 months (range, 12 to 180 months).

Progression to Cirrhosis and Survival

Progression to Cirrhosis. At the first histologic evaluation, cirrhosis was found in 7 HIV-positive patients and in 3 HIV-negative patients ($P = .32$, Table 1). Baseline alcohol consumption (>80 g/d) was the only factor significantly associated with cirrhosis at baseline ($P = .002$), whereas liver biopsy did not evidence any sign of alcohol-induced hepatitis associated with cirrhosis. During follow-up, 10 additional patients (7 HIV positive and 3 HIV negative) developed cirrhosis, with a mean delay of 102 ± 47 months in HIV-negative patients and 64 ± 34 months in HIV-positive patients. All cases of cirrhosis were histologically proven after a clinical or ultrasonographic suspicion. The prevalence of cirrhosis at the end of follow-up was 17.5% in HIV-positive patients and 7.5% in HIV-negative patients ($P = .056$). The actuarial rate of cirrho-

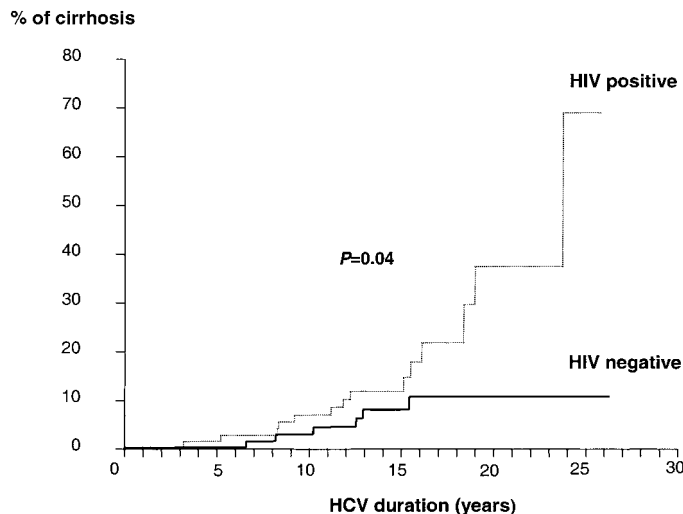


FIG. 1. Progression to cirrhosis: comparison between HIV-positive and HIV-negative patients.

TABLE 1. Baseline Characteristics of HIV-Positive and HIV-Negative Patients

	HIV Positive	HIV Negative	P
Number	80	80	
Age* (yr)	31 \pm 5	31 \pm 5	.85
Gender* (M/F)	58/22	58/22	1
Route of HCV transmission (%IVDUs)	100%	100%	1
Duration of HCV infection* (yr)	10.6 \pm 4.7	10.2 \pm 4.5	.58
Alcohol consumption			
0 g/d	37	45	
<80 g/d	21	23	.151
>80 g/d	22	12	
ALT (U/L)	204 \pm 281	158 \pm 96	.176
AST (U/L)	144 \pm 178	74 \pm 49	.001
GGT (U/L)	187 \pm 222	86 \pm 150	.002
CD4 lymphocyte count (/mm ³)	482 \pm 322	—	
Cirrhosis on the first biopsy	7	3	.33
First total Knodell score	7.5 \pm 2.9	6.5 \pm 2.2	.011
First necroinflammatory score	6.0 \pm 2.7	5.0 \pm 1.9	.009
First fibrosis score	1.6 \pm 1.2	1.4 \pm 1.1	.199
Serum HCV RNA level† (MEq/mL)	9.3 \pm 10.9	3.6 \pm 2.9	.012
HCV genotype‡			
1a	29% (n = 9)	22% (n = 10)	
1b	23% (n = 7)	18% (n = 8)	
2a	0%	7% (n = 3)	.32
3a	42% (n = 13)	53% (n = 24)	
4	3% (n = 1)	0%	
Others	3% (n = 1)	0%	
Interferon therapy	47	61	.041

NOTE. Patients were matched according to age, gender, and duration of HCV infection. Quantitative variables are expressed as mean \pm SD. Virologic data were available in a subset of 76 patients (31 HIV positive) for HCV genotype, and 62 patients (31 HIV positive) for HCV-RNA load. Baseline alcohol consumption was not different between HIV-positive and HIV-negative patients. However, there was a trend for a more frequent alcohol consumption of more than 80 g/d in HIV-positive patients. This is why subsequent analyses considered alcohol consumption as a dichotomous variable defined by 80 g/d.

