Liver Fibrosis Progression in Human Immunodeficiency Virus and Hepatitis C Virus Coinfected Patients

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The natural history of hepatitis C virus (HCV) infection in human immunodeficiency virus (HIV)-infected patients has never been studied according to the concept of liver fibrosis progression. The aim of this work was to assess the fibrosis progression rate in HIV-HCV coinfected patients and in patients infected by HCV only. A cohort of 122 HIV-HCV coinfected patients was compared with a control group of 122 HIV-negative HCV-infected patients. Groups were matched according to age, sex, daily alcohol consumption, age at HCV infection, and duration and route of HCV infection. The fibrosis progression rate was defined as the ratio between fibrosis stage (METAVIR scoring system) and the HCV duration. The prevalence of extensive liver fibrosis (METAVIR fibrosis scores 2, 3, and 4) and moderate or severe activity were higher in HIV-infected patients (60% and 54%, respectively) than in control patients (47% and 30%, respectively; $P < .05$ and $P < .001$, respectively). The median fibrosis progression rate in coinfected patients and in control patients was 0.153 (95% confidence interval [CI], 0.117-0.181) and 0.106 (95% CI, 0.084-0.125) fibrosis units per year, respectively ($P < .0001$). HIV seropositivity ($P < .0001$), alcohol consumption (>50 g/d, $P = .0002$), age at HCV infection (<25 years old, $P < .0001$), and severe immunosuppression (CD4 count ≤200 cells/μL, $P < .0001$) were associated with an increase in the fibrosis progression rate. In coinfected patients, alcohol consumption (>50 g/d), CD4 count (≤200 cells/μL), and age at HCV infection (<25 years old) ($P < .0001$, respectively) were associated with a higher fibrosis progression rate. HIV seropositivity accelerates HCV-related liver fibrosis progression. In coinfected patients, a low CD4 count, alcohol consumption rate, and age at HCV infection are associated with a higher liver fibrosis progression rate. (HEPATOLOGY 1999;30:1054-1058.)

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) share the same parenteral routes of transmission. The prevalence of HCV antibodies in HIV-infected patients ranges from 8% in homosexual men,[1] to 60% in hemophiliacs,[2] or 80% in intravenous (IV) drug users.[3] An increase in survival of HIV-infected persons related to active antiretroviral therapies[4,5] highlights the problem of chronic hepatitis C in HIV-coinfected patients. HCV-related liver disease may be more severe in HIV-infected people than in non–HIV-infected individuals.[6-9] The prevalence of cirrhosis may be 3-fold higher in HIV-HCV coinfected patients than in HIV-negative HCV-infected patients,[9,10] and one third of coinfected patients is at risk of dying of liver disease.[11] These results were obtained by comparing HIV-positive patients with HIV-negative patients matched only with respect to the route of infection, sex, or age. No attention was given to alcohol consumption, duration of HCV infection, or age at HCV infection. However, in HIV-negative HCV-infected individuals, age at infection, alcohol consumption, and sex are independent factors influencing the rate of HCV-related liver fibrosis progression.[12] Thus, a greater severity of HCV infection, especially related to HIV coinfection, remains to be shown by using a multivariate analysis considering these factors. Moreover, the concept of liver fibrosis progression, as previously defined,[12] may be a reliable tool to perform such an analysis. Thus, the aims of this study were (1) to determine the fibrosis progression rate in HIV-HCV coinfected patients compared with HIV-negative HCV-infected patients, (2) to investigate the role of HIV coinfection on the fibrosis progression rate, and (3) to identify factors independently correlated with the fibrosis progression rate in HIV-infected patients, with specific attention to the immune status and factors affecting the liver fibrosis progression previously identified in patients infected only with HCV.

PATIENTS AND METHODS

Patients

Patients included in the study belonged to a single center cohort (DOSVIRC). This cohort includes all the patients with hepatitis C (defined as a positive serology result by at least a second generation enzyme-linked immunosorbent assay [ELISA] test) followed-up in

Abbreviations: HIV, human immunodeficiency virus; HCV, hepatitis C virus; IV, intravenous; ELISA, enzyme-linked immunosorbent assay; METAVIR, xxx; HAART, highly active antiretroviral therapy; NRTI, nucleoside analogue reverse transcriptase inhibitors; CI, confidence interval.

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the Liver and Gastroenterology Department of the Pitié-Salpêtrière Hospital before 1993 retrospectively and prospectively thereafter. For each patient, a specific questionnaire containing 129 items was collected. This included 26 social-demographic–administrative items, 30 risk factor items, 29 clinical items from each visit, 21 biological and virological items, 14 histological items when the liver biopsy was performed, and 9 treatment items.

