Effects of Sustained Viral Response in Patients With HIV and Chronic Hepatitis C and Nonadvanced Liver Fibrosis

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Objective: We assessed the effects of sustained viral response (SVR), after treating with interferon–ribavirin (IF-RB), on mortality, liver-related (LR) events (decompensation, hepatocellular carcinoma), HIV progression, and liver stiffness in HIV/hepatitis C virus (HCV)-coinfected patients with nonadvanced liver fibrosis.

Methods: From a cohort of HIV/HCV-coinfected patients treated with IF-RB, we selected those with baseline liver fibrosis stages F0, F1, or F2 according to METAVIR. The study started when IF-RB was stopped and ended at death or at the last follow-up visit.

Results: A total of 695 patients were included (HCV genotype 1 or 4, 431; F0, 77; F1, 290; and F2, 328), and 274 patients achieved SVR. After a median follow-up of 4.9 years, the adjusted hazard ratio (aHR) [95% confidence interval (CI)] of LR events or overall death, for patients with SVR taking the group of patients with no SVR as a reference was 0.217 (0.079 to 0.599) ($P = 0.003$) for the whole cohort with F0 to F2. For patients with F0, the aHR (95% CI) was 0.514 (0.040 to 6.593) ($P = 0.609$), for patients with F1, the aHR (95% CI) was 0.305 (0.053 to 1.762) ($P = 0.185$), and for patients with F2, it was 0.075 (0.009 to 0.662) ($P = 0.020$). We also found that, in comparison with no SVR, SVR was followed by less frequent HIV progression for the entire population (F0 to F2) and less frequent liver stiffness across all categories of fibrosis.

Conclusions: SVR in HIV/HCV-coinfected patients with moderate stages of liver fibrosis is associated with a reduction of mortality and LR events, and with a reduction of progression of HIV and liver fibrosis.

Key Words: HIV infections/*complications/*drug therapy, hepatitis C, chronic/*complications/*drug therapy, interferons/administration and dosage/*therapeutic use, follow-up studies, treatment outcome

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INTRODUCTION

HIV infection is a well-known enhancer of the progression of hepatitis C virus (HCV)-related liver fibrosis that increases the risk of developing cirrhosis and decompensated liver disease.[1,2] This accelerated fibrogenesis may be explained in part by HIV-related immunosuppression and lifestyle factors such as alcohol consumption[1]; however, recent studies suggest a potential direct role of HIV in liver fibrosis/inflammation.[3,4]

Since the introduction of combination antiretroviral therapy (cART), liver disease has become a major cause of morbidity and mortality in HIV-infected persons[5] and is currently one of the most frequent causes of non–AIDS-related death among HIV-infected persons.[6] Whether HCV has a negative impact on the progression of HIV infection has been extensively debated; however, there is increasing evidence that HCV coinfection has a harmful effect on the progression

of HIV infection and on comorbid conditions,[7] and may increase the risk of mortality despite the use of cART.[8–10]

Sustained viral response (SVR) (equivalent to eradication of HCV) after administering anti-HCV therapy is associated with improved survival and reduced liver decompensation in patients with chronic hepatitis C with or without HIV infection.[11–13] In HIV/HCV coinfection, SVR may also decrease the progression of HIV infection and mortality not related to liver disease.[14]

The clinical benefits associated with the eradication of HCV have been well characterized in patients with advanced fibrosis or cirrhosis but not in patients with less advanced stages of liver fibrosis. This is a relevant question, particularly in HIV/HCV-coinfected patients, for whom the delivery of effective HCV treatment could be a priority even in mild to moderate stages of liver fibrosis. Therefore, we assessed the effects of SVR after treatment with interferon plus ribavirin on mortality and liver-related (LR) events, and on HIV progression, in HIV/HCV-coinfected patients with biopsy-proven nonadvanced liver fibrosis.

PATIENTS AND METHODS

Design and Patient Selection

The patients in this study were selected from the cohort of the "Grupo de Estudio del SIDA" (AIDS Study Group, GESIDA) of the "Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica" (Spanish Society of Infectious Diseases and Clinical Microbiology, SEIMC). This cohort was composed of patients who were naive to anti-HCV therapy and had been treated with interferon and ribavirin. It was established in 2003 to follow HIV/HCV-coinfected patients who started therapy with these drugs between January 2000 and January 2008 at 19 institutions in Spain and has been described in detail elsewhere.[13–15] The local ethics committees approved the analysis of anonymous routine clinical data without written informed consent with a view to scientific publication.