Abbreviation: IVDUs, intravenous drug users.

*Matching factors.

†Data available for 62 patients.

‡Data available for 76 patients.

sis was significantly higher in HIV-positive patients than in HIV-negative patients: 7% vs. 3% at 10 years from HCV infection, 37% vs. 10% at 20 years, and 69% vs. 10% at 25 years ($P = .040$, Fig. 1). It was also higher in patients with high total Knodell score at baseline ($P = .012$), in patients who did not receive interferon therapy ($P = .006$), and was correlated with age at HCV infection ($P < .001$) and low CD4 cell count ($<200/\text{mm}^3$) during follow-up ($P = .018$). Conversely, no relationship was found between progression to cirrhosis and continued alcohol consumption. In interferon-treated patients without cirrhosis at baseline ($n = 103$), an end-of-treatment biochemical response to interferon was associated with a lower rate of subsequent cirrhosis ($P = .003$). Conversely, neither gender nor self-reported alcohol consumption at baseline had significant influence on the progression to cirrhosis (Table 2). Multivariate analysis identified 3 independent predictors of subsequent cirrhosis: HIV coinfection with low CD4 cell count during follow-up (relative risk [RR] = 4.06), old age at HCV infection, and absence of interferon therapy (RR = 4.76) (Table 2).

Survival. Death occurred in 10 HIV-positive and 3 HIV-negative patients. HCV-related cirrhosis was present at the time of death in 8 HIV-positive and 3 HIV-negative patients. Five HIV-positive patients died of HCV-related cirrhosis. One HIV-infected patient, who kept a CD4 cell count of more than $400/\text{mm}^3$ during the whole follow-up, died from hepatocellular carcinoma. The others died from variceal bleeding ($n = 3$) and spontaneous peritonitis ($n = 1$). Death was related to AIDS in 5 HIV-positive patients (including 2 cirrhotic patients). The actuarial rate of death related to cirrhosis was higher in HIV-positive patients with a CD4 cell count of less than $200/\text{mm}^3$ (RR = 11.91, $P = .007$), in heavy drinkers (RR = 10.78, $P = .001$), and was positively correlated to age ($P = .026$). Patients who received interferon therapy had a lower risk of death related to cirrhosis (RR = 0.20, $P = .031$), (Table 3).

Biochemical, Virologic, and Histologic Features of Liver Disease

Biochemical Liver Tests. Biochemical liver tests showed more frequent abnormalities in HIV-positive patients compared with HIV-negative patients: serum aspartate transaminase

TABLE 2. Predictors of the Progression to HCV-Related Cirrhosis

	N	β	SE (β)	RR	95% CI of RR	Wald t	P
Univariate analysis							
HIV coinfection	160	1.01	0.49	2.74	1.05 to 7.15	2.054	.040
Gender (male)	160	1.17	0.64	3.22	0.91 to 11.34	1.820	.069
Age at HCV infection	160	0.21	0.04	1.23	1.13 to 1.33	5.004	.000
Baseline and continued alcohol consumption > 80 g/d							
Interferon therapy	160	-1.25	0.45	0.29	0.12 to 0.70	-2.758	.006
CD4 < 200	160	1.40	0.59	4.07	1.27 to 13.07	2.363	.018
First Knodell score	160	0.19	0.08	1.21	1.04 to 1.41	2.502	.012
End of treatment biochemical response to IFN therapy							
Sustained biochemical response to IFN therapy	103	-2.53	0.85	0.08	0.02 to 0.42	-2.965	.003
Multivariate analysis							
Age at HCV infection	160	0.16	0.05	1.18	1.07 to 1.29	3.429	.001
Interferon therapy	160	-1.56	0.49	0.21	0.08 to 0.55	-3.199	.001
CD4 cell count < 200	160	1.40	0.62	4.06	1.20 to 13.68	2.260	.024

NOTE. Data are the predictors of the progression to cirrhosis in 80 HIV-positive and 80 HIV-negative injection drug users. Univariate analyses used the log-rank test with time-dependent correction for the factors recorded after HCV infection. Multivariate analysis (Cox model) considered only 3 variables (because of the small number of events) on the basis of absence of colinearity and results of the univariate analyses.