HIV-Positive Patients. HIV-positive patients were included in this study if they met the following inclusion criteria: coinfection with HIV and HCV, known date of HCV infection, IV drug use or transfusion, HCV-related infection, and an interpretable liver biopsy with fibrosis graded according to the METAVIR scoring system.[13] Date of infection was defined as the date of first transfusion, or date of the first IV drug use. HIV infection was defined by the positivity of both ELISA and Western blot assays. HCV infection was defined by the positivity of both a second generation ELISA and HCV-RNA polymerase chain reaction. Exclusion criteria were the presence of hepatitis B surface antigen or Delta antigen or antibodies; interferon or ribavirin therapy before liver biopsy; signs of alcoholic hepatitis on liver biopsy; and infectious, autoimmune, tumoral, biliary, or vascular-associated liver disease.

HIV-Negative Patients. The control group included patients infected only by HCV. All patients had negative HIV serological makers (determined by ELISA assay). Patients in the control group were matched according to age at HCV infection (±2 years), duration of HCV infection (±2 years), sex, alcohol consumption (according to the following classes: 50 g or less and more than 50 g of pure alcohol equivalent per day; within these classes, patients were matched ±20 g), and routes of infection (transfusion, IV drug use). The matching process was made without knowing the fibrosis stages. The same data and inclusion and exclusion criteria were applied to HIV-negative patients and for HIV-positive patients.

Simulated Group. A second control group of virtual patients was built using a simulation. The mathematical model has been previously validated in HIV-negative patients with chronic hepatitis C.[12] Briefly, it estimates the fibrosis progression rate using 3 relevant variables (age at HCV infection, alcohol consumption expressed in grams per day, and sex) by the following formula: expected fibrosis progression rate per year = 0.058 − (0.0035 × duration of infection in years) + (0.0037 × age at infection in years) + (0.021 × sex (0 if female, 1 if male) + (0.028 × alcohol consumption [0 if 50 g/d or less, 1 if more than 50 g/d]).[3] The simulated group was obtained using the same values for these 3 variables observed in HIV-positive patients.

Methods

Histological Evaluation. Liver biopsy specimens of more than 10 mm in length were fixed, paraffin-embedded, and stained with either hematoxylin-eosin safran and Masson's trichrome or picrosirius red for collagen. For each liver biopsy, a stage of fibrosis and a grade of activity were established. Liver fibrosis was staged on a scale of 0 to 4 (0 = no fibrosis, 1 = portal fibrosis without septa, 2 = few septa, 3 = numerous septa without cirrhosis, 4 = cirrhosis).[13] These features have been shown to be highly reproducible between pathologists.[13] The grading of activity,[14] which evaluates the intensity of necroinflammatory lesions was indicated as follows: A0 = no histological activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity. All histological examinations were assessed by a single experienced pathologist (F.C.) who was not aware of the clinical and biological data.

Determination of the Fibrosis Progression Rate. The principle of fibrosis progression rate modeling has been extensively described previously.[12,15] Briefly, the fibrosis progression rate per year was defined as the ratio between the fibrosis stage (expressed according to the METAVIR scoring system) and the estimated duration of infection in years. For example, for a patient with fibrosis stage 2 and an 8-year duration of infection, the fibrosis progression rate was 0.250 fibrosis units per year.

Virological Methods. Polymerase chain reaction for HCV RNA was performed in all patients by Amplicor HCV Monitorth (Roche Diagnostic Systems, Neuilly sur Seine, France). HCV genotypes were identified using Competitive oligonucleotide priming–polymerase chain reaction.[16] All virological tests were run at the same laboratory and under the same conditions.

Statistical Analysis. Gender, mode of infection (IV drug use or transfusion), alcohol consumption (≤50 g/d and >50 g/d), age at HCV infection (≤25 years old and >25 years old), virus C genotype (1 or others) were compared using the χ^2 test. The relationship among liver fibrosis progression rate and the following factors: age at biopsy, estimated duration of HCV infection, age at HCV infection, and antiretroviral therapy drug regimens were compared by variance and Kruskal Wallis analyses. A multivariate regression analysis was performed to assess the independent association of HIV status (yes or no), sex, alcohol consumption (≤50 g/d or >50 g/d), age at HCV infection (≤25 years old or >25 years old), and severe immunosuppression with fibrosis progression rate. Severe immunosuppression status was defined as a CD4 count (≤200 cells/μL). HIV seronegative control patients had more than 200 CD4 cells/μL. In HIV-HCV coinfected patients, these remaining factors were also analyzed in a multivariate regression model.