We selected patients with a liver biopsy performed before the initiation of therapy with interferon plus ribavirin and with the following stages of liver fibrosis according to the METAVIR Cooperative Study Group criteria: F0, no fibrosis; F1, portal fibrosis; and F2, periportal fibrosis or rare portal–portal septa.[16] We excluded patients with stage F3 fibrosis (fibrous septa with architectural distortion and no obvious cirrhosis, ie, bridging fibrosis), patients with stage F4 fibrosis (definite cirrhosis), and patients for whom a baseline liver biopsy specimen was not available.

Investigations

All the information was entered directly into a common database at each institution by trained personnel using an online application. This database included all demographic, clinical, virological (HIV and HCV), and laboratory data. Local pathologists, who all had extensive experience in scoring samples from patients with viral hepatitis, scored liver biopsy samples following the criteria established by the METAVIR Cooperative Study Group.[16] All the study centers were monitored to verify that all the information in the database was consistent with the patient's medical history.

Assessment of Response to Interferon Plus Ribavirin

Response to therapy with interferon plus ribavirin was classified into 3 categories: SVR, defined as an undetectable serum HCV-RNA level 24 weeks after discontinuation of therapy; viral relapse, defined as an undetectable serum HCV-RNA level at the end of programmed therapy (48 weeks), with subsequent relapse; and no response, when patients did not fulfill the criteria for SVR or viral relapse. This last category included patients in which interferon plus ribavirin was not effective and patients who stopped therapy because of intolerability. Safety was assessed using laboratory tests and an evaluation of clinical adverse events made during therapy.

Follow-Up

After the completion of the treatment, patients were actively monitored to analyze clinical and laboratory parameters, including survival, presence of liver decompensation, antiretroviral therapy, $CD4^+$ cell count, HIV viral load, and HCV viral load. Liver fibrosis was also assessed. The study period lasted from the date interferon plus ribavirin was stopped until death or the last follow-up visit. The administrative censoring date was July 31, 2010.

Clinical Endpoints

The clinical endpoints were as follows: (1) LR complications, including ascites, hepatic encephalopathy, variceal bleeding, and hepatocellular carcinoma; (2) HIV progression, defined as the occurrence of any new AIDS-defining conditions; and (3) Mortality, classified as (i) LR death, when the train of events that ended in death was caused by liver decompensation or hepatocellular carcinoma; (ii) AIDS-related death, when death was directly related to an AIDS-defining condition; and (iii) non–LR non–AIDS-related deaths.[15]

Liver Stiffness After Interferon Plus Ribavirin

Liver stiffness (LS) was measured using transient elastography after treatment with interferon plus ribavirin in some patients, depending on hospital availability. Transient elastography was performed using a FibroScan device (EchoSens, Paris, France). A median value of 10 successful acquisitions was considered the representative measurement of LS. We considered 10 acquisitions with a success rate $\geq$60% and an interquartile range (IQR) $<$30% of the median value as a representative measurement.[17]

Statistics

Differences between groups were analyzed using the χ^2 test, *t* test, or Mann–Whitney test, as appropriate. Analysis of normality was performed using the Kolmogorov–Smirnov test. Logistic regression models were used to explore baseline

factors predicting SVR. We calculated the frequency, incidence rate, and survival function (Kaplan–Meier) for the different endpoints. Multivariate analysis was performed using Cox regression analysis. Statistical analysis was performed using SPSS 18.0 (SPSS Inc, Chicago, IL).

As several patients underwent retreatment with interferon plus ribavirin, we performed 3 types of analysis. In the first, which was the primary analysis, the follow-up of retreated patients was censored on the day the patient started the second course with interferon plus ribavirin. In the second analysis, those who achieved SVR after retreatment were included in the SVR group. In the third analysis, patients who were retreated were excluded from the analysis. For patients who had >1 event, only the first was included in the analysis of the association between category of response and "any event."

RESULTS

Patient Characteristics

From the 1599 patients who started treatment between January 2000 and January 2008 included in the database, we selected the 695 patients with a liver biopsy performed before the initiation of therapy showing nonadvanced liver fibrosis (F0, n = 77; F1, n = 290; and F2, n = 328). Their baseline characteristics are shown in Table 1.

In brief, 72.6% were male, their median age was 39.8 years, 19.8% had prior AIDS-defining conditions, the median baseline CD4 cell count was 546 cells per cubic millimeter, 66.4% had an undetectable HIV viral load, 63.7% were infected by genotypes 1 or 4, 70% had HCV RNA ≥500.000 IU/mL, and 2.8% were HBsAg positive.