(AST), ALT, and gamma glutamyl transpeptidase (GGT) levels were higher in HIV-positive than in HIV-negative patients, and an AST/ALT ratio higher than 1 was more frequently observed in HIV-positive patients (22% vs. 2.3%, $P < .001$). In multivariate analysis, a high serum AST level was independently associated with HIV infection ($P = .003$) and with young age ($P = .021$), a high GGT level was associated with HIV infection ($P = .006$) and baseline alcohol consumption ($P = .009$), and an AST/ALT ratio higher than 1 was associated with HIV infection ($P < .001$) and cirrhosis ($P < .001$).

Virologic Status of HCV Infection. HCV genotype, characterized in 31 HIV-positive and 45 HIV-negative patients similar with respect to age, gender, and previous duration of HCV infection, was not differently distributed according to HIV status (Table 1). Serum HCV-RNA levels were measured in 31 HIV-positive and 31 HIV-negative patients similar with respect to gender, age, and previous duration of chronic hepatitis C. Mean serum HCV-RNA levels were higher in HIV-positive than in HIV-negative patients ($P = .012$, Table 1). A CD4 lymphocyte count less than $400/\text{mm}^3$ was significantly associated with a higher HCV-RNA level ($12.9 \pm 14.3 \times 10^6$ Eq/mL vs. $4.4 \pm 3 \times 10^6$ Eq/mL, $P = .001$). A significant relation was found between baseline alcohol consumption and high serum HCV-RNA level ($8.9 \pm 11.2 \times 10^6$ Eq/mL vs. $4.4 \pm 4.4 \times 10^6$ Eq/mL, $P = .011$). In multivariate analysis, a CD4 cell count of less than $400/\text{mm}^3$ was the only factor that

correlated with high serum HCV-RNA levels ($P = .001$, Table 4); there was a trend for alcohol to increase the HCV-RNA level ($P = .091$).

Histologic Evaluation of the Liver. The total Knodell score was higher in HIV-positive patients ($P = .011$, Table 1) because of the increase of piecemeal necrosis (1.7 ± 1.1 vs. 1.2 ± 0.9 , $P = .005$), lobular inflammation (1.8 ± 1.2 vs. 1.2 ± 1.0 , $P = .001$), and fibrosis (1.6 ± 1.2 vs. 1.4 ± 1.1 , $P = .199$). In HIV-positive patients, fibrosis was negatively correlated with CD4 cell count ($r = -0.25$, $P = .039$). Conversely, no significant relationship was found between the necroinflammatory score and the CD4 cell count. Serum HCV-RNA level was positively correlated with necroinflammatory score ($r = 0.27$, $P = .022$), but not with fibrosis ($r = 0.04$, $P = .72$). The respective influences of HIV, serum HCV-RNA level, and immunodepression on necroinflammatory and fibrosis scores are summarized in Table 5.

Response to Interferon Therapy

An end-of-treatment biochemical response to interferon therapy, defined by the normalization of serum ALT at the end of treatment, was observed in 22 HIV-positive and 38 HIV-negative patients (46.8% vs. 62.3%, not significant). A sustained biochemical response to interferon therapy, defined by serum ALT remaining within normal values during the 6 months after the end of treatment, was observed in 3 HIV-

TABLE 3. Predictors of Mortality Related to HCV Cirrhosis: Results of Univariate Analyses

Variables	β	SE (β)	RR	95% CI (RR)	Wald t	P
HIV infection	1.14	0.75	3.13	0.72 to 13.56	1.525	.127
CD4 < $200/\text{mm}^3$ at baseline	2.48	0.92	11.91	1.95 to 72.54	2.687	.007
Gender (male)	0.16	0.74	1.35	0.27 to 5.00	0.213	.83
Age at baseline	0.15	0.07	1.17	1.03 to 1.34	2.232	.026
Alcohol > 80 g/d at baseline	2.38	2.38	10.78	2.49 to 46.62	3.183	.001
Histologic activity index at baseline	0.24	0.16	1.27	0.92 to 1.74	1.454	.146
Interferon therapy	-1.61	0.75	0.20	0.05 to 0.87	-2.154	.031

NOTE. Univariate analyses used log-rank test considering variables recorded at baseline in the whole population (160 patients). The small number of cases of liver-related death ($n = 8$) did not allow multivariate analysis.