A validation method compared the estimated fibrosis progression rates with the rate observed in paired liver biopsies (24 biopsies) in 12 HIV-HCV coinfected patients who had never been treated and were without cirrhosis at the first biopsy. For these patients, the observed fibrosis progression rate was calculated as the difference between the scores at 2 consecutive biopsies divided by the time in years elapsed between these 2 biopsies.

RESULTS

From January 1995 to April 1998, 169 consecutive HIV-HCV coinfected patients were recorded. Forty-seven patients were excluded because of nonavailability of liver biopsy (n = 20), insufficient size of liver biopsy sample (n = 2), hepatitis B surface antigen seropositivity (n = 17), or unknown date of HCV infection (n = 31). A total of 122 coinfected patients and 122 HIV-negative–matched patients were included. All of these patients had a liver biopsy within 3 months after the first visit. Their characteristics are shown in Table 1. Patients were correctly matched for age, sex ratio, risk factors for HCV infection, alcohol consumption, age at HCV infection, age at liver biopsy, and estimated duration of HCV infection. A simulated control group of 122 patients was generated.

Information about antiretroviral therapies was available for 110 of 122 HIV-HCV coinfected patients. Treated patients (n = 74, 67.2%) were receiving various combinations of anti-HIV drug regimens including indinavir, ritonavir, saquinavir, zidovudine, didanosine, stavudine, lamivudine, and zalcitabine. Twelve (10.9%) patients were treated with highly active antiretroviral therapy (HAART) that included a protease inhibitor in association with 2 nucleoside analogue reverse transcriptase inhibitors (NRTI) for 12.1 (95% confidence interval [CI], 3.8-16.3) months before liver biopsy, 48 (43.6%) patients with 2 NRTI only for 33 (95% CI, 19.5-48.2) months, and 14 (12.7%) patients with 1 NRTI only for 30 (95% CI, 18.5-42.3) months. No patient received non-NRTI therapy.

The prevalence of patients with a liver fibrosis score of 2, 3, or 4 was higher in HIV-infected patients (60%) than in HIV-negative control patients (47%) ($P < .05$). Moderate (A2) and severe (A3) necroinflammatory liver activity was found in 54% and 30% of HIV-infected patients and HIV-negative control patients, respectively ($P < .001$).

TABLE 1. Characteristics of Patient Populations

Populations	HIV and HCV Infected	Matched HCV Control Patients
Total number of patients	122	122
Mean age in years (95% CI)	35.5 (34.5-36.7)	35.6 (34.4-36.5)
Women (%)	35 (28.7%)	35 (28.7%)
Transfusion (%)	12 (9.8%)	12 (9.8%)
IV drug use (%)	110 (90.1%)	110 (90.1%)
Mean alcohol consumption (g/d) (95% CI)	57 (41.5-73.5)	50 (39.2-59.3)
≤50 g/d (%)	83 (68.0%)	88 (72.2%)
>50 g/d (%)	39 (31.9%)	34 (27.8%)
Mean duration of HCV infection in years (95% CI), range	13.3 (12.4-14.1) 2-27	13.5 (12.6-14.4) 1-28
Mean fibrosis score (95% CI)	2.0 (1.78-2.21)	1.62 (1.38-1.87)*
No fibrosis (F0)	11 (9.0%)	15 (12.3%)
Portal fibrosis (F1)	38 (31.1%)	50 (41.0%)
Few septa (F2)	32 (26.2%)	36 (29.5%)
Many septa (F3)	22 (18.0%)	8 (6.5%)†
Cirrhosis (F4)	19 (15.6%)	13 (10.6%)
Mean activity score (95% CI)	1.5 (1.3-1.7)	1.3 (1.0-1.4)
None (A0)	12 (12.3%)	16 (13.1%)
Mild (A1)	41 (33.6%)	69 (56.5%)‡
Moderate (A2)	56 (45.9%)	30 (24.6%)‡
Severe (A3)	10 (8.2%)	7 (5.7%)
Mean serum ALT (×normal upper limit) (95% CI), range	3.3 (3-3.7) 0.3-13.4	3.3 (2.8-3.8) 0.6-14.7
Genotype		
Number of samples	31	56
1a or 1b	18 (58.0%)	27 (48.2%)
Median CD4 lymphocyte count (μL) (95% CI)	305 (268-356)	ND

Abbreviation: ND, not determined.
*$P = .002$.
†$P < .02$.
‡$P < .001$.