A total of 351 patients (50%) were treated with pegylated-IF-α2a plus ribavirin, 242 (35%) were treated with pegylated-IF-α2b plus ribavirin, and 102 (15%) were treated with standard thrice-weekly IF-α plus ribavirin. The median (IQR) interval time in months from biopsy to treatment initiation was 6 (3–16) for those with F0 or F1, and 4 (2–12) for those with F2, $P < 0.001$. During treatment of hepatitis C, 565 patients (81%) were on cART.

Treatment Response

A total of 274 (39.4%) patients achieved SVR; 119 patients (27.6%) infected by genotypes 1 or 4 and 149

TABLE 1. Characteristics of 695 HIV/HCV-Coinfected Patients With Biopsy-Confirmed Liver Fibrosis Stages F0, F1, and F2, Stratified According to Response to Interferon Plus Ribavirin

Characteristic	No SVR (n = 421)	SVR (n = 274)	Total (N = 695)
Male sex, no. (%)	314 (74.7)	190 (69.3)	504 (72.6)
Age, yrs, median (IQR) (baseline)	39.8 (36.5–43)	39.8 (36.3–42.4)	39.8 (36.3–42.7)
Weight, kg, median (IQR)	68 (60–75)	68 (59–75)	68 (60–75)
Low educational level, no. (%)	211/333 (63.4)	132/222 (59.5)	343/555 (61.8)
Prior injection drug use, no. (%)	349/420 (83.1)	225/271 (83.0)	574/691 (83.1)
CDC disease category C, no. (%)*	93/416 (22.4)	43/270 (15.9)†	136/686 (19.8)
$CD4^+$, nadir, cells/mm^3, median (IQR)	219.5 (118–316)	249 (129.5–369)	228 (124–340)
$CD4^+$, baseline, cells/mm^3, median (IQR)	536 (385–727)	562 (411–752)	546 (400–741)
Undetectable HIV RNA load at baseline, no. (%)‡	267/410 (65.1)	182/266 (68.4)	449/376 (66.4)
Duration of HCV infection, yrs, median (IQR)	17 (13–22)	18 (12–22)	17 (13–22)
HCV genotype, no. (%)§			
1 or 4	312 (76.3)	119 (44.4)†	431 (63.7)
2 or 3	97 (23.7)	149 (55.6)†	246 (36.3)
Unknown	12	6	18
HCV-RNA ≥500,000 IU/mL, no. (%)	275/364 (75.5)	153/247 (61.9)†	428/611 (70)
METAVIR fibrosis score, no. (%)			
F0, no. (%)	47 (11.2)	30 (10.9)	77 (11.1)
F1, no. (%)	169 (40.1)	121 (44.2)	290 (41.7)
F2, no. (%)	205 (48.7)	123 (44.9)	328 (47.2)
HBsAg, no. (%)			
Positive	12 (2.9)	7 (2.6)	19 (2.8)
Negative	389 (93.3)	261 (96.7)	650 (94.6)
Unknown	16 (3.8)	2 (0.7)†	18 (2.6)
Current alcohol intake >50 g/d, no. (%)	22/383 (5.7)	4/262 (1.5)†	26/645 (4)
Current methadone use, no. (%)	52/396 (13.1)	23/256 (9)	75/652 (11.5)
Months in HCV treatment, median (IQR)	7.3 (5.7–11.2)	11.2 (10.1–11.9)†	10.8 (6.2–11.7)

*A, asymptomatic acute HIV or persistent generalized lymphadenopathy; B, symptomatic non-C conditions; C, AIDS-defining conditions.
†$P < 0.05$ with the no-SVR group.
‡Baseline HIV viral load was determined in 682 patients using commercial assays with different lower limits of detection in HIV-RNA copies per milliliter: <400 (n = 8), <200 (n = 67), <80 (n = 12), < 50 (n = 476), <40 (n = 28), and <20 (n = 91).
§HCV genotype was determined in 677 patients.
HBsAg, hepatitis B surface antigen.

patients (60.6%) infected by genotypes 2 or 3. Of the 421 patients who did not achieve SVR, 74 received a second course of interferon plus ribavirin; 25 (33.8%) achieved SVR after retreatment.