TABLE 4. Factors Associated With an Increase of Serum HCV-RNA Level: Results of the Multivariate Analysis

Variables	Multiple Regression Analysis (N = 62, r ² = 0.29)				
	β	SE (β)	95% CI (β)	Wald t	P
Intercept	131.76	90.93	-46.46 to 309.98	1.449	.147
Age	-1.31	3.47	-8.11 to 5.49	-0.378	.71
Gender (male)	14.60	24.63	-33.67 to 62.87	0.593	.55
HCV duration	1.00	3.38	-5.62 to 7.62	0.296	.77
CD4 > 400/mm ³	-78.96	23.86	-125.73 to -32.19	-3.309	.001
Alcohol > 80 g/d at baseline	46.48	27.48	-7.38 to 100.34	1.691	.091
Cirrhosis at baseline	63.75	46.18	-26.76 to 154.26	1.380	.167

NOTE. HCV-RNA load was considered a continuous quantitative variable. The multiple regression analysis was performed in the 62 patients (31 HIV positive) for whom serum HCV-RNA load was available.

positive and 16 HIV-negative patients (6.4% vs. 26.2%, $P = .009$). The other factors associated with sustained biochemical response to interferon therapy were low pretherapeutic serum HCV-RNA level ($P = .040$), infection with HCV genotype 2 or 3 ($P = .036$), low serum GGT activity ($P = .003$), and low serum AST activity at baseline ($P = .041$). The low number of patients with sustained biochemical response to interferon therapy did not allow any multivariate analysis.

Outcome of HIV Infection

A significant decrease of CD4 cell count with time was observed in the large majority ($n = 71$) of patients, but only a few patients with CD4 more than 200 at baseline ($n = 5$) showed a marked decline in the CD4 cell count (below 200) during follow-up. Twelve patients developed opportunistic infection and 5 died of AIDS 65 ± 44 months after inclusion. Among the whole population of HIV-infected patients, the relevant predictors of mortality at baseline were a CD4 cell count of less than 200/mm³ (RR = 11.32, $P = .001$) and an alcohol consumption more than 80 g/d (RR = 4.23, $P = .033$).

DISCUSSION

Our retrospective study shows a detrimental influence of HIV infection on the outcome of chronic hepatitis C, showing a more rapid progression to cirrhosis and an increased risk of cirrhosis-related death in cases of HIV-related immunodepression. It shows also a significant effect of HIV infection on HCV-RNA levels, biochemical liver tests, liver histologic necroinflammatory lesions, and biochemical responses to interferon therapy. This negative influence of HIV on the course of chronic hepatitis C has already been reported in injection drug users in some studies,^{2,3,19} but not in all.^{7,8} However, our

study provides stronger evidence than previous studies for the following reasons: it provides a long-term follow-up with histologic assessment of a relatively large number of patients, matched for the main prognostic factors (age, duration of HCV infection, gender) and includes multivariate analysis including excessive alcohol consumption, that is common in such a population. Conversely to the study of Benhamou et al.¹⁹ based on a mathematic model from cross-sectional data, our study provides a true longitudinal observation. We observed a 20-year rate of cirrhosis of 37% and 10% in HIV-positive and HIV-negative patients, respectively. The relatively low rates of cirrhosis observed in both groups, particularly in the HIV-negative individuals, may be explained by the young age (mean age at HCV infection was 21 years), consistent with that reported in young women²⁰ and young military recruits.²¹