Comparison of Fibrosis Progression Rates. The mean fibrosis progression rates of HIV-HCV coinfected patients and patients infected only by HCV were 0.181 (95% CI, 0.162-0.200) fibrosis units per year and 0.135 (95% CI, 0.126-0.144) fibrosis units per year ($P < .0001$), respectively. These rates were not normally distributed, with a median of 0.153 (95% CI, 0.117-0.181) in HIV-HCV coinfected patients and 0.106 (95% CI, 0.084-0.125) in patients infected by HCV only. At this rate of fibrosis progression, the median duration from HCV infection to cirrhosis was 26 (22 to 34) years in HIV-infected patients and 38 (32 to 47) years in non–HIV-infected patients, *i.e.*, 4 METAVIR units divided by the medians of fibrosis progression rates (Fig. 1). Medians of liver fibrosis progression rate in HIV-infected patients who received HAART, 2 and 1 NRTI, and untreated patients were 0.099 (95% CI, 0.043-0.115) fibrosis units per year, 0.173 (95% CI, 0.117-0.210) fibrosis units per year, 0.205 (95% CI, 0.154-0.258) fibrosis units per year, and 0.137 (95% CI, 0.074-0.187) fibrosis units per year, respectively. These differences were not statistically significant ($P = .89$).

Paired liver biopsy samples were available in 12 HIV-HCV coinfected patients. The median length of elapsed time between the 2 biopsies was 3.7 (95% CI, 1-6.3) years. Medians of observed and estimated fibrosis progression rates were 0.142 (95% CI, 0-0.315) fibrosis units per year and 0.158 (90% CI, 0.071-0.285) fibrosis units per year, respectively ($P = .97$). Median liver fibrosis progression rate of the simulated control group (0.106 [95% CI, 0.084-0.125] fibrosis unit per year) was lower than in HIV-infected patients ($P < .0001$) and not different from the HIV-negative–matched control group ($P = .8$) (Fig. 1).

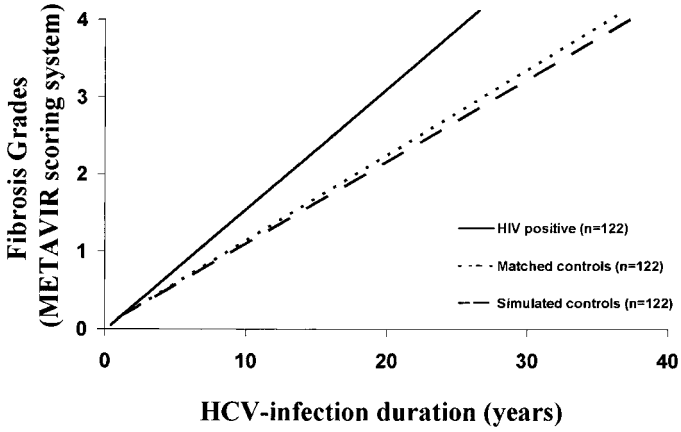

FIG. 1. Expected time to cirrhosis according to HIV status.

Risk Factors for Fibrosis Progression. Multivariate analysis considering HIV status, sex, alcohol consumption (>50 g/d or ≤50 g/d), age at HCV infection (≤25 years old or >25 years old), and severe immunosuppression (yes or no; *i.e.*, CD4 count ≤ or > 200 cells/μL), showed that HIV seropositivity, alcohol consumption (>50 g/d), age at HCV-infection (>25 years old), and severe immunosuppression (CD4 count (≤200 cells/μL) were independent factors associated with a higher fibrosis progression rate ($P < .0001$, $P < .0001$, $P < .0001$, and $P < .0002$, respectively) (Table 2). Among HIV-HCV coinfected patients, alcohol consumption (>50 g/d), CD4 count (≤200 cells/μL), and age at infection (>25 years old) ($P < .0001$, respectively) were independent factors associated with the fibrosis progression rate (Table 3). Median expected times from HCV infection to cirrhosis in the 2 groups of patients according to the daily alcohol intake and CD4 cell count at liver biopsy is shown in Fig. 2. An HIV-infected patient with 200 CD4 cells/μL or less and drinking more than 50 g of alcohol daily had a liver fibrosis progression rate of 0.250 fibrosis units per year (median expected time to cirrhosis 16 years), whereas it was 0.111 fibrosis units per year (median expected time to cirrhosis 36 years) for an HIV-infected patient with greater than 200 CD4 cells/μL, drinking 50 g or less of alcohol daily. On the other hand, a nondrinker and non–HIV-infected patient had fibrosis progression rate of 0.101 fibrosis units per year (expected time to cirrhosis 40 years) (Fig. 2).