We developed a multiple logistic regression analysis model to identify pretreatment factors that were predictive of SVR. The model included 4 baseline factors that were associated with SVR by univariate regression analysis: HCV genotype, HCV-RNA level, prior AIDS-defining conditions, and alcohol intake >50 g/d (assessed at baseline). The final model identified 3 variables that were independently associated with increased odds of SVR: HCV genotype 2 or 3 [odds ratio (OR), 4.24; 95% confidence interval (CI): 2.91 to 6.19; $P < 0.001$], HCV-RNA level <500,000 IU/mL (OR, 1.88; 95% CI: 1.27 to 2.78; $P = 0.001$), and alcohol intake <50 g/d (OR, 4.04; 95% CI: 1.11 to 14.8; $P = 0.035$).

Clinical Outcomes

The median follow-up in months (IQR) since the date interferon plus ribavirin was stopped was 59.3 (40.6–79.2) for nonresponders and 59.5 (42.8–81.8) for responders. During follow-up, the proportion of patients with HIV viral load below the limit of detection, and the proportion of patients with $CD4^+$ cell count <200 cells per milliliter, was not significantly different between responders and nonresponders (data not shown). The frequencies and rates of events during follow-up stratified by response to interferon plus ribavirin are shown in Table 2. The main findings are summarized below.

Mortality

Overall mortality rates and LR mortality rates were significantly lower in responders than in nonresponders. When we performed this analysis by fibrosis stage, the rates were also significantly lower in patients with stage F2, but not in patients with stages F0 and F1. Kaplan–Meier estimates of the survival function showed that the probability of overall mortality (Figure 1A) and LR mortality (Figure 1B) was significantly lower in responders than in nonresponders.

Clinical Events

Rates of liver decompensation (ie, ascites, hepatic encephalopathy, and variceal bleeding) were significantly lower in responders than in nonresponders. Similar findings were recorded for patients with stage F2 but not for patients with stages F0 and F1. Kaplan–Meier estimates of the survival function showed that the probability of liver decompensation (Figure 1C) and LR events (liver decompensation or hepatocellular carcinoma) (Figure 1D) were significantly lower in responders than in nonresponders.

The rates of new AIDS-defining conditions were significantly lower in responders than in nonresponders. However, no statistically significant differences were found in rates of new AIDS-defining conditions between the groups when we performed a separate analysis in patients with stages F0 and F1 or in patients with stage F2 disease.

Predictors of Clinical Events

SVR was significantly associated with a reduced hazard of overall mortality or LR events, whichever occurred first, by multivariate Cox regression analysis when considering the entire F0 to F2 cohort and the F2 cohort, but not the F0 or the F1 cohorts. This analysis was adjusted for age, sex, history of injection drug use, Centers for Disease Control and Prevention (CDC) clinical category, nadir $CD4^+$ cell count, cART, HIV RNA at baseline, HCV genotype, HCV RNA viral load, and alcohol intake (Fig. 2). The SVR was also significantly associated with a reduced hazard of new AIDS-defining conditions when considering the entire F0 to F2 cohort, adjusted hazard ratio (95% CI) 0.088 (0.009 to 0.879) ($P = 0.039$) but not when separately considering the F0, F1, or F2 cohorts.

The results of 2 sensitivity analyses (the first based on those who achieved SVR after retreatment in the SVR group, and the second in which we excluded patients who were retreated) did not change the findings of the primary analysis (data not shown).

Alanine Aminotransferase Levels

We recorded alanine aminotransferase (ALT) levels at baseline, at the end of therapy with interferon plus ribavirin, and 24 weeks after the end of therapy. When we analyzed the proportion of patients with normal ALT levels (defined as <41 IU/L), the proportion of patients with normal ALT levels at baseline was significantly lower in responders than in nonresponders [18/274 (6.6%) vs. 52/421 (12.4%); $P < 0.05$]. However, the proportion of patients with normal ALT levels was significantly higher in responders than in nonresponders both at the end of therapy [235/274 (86.4%) vs. 203/421 (49.2%); $P < 0.05$] and 24 weeks after the end of therapy [248/274 (90.5%) vs. 97/421 (25.5%), respectively; $P < 0.05$].

Liver Stiffness After Interferon Plus Ribavirin Therapy

Of the 695 HIV/HCV-coinfected patients included in this study, we selected the 294 who had both a baseline liver biopsy and a posttreatment transient elastography result and who had not been retreated. No significant differences in the proportion of patients with baseline F0, F1, and F2 were found between the 226 responders [24 (11%), 97 (43%), 105 (47%)] and the 68 nonresponders [9 (13%), 28 (41%), 31 (46%)]; however, the median interval of time in months (IQR) between the date interferon plus ribavirin was stopped, and the last transient elastography value was significantly longer in nonresponders than in responders; 61.2 (41.9–80.1) versus 51.7 (32.9–70.4), respectively, $P < 0.05$. The results of transient elastography categorized by treatment response are shown in Figure 3. We found that the last transient elastography values were significantly lower in responders than in nonresponders, something that was also found when we analyzed only those patients with undetectable HIV viral load (data not shown). We also found that the proportion of patients with a transient elastography value <7 kPa (a cut-off point for which absent or mild fibrosis is likely) was