One limitation of our study is that the small number of events, especially liver-related death, did not allow complete multivariate analyses for each outcome measure. Type 1 and type 2 errors may also have been introduced by the small numbers of events. Hence, only positive results should be considered as true and negative results should be considered cautiously. Another limitation was that our HIV-positive population was not reflective of the present HIV-positive population, which often receives HAART; however, this fact allows a better demonstration of a more severe liver disease induced by HIV coinfection, because HAART has been reported to worsen HCV infection despite improvement of HIV parameters^{22,23} or to induce hepatotoxicity.²⁴⁻²⁷ The long-term follow-up, up to 15 years, in this study, permitted us to confirm that HCV-related liver disease was able to cause death, even in HIV-infected patients whose survival was not improved by new

TABLE 5. Factors Associated With an Increase of Histologic Activity and Liver Fibrosis: Results of Univariate Analyses

Variable	Necroinflammatory Score				Fibrosis			
	β	SE (β)	95% CI (β)	P	β	SE (β)	95% CI (β)	P
HIV coinfection	1.02	0.38	0.26 to 1.77	.009	0.15	0.12	-0.09 to 0.39	.211
CD4 < 400/mm ³	0.89	0.47	-0.04 to 1.82	.062	-0.38	0.15	-0.67 to -0.09	.011
Gender (male)	0.02	0.04	-0.06 to 0.10	.55	0.03	0.14	-0.24 to 0.30	.83
Age	0.04	0.06	-0.08 to 0.16	.50	-0.01	0.01	-0.03 to 0.01	.32
Alcohol > 80 g/d at baseline	0.60	0.48	-0.34 to 1.55	.214	0.17	0.17	-0.12 to 0.46	.257
HCV duration	0.03	0.04	-0.06 to 0.11	.54	-0.01	0.01	-0.03 to 0.01	.32
HCV-RNA level	0.008	0.033	0.00 to 0.01	.022	0.0004	0.0011	-0.00 to 0.00	.72
HCV genotype 1	0.61	0.47	-0.31 to 1.54	.195	-0.02	0.15	-0.31 to 0.27	.89

NOTE. The necroinflammatory score and the fibrosis score are considered continuous quantitative variables. Univariate analyses considered the whole population ($n = 160$) and used either Student's *t* test (for dichotomous studied variables) or correlation test (for continuous quantitative variables).

antiretroviral therapies. This observation in injection drug users is consistent with that reported in hemophiliacs.²⁸

According to our results, the deleterious impact of HIV on chronic hepatitis C may not be the consequence of a single phenomenon. HIV-related immunodepression was associated with an increase of liver fibrosis independently of the duration of HIV-HCV coinfection. This finding illustrates that HIV-related immunodepression is a factor strongly involved in the relationship between HIV infection and the severity of chronic hepatitis C. This is in accordance with that observed in other groups of immunocompromized patients such as patients with hypogammaglobulinemia,²⁹ or transplant recipients,³⁰ who were reported to rapidly develop extensive liver fibrosis or cirrhosis. This is also in accordance with that reported in HIV-infected hemophiliacs, in which the risk of liver failure was 11- to 21-fold increased compared with HIV-negative patients and was associated with HIV-related immunodepression.^{4,5} However, when considering only necroinflammatory liver lesions, we noted that HIV infection, but not the level of immunodeficiency (as assessed by a low CD4 cell count), was associated with an increase of lesions, suggesting that HIV may *per se* increase HCV-related liver damage. The mechanism involved in such a phenomenon remains to be determined. One may hypothesize that the infection of Kupffer cells and endothelial cells by HIV may induce an increase of the Th1-like cytokines released from Kupffer cells and an overexpression of adhesion molecules in endothelial cells favoring both the margination and the activation of peripheral blood mononuclear cells.^{31,32} Both phenomena may contribute to increase immune-mediated lobular inflammation and hepatocyte necrosis.

HIV coinfection was also associated with an increase of HCV-RNA level, more marked in patients with low CD4 cell count, consistently with previous reports.^{5,33-35} In our patients, serum HCV-RNA levels were positively correlated with necroinflammatory lesions ($P = .019$). Although multivariate analysis failed to prove an independent relationship between HCV-RNA level and progression to cirrhosis, we cannot rule out that the increase of HCV-RNA level in HIV-positive patients may play a role in liver damage. Our multivariate analysis, which was conducted in a restricted group of patients (because of missing serum samples), may have underestimated its influence.