TABLE 2. Risks Factors for Fibrosis Progression in 244 HCV-Infected Patients: Results of the Multivariate Regression Analysis

	β	SE	OR	95% CI OR	P
Gender (men)	0.01	0.049	1.010	0.916-1.113	.7
HIV infection	0.200	0.046	1.221	1.115-1.337	<.0001
Severe immunosuppression*	0.260	0.069	1.296	1.132-1.484	.0002
Age at infection (>25 years old)	0.497	0.054	1.643	1.476-1.829	<.0001
Alcohol consumption (>50 g/d)	0.499	0.048	1.647	1.496-1.812	<.0001

NOTE. Variability of the fibrosis progression rate explained by the model: $r^2 = 0.53$.
Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval.
*CD4 ≤200 cell/μL, HIV-seronegative patients were considered to have more than 200 CD4 cells/μL.

TABLE 3. Risks Factors for Fibrosis Progression in 122 HCV-Infected Patients: Results of the Multivariate Regression Analysis

	β	SE	OR	95% CI OR	P
Gender (men)	6.50×10^{-4}	1.60×10^{-2}	1.00	0.97-1.03	.96
Age at infection (>25 years old)	0.10	1.85×10^{-2}	1.10	1.07-1.15	<.0001
Alcohol consumption (>50 g/d)	8.90×10^{-2}	1.54×10^{-2}	1.10	1.06-1.12	<.0001
CD4 cell count (≤200 μL)	6.67×10^{-2}	1.63×10^{-2}	1.07	1.03-1.10	<.0001

NOTE. Variability of the fibrosis progression rate explained by the model: $r^2 = 0.40$.

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval.

DISCUSSION

We have conducted a study of the natural history of HCV infection in HIV-infected patients according to the concept of liver fibrosis progression. This concept has been validated in a large series of HCV-positive untreated patients with paired biopsies.[12] Our main finding was that liver fibrosis progressed faster in HIV-HCV coinfected patients than in patients infected only by HCV. According to the median fibrosis progression rate in untreated patients, the expected time to cirrhosis was 26 years in HIV-infected patients and 34 years in non–HIV-infected patients. Multivariate analysis showed that HIV infection, alcohol consumption (>50 g/d), age at HCV infection (>25 years old), and CD4 cell count (≤200 cells/μL) were independent factors associated with higher liver fibrosis progression rates. The fibrosis progression rate was lower in the simulated group than in the HIV-positive group. This difference also suggests the influence of HIV infection because these 2 groups differed only according to HIV seropositivity. Gender did not influence fibrosis progression of HIV-HCV coinfected patients; however, a large proportion of males were included in our study. Previous studies have shown more severe liver damage in HIV-positive patients than in HIV-negative patients.[6,7,9,10,11,17-19] However, these studies were mostly retrospective, included a small number of patients, and did not distinguish fibrosis from necroinflammatory activity. To characterize liver fibrosis and the activity grades, we used a highly reproducible method (METAVIR scoring system).[13,14] HIV-positive patients had never been matched to HIV-negative patients according to the factors involved in the natural history of liver fibrosis progression in chronic hepatitis C. Correct matching should be an important point because the HIV-HCV coinfected population and the population of patients infected only by HCV may be different. As shown in the current study, the HIV-HCV coinfected group has a younger age at HCV infection, included more alcohol drinkers (more than 50 g/d of alcohol), and more men than previously reported in the whole population of patients infected only by HCV.[12] Bias of selection was reduced by the careful match of HIV-negative control patients with HIV-positive patients regarding sex, alcohol consumption, risk factors for HCV infection, age at HCV infection, and age at liver biopsy.