TABLE 2. Frequency and Rate of Events During Follow-Up in HIV/HCV-Coinfected Patients Stratified According to Response to Interferon Plus Ribavirin*

	Frequency of Events, No. (%)		Rate/100 Person-Years (95% CI)	
Event	**No SVR**	**SVR**	**No SVR**	**SVR**
Patients with F0, F1, F2 (N = 695)	421	274	421	274
Lost to follow-up	73 (17.3)	28 (10.2)†	3.25 (2.51 to 4)	2.02 (1.27 to 2.77)†
Overall mortality	22 (5.2)	4 (1.5)†	1.07 (0.62 to 1.52)	0.29 (0.01 to 0.57)†
LR	11 (2.6)	1 (0.4)†	0.53 (0.22 to 0.85)	0.07 (0 to 0.21)†
AIDS-related	1 (0.2)	0 (0)	0.05 (0 to 0.14)	0 (0 to 0)
Non–LR non–AIDS-related	9 (2.1)	3 (1.1)	0.44 (0 to 0.72)	0.22 (0 to 0.46)
Unknown	1 (0.2)	0 (0)	0.05 (0 to 0.14)	0 (0)
CDC category C disease	14 (3.3)	2 (0.7)†	0.69 (0.33 to 1.05)	0.14 (0 to 0.35)†
Liver decompensation	26 (6.2)	3 (1.1)†	1.31 (0.8 to 1.81)	0.22 (0 to 0.46)†
Hepatocarcinoma	3 (0.7)	1 (0.4)	0.15 (0 to 0.31)	0.07 (0 to 0.21)
Liver transplantation, no. (%)	2 (0.5)	2 (0.7)	0.1 (0 to 0.23)	0.14 (0 to 0.34)
Patients with F0 (n = 77)	47	30	47	30
Lost to follow-up	7 (0.1)	4 (0.1)	2.63 (0.68 to 4.58)	2.54 (0.05 to 5.02)
Overall mortality	3 (0.1)	2 (0.1)	1.21 (0 to 2.57)	1.24 (0 to 2.96)
LR	1 (0)	0 (0)	0.4 (0 to 1.19)	0 (0 to 0)
AIDS-related	1 (0)	0 (0)	0.4 (0 to 1.19)	0 (0 to 0)
Non–LR non–AIDS-related	1 (0)	2 (0.1)	0.4 (0 to 1.19)	1.24 (0 to 2.96)
CDC category C disease	3 (0.1)	1 (0)	1.22 (0 to 2.59)	0.63 (0 to 1.87)
Liver decompensation	3 (0.1)	0 (0)	1.26 (0 to 2.69)	0 (0 to 0)
Hepatocarcinoma	0 (0)	0 (0)	0 (0 to 0)	0 (0 to 0)
Liver transplantation, no. (%)	1 (0)	0 (0)	0.4 (0 to 1.19)	0 (0 to 0)
Patients with F1 (n = 290)	169	121	169	121
Lost to follow-up	20 (0.1)	11 (0.1)	2.12 (1.19 to 3.06)	1.83 (0.75 to 2.91)
Overall mortality	4 (0)	1 (0)	0.47 (0.01 to 0.92)	0.17 (0 to 0.49)
LR	0 (0)	0 (0)	0 (0 to 0)	0 (0 to 0)
AIDS-related	0 (0)	0 (0)	0 (0 to 0)	0 (0 to 0)
Non–LR non–AIDS-related	4 (0)	1 (0)	0.47 (0.01 to 0.92)	0.17 (0 to 0.49)
CDC category C disease	3 (0)	0 (0)	0.35 (0 to 0.76)	0 (0 to 0)
Liver decompensation	6 (0)	2 (0)	0.72 (0.14 to 1.3)	0.33 (0 to 0.79)
Hepatocarcinoma	0 (0)	1 (0)	0 (0 to 0)	0.17 (0 to 0.49)
Liver transplantation, no. (%)	1 (0)	2 (0)	0.12 (0 to 0.35)	0.33 (0 to 0.79)
Patients with F2 (n = 328)	205	123	205	123
Lost to follow-up	46 (22.4)	13 (10.6)†	4.44 (3.16 to 5.72)	2.08 (0.95 to 3.2)†
Overall mortality	15 (7.3)	1 (0.8)†	1.57 (0.78 to 2.37)	0.16 (0 to 0.47)†
LR	10 (4.9)	1 (0.8)†	1.05 (0.4 to 1.7)	0.16 (0 to 0.47)†
AIDS-related	0 (0)	0 (0)	0 (0 to 0)	0 (0 to 0)
Non–LR non–AIDS-related	4 (2)	0 (0)	0.42 (0.01 to 0.83)	0 (0 to 0)
Unknown	1 (0.5)	0 (0)	0.10 (0 to 0.31)	0 (0)
CDC category C disease	8 (3.9)	1 (0.8)	0.85 (0.26 to 1.45)	0.16 (0 to 0.48)
Liver decompensation	17 (8.3)	1 (0.8)†	1.85 (0.97 to 2.73)	0.16 (0 to 0.47)†
Hepatocarcinoma	3 (1.5)	0 (0)	0.32 (0 to 0.67)	0 (0 to 0)
Liver transplantation—n (%)	0 (0)	0 (0)	0 (0 to 0)	0 (0 to 0)

*Median follow-up times in months (IQR) for no-SVR and SVR groups were 59.3 (40.6–79.2) and 59.5 (42.8–81.8).
†$P < 0.05$ with the No-SVR group.

significantly higher in responders than in nonresponders, results that were confirmed when we carried out separate analyses for F2 and for F0–F1. Likewise, the proportion of patients with transient elastography values ≥12.5 kPa (a cut-off point for which cirrhosis is likely) was significantly lower in responders than in nonresponders, results that were confirmed for F2 but not for F0–F1.

DISCUSSION

We assessed the clinical outcomes of almost 700 HIV/HCV-coinfected patients with biopsy-proven nonadvanced liver cirrhosis who were followed up for a median period of approximately 5 years after the discontinuation of therapy with interferon plus ribavirin. The main findings were that, in this period of time, SVR was independently associated with

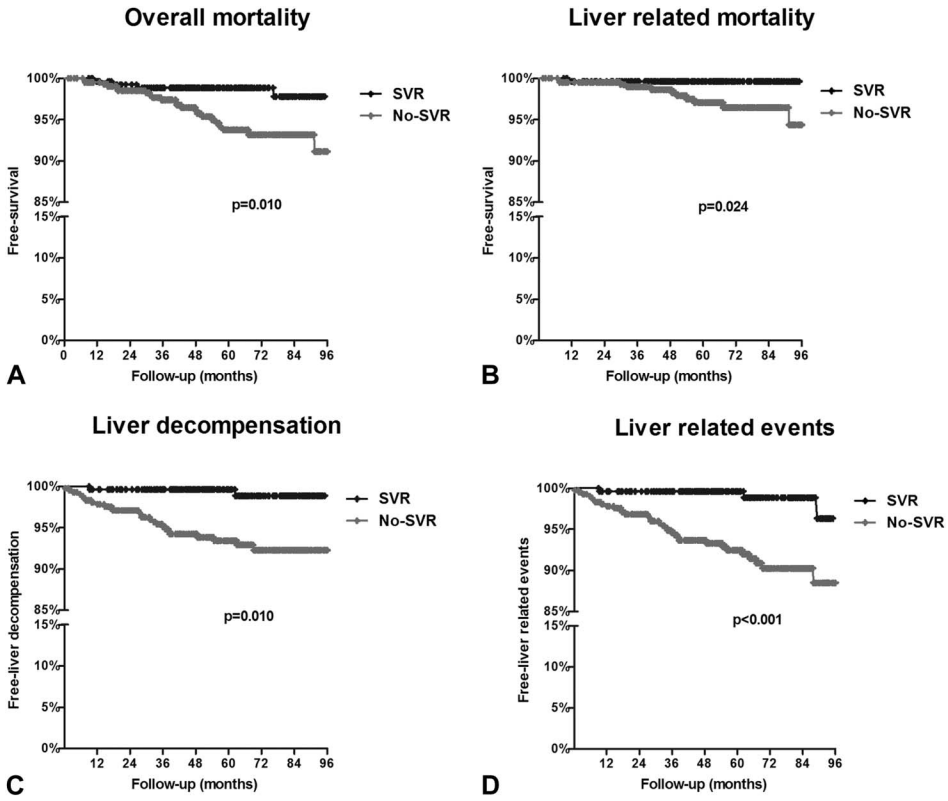

FIGURE 1. Proportion of patients free from events according to treatment response. A, Overall mortality. B, LR mortality. C, Liver decompensation (ascites, hepatic encephalopathy, and variceal bleeding). D, LR events (liver decompensation or hepatocellular carcinoma, whichever occurred first). *P* values according to log-rank test.

a reduction in the hazard of overall mortality or LR events. When we performed a separate analysis stratified by stage of fibrosis, we found that the clinical benefits associated with SVR were confirmed in patients with stage F2 fibrosis, but not in patients with stages F0 or F1 of fibrosis. We also found that, in comparison with no response, SVR was associated with a higher frequency of normal ALT levels and lower LS in all strata of fibrosis, suggesting an improvement in liver necroinflammatory activity[18] and fibrosis.[19] Finally, SVR was also associated with a reduction in the hazard of new AIDS-defining conditions, when considering the whole F0 to F2 cohort, as reported in a previous study by our group.[14]

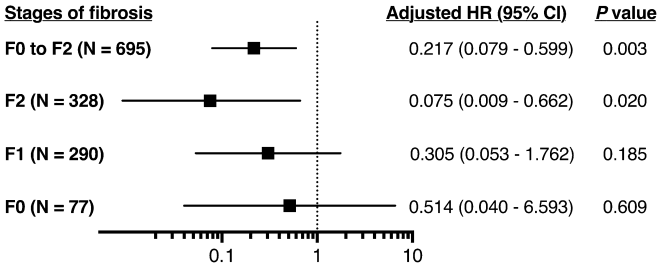

FIGURE 2. Multivariate analysis of factors associated with overall death or LR events (liver decompensation or hepatocellular carcinoma) whichever occurred first, by Cox regression analysis in patients with F0 to F2, in patients with F2, in patients with F1, and in patients with F0. All values were adjusted for age, sex, prior injection drug use, Centers for Disease Control and Prevention clinical category (C vs. A/B), nadir CD4$^+$ cells, cART, undetectable HIV RNA, HCV genotype (1–4 vs. 2–3), HCV-RNA ($\geq$500,000 vs. $<$500,000 IU/mL), and intake of alcohol $>$50 per day.

Assessment of the severity of liver fibrosis is an important aspect of the management of patients with chronic hepatitis C infection. In HCV-monoinfected patients, the recommendation is that all treatment-naive patients with compensated disease should be considered for anti-HCV therapy and that treatment should be initiated promptly in patients with stage F3–F4 disease. Treatment is strongly recommended for patients with F2 fibrosis, whereas in patients with F0–F1 fibrosis, treatment should be decided on an individual basis.[20]

In HIV/HCV-coinfected patients, effective cART is associated with a deceleration of the progression of liver fibrosis[21] and decreased risk of liver decompensation.[22,23] However, the most striking effect in terms of the reduction in the number of LR events and death in this population group is SVR after anti-HCV therapy.[13,14] The achievement of end-of-treatment response with subsequent relapse after therapy with interferon plus ribavirin also reduces decompensation and mortality in comparison with no response.[15]

A recent study analyzing clinical outcomes in coinfected patients according to baseline fibrosis stage found that rates of LR events increased gradually according to baseline METAVIR stage.[23] In that study, patients without fibrosis had a very low risk of developing LR events, whereas the risk was the highest for patients with stage F4 disease. Interestingly, over approximately 6 years of follow-up, the incidence of LR events and LR death was not significantly different for patients with F2 fibrosis in comparison with that for patients with F3 fibrosis.[23]

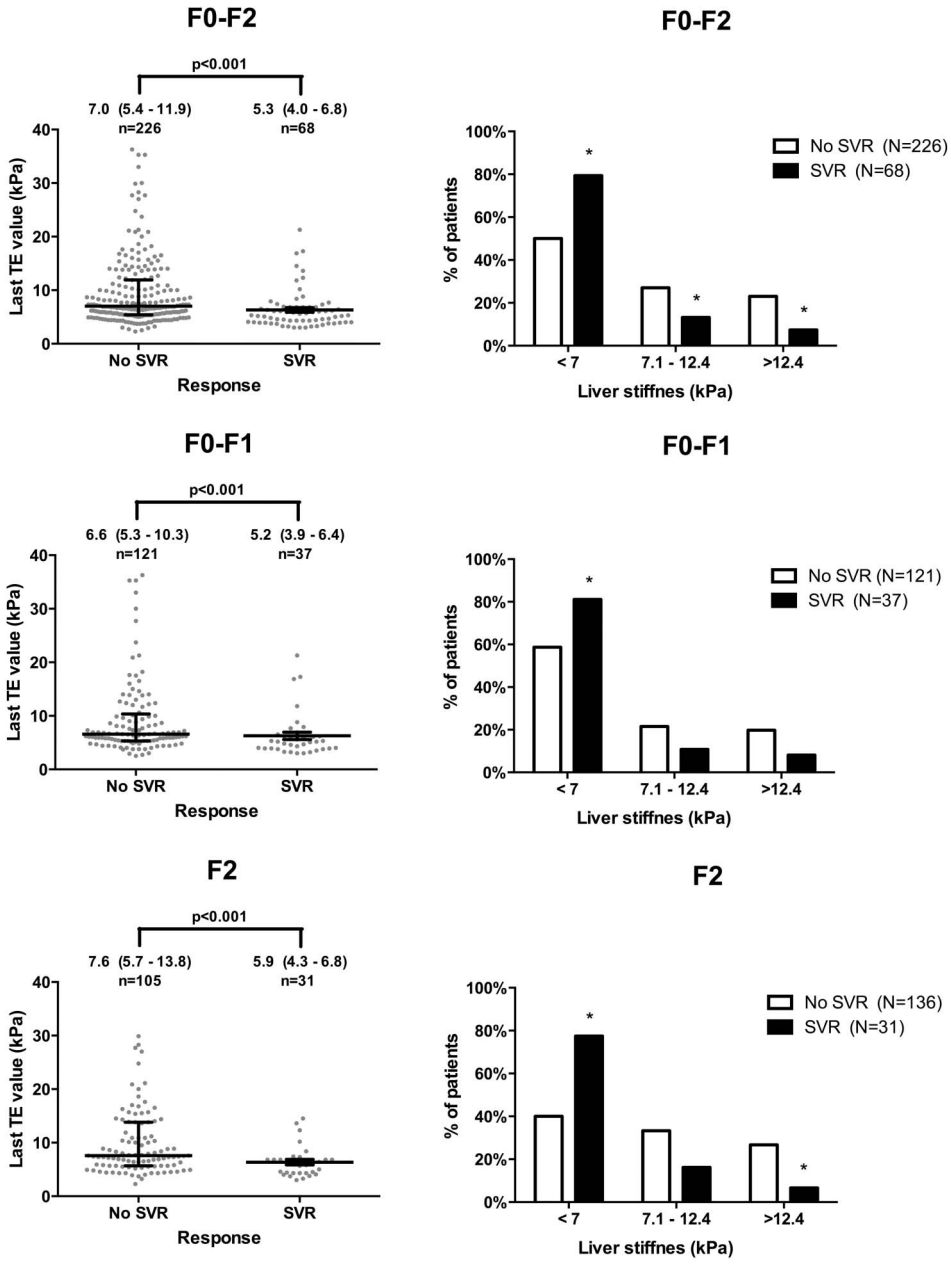

FIGURE 3. Transient elastography (TE) results categorized by response to interferon plus ribavirin and baseline liver biopsy stages in the 294 HIV/HCV-coinfected patients who had both a baseline liver biopsy and a posttreatment transient elastography measurement, and who had not been retreated. Scatter plots on the left show the distribution of the last TE value categorized by baseline liver biopsy stages and response to interferon plus ribavirin. Bar graphs on the right show the last TE value classified according to different cut-off values (≤7 kPa, between 7.1 and 12.4 kPa, and >12.4 kPa) categorized by baseline liver biopsy stages and response to interferon plus ribavirin.

The findings of our study emphasize the importance of anti-HCV treatment in patients with stage F2 fibrosis, because after a median follow-up of approximately 5 years, eradication of HCV was associated with reduced liver decompensation and mortality. Such benefits were not documented in patients with F0 or F1 disease during this period; nevertheless, SVR was associated with an improvement in liver fibrosis in this group, as assessed by transient elastography. Conceivably, the clinical benefits associated with the eradication of HCV could also be observed in patients with no or mild fibrosis after a longer follow-up.

Our study has several limitations, the most important being that it is not entirely prospective. However, we believe that its characteristics make it unlikely that the results differ considerably from those that would have been obtained in an entirely prospective study. This is because the follow-up was conducted by the same physicians in the same reference hospitals throughout the course of the disease, with standard clinical and laboratory parameters assessed every 6 months. Further, all the information in the database was monitored to verify that it was consistent with the patient's medical history. In addition, we performed sensitivity analyses to overcome the potential bias of patients who were retreated with interferon plus ribavirin; the results confirmed the