This study also evaluated if age, gender, or alcohol consumption, which are the most important factors associated with the severity of HCV-related liver disease in HIV-negative patients,^{15,16} still plays a role in HIV-positive patients. Indeed, age at HCV infection had been previously suggested to have an important impact on the progression of HCV-related disease in HIV-infected patients in 3 published case-reports.³⁶⁻³⁸ In those reports, 5 HIV-infected patients developed HCV-related cirrhosis 2 to 4 years after infection; they were 48 to 61 years old at infection. But the respective impact of age and HIV coinfection was not evaluated. In our multivariate analysis, the influence of age was strongly evidenced: age at infection was a predictor of subsequent cirrhosis, independently of HIV status. The impact of gender on the course of chronic hepatitis C was not significant in our study. Finally, another cofactor of HCV-related liver disease severity was alcohol consumption. Although there was no significant difference in alcohol consumption between HIV-positive and HIV-negative patients, there were more heavy alcohol consumers among HIV-posi-

tive patients (27.5%) than among HIV-negative patients (15.0%) at baseline ($P = .054$). Alcohol was strongly associated with the presence of HCV-related cirrhosis at baseline ($P = .002$). Continued alcohol consumption did not appear as a cofactor of progression to cirrhosis. This might be related to the absence or reduction of alcohol consumption induced by medical counseling during follow-up.³⁹ However, one cannot rule out the possibility of a relative inaccuracy in the self-reported alcohol consumption during follow-up. Excessive baseline alcohol consumption was also associated with an 11-fold increased risk of cirrhosis-related mortality and a 12-fold increased risk of mortality in HIV-HCV-coinfected patients. Another retrospective study identified both alcohol and HIV to have a deleterious effect on chronic hepatitis C in drug users but failed to find an additive deleterious effect of alcohol in HIV-positive patients.³ In our study, the deleterious effect of alcohol on the course of HCV-related liver disease was independent of HIV status, consistent with that seen in HIV-negative patients.^{15,16} Moreover, a relationship between alcohol and serum HCV-RNA level was observed in our study, as well as previously reported in HIV-negative patients.⁴⁰ This relationship may explain in part the additive deleterious effect of alcohol on liver damage in HIV-positive patients.

Because this study provided follow-up information, it was impossible not to consider patients treated by interferon. Interferon therapy had been more often given in HIV-negative patients, patients without alcohol consumption, and patients with more severe liver disease at baseline. Considering the whole population, a significant influence of interferon therapy was found on decreasing the rate of cirrhosis, whatever the age and the HIV status were. A confounding factor should be that the response to interferon therapy was influenced by the degree of fibrosis on the pretreatment liver biopsy. We tested this hypothesis and found no significant association between baseline liver fibrosis and biochemical response to interferon therapy (data not shown). Interferon therapy was also associated with a decrease of cirrhosis-related mortality. Such relationship could not be investigated through multivariate analysis because of the small number of cirrhosis-related deaths. These findings remain to be cautiously interpreted because of the retrospective and uncontrolled design of this study. Our results are in accordance with studies that showed a beneficial effect of interferon therapy on the progression of liver fibrosis in HIV-negative patients, even in patients who did not develop sustained virologic biochemical response.⁴¹⁻⁴³

In conclusion, we observed that HIV infection is associated with a worsened course of chronic hepatitis C, even before the occurrence of marked decline in CD4 cell count, and that host factors involved in the severity of chronic hepatitis C (*i.e.*, age and alcohol) are still true in HIV-infected patients. Thus, it is possible that the deleterious influence of HIV on the outcome of chronic hepatitis C will still persist in HIV-infected patients receiving HAART. HCV-related mortality may thus increase, because the decrease of HIV-related mortality may allow for the progression of HCV infection to end-stage liver disease. In this setting, alcohol withdrawal should be a major recommendation to prevent HCV-related cirrhosis and to increase survival of HIV-HCV-coinfected patients. In this population, treatment against HCV seems efficient to prevent the occurrence of cirrhosis. These results support the consideration of therapy for chronic hepatitis C at an early stage in HIV-positive patients. Randomized controlled trials of a combination

of interferon (in particular pegylated interferon) with ribavirin are needed in this population of patients.

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