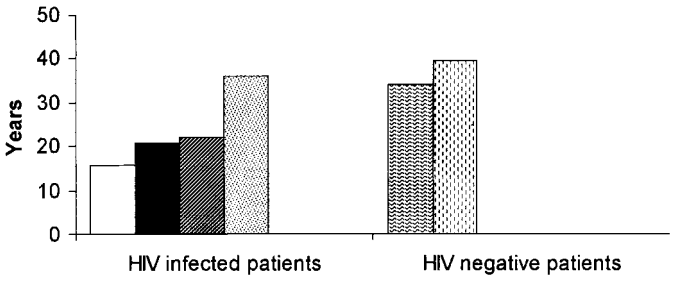

FIG. 2. Median expected time to cirrhosis according to CD4 cell count and alcohol consumption in HIV-positive patients and HIV-negative control patients. (□) CD4 ≤200 cells/μL and alcohol consumption >50 g/d; (■) CD4 >200 cells/μ/L and alcohol consumption >50 g/d; (▨) CD4 ≤200 cells/μL and alcohol consumption ≤50 g/d; (▩) CD4 >200 cells/μ/L and alcohol consumption ≤50 g/d; (▩) Alcohol consumption >50 g/d; (▩) Alcohol consumption ≤50 g/d.

Among HIV-HCV coinfected patients, age at HCV-infection (>25 years old) and alcohol consumption (>50 g/d), together with the CD4 cell count (≤200 cells/μL), were independently associated with higher liver fibrosis progression rates. Therefore, an HIV-infected patient with 200 CD4 cells/μL or less and drinking more than 50 g/d of alcohol may develop cirrhosis in 16 years whereas an HIV-infected patient with more than 200 CD4 cells/μL and drinking 50 g or less of alcohol daily may have an expected time to cirrhosis of 36 years. As observed in experimental studies, this finding is consistent with the role of immunity in the fibrosis progression process.[20] In HIV-infected patients, the CD4 lymphocyte counts are negatively correlated with HCV viral load.[21] A high serum HCV-RNA load related to impaired immune functions could be involved in the severity of liver disease.[22]

Our study presents some limitations. The estimated fibrosis progression rate per year was defined as the ratio between the fibrosis stage and the estimated duration of HCV infection. In this model it is assumed that the patient has no liver fibrosis the day of infection and that fibrosis progression is constant. However, duration of HCV infection remains an estimate. To accurately estimate the duration of HCV infection, the studied population included only IV drug users and transfused patients. In this population, contamination occurs at the date of the first transfusion or during the first year of IV drug injection in 90% of patients.[23] Furthermore, it is also possible that some patients already had fibrosis (*i.e.*, owing to alcohol) the day of infection. Thus, an ideal assessment would have been to prospectively follow-up a large representative sample of patients from HCV infection to death, with repeated liver biopsy and without treatment. Obviously, such a study is both ethically and pragmatically impossible. However, our observation of paired biopsies performed in a large number of untreated HCV-infected patients[12] and in a small number of HIV-HCV coinfected patients showed that estimated and observed fibrosis progression rates were not different. Thus, although not perfect, the estimation of liver fibrosis progression rates using a single liver biopsy remains an interesting tool for the study of the natural history of chronic hepatitis C.

Other factors were not investigated in our study. The influence of HCV genotypes could not be assessed because it was only available in a small number of patients. However, the HCV genotype is not associated with the fibrosis progression rate in patients infected only by HCV[12,24] and its influence on the severity of liver disease is controversial in liver transplant recipients.[25]

Combination antiretroviral therapies may also play a role in the fibrosis progression rate. The influence of HIV-1 protease inhibitor therapies on the natural history of liver fibrosis progression rate of HIV-HCV coinfected patients is

unstudied. Although the liver fibrosis progression rate was lower in patients who received HAART, the difference did not reach significance in our study; however, the number of HAART-treated patients was small. Studies including more patients are needed to reevaluate the impact of HAART on liver fibrosis progression. An increase of the CD4 cell count related to such therapies is expected to reduce the fibrosis progression rate of HCV-HIV coinfected patients, although long-term use of combination antiretroviral therapy that includes an HIV protease inhibitor does not influence HCV viral load.[26] On the other hand, antiretroviral therapy may induce liver damage.[27] The control of HIV with effective combination antiretroviral therapy together with a major reduction of alcohol consumption may delay the expected time to cirrhosis. The recommendations of limiting alcohol consumption and maintaining a high CD4 count are mandatory especially in HIV-coinfected patients, who are poor responders to interferon therapy.[28]

We conclude that HIV seropositivity accelerates fibrosis progression related to chronic hepatitis C. HIV infection, alcohol consumption of more than 50 g/d, CD4 lymphocyte count of less than 200 cells/μL, and age of more than 25 years at HCV infection are associated with an increased rate of liver fibrosis progression in HCV-coinfected patients. These factors should be considered in anti-HCV therapeutic strategies.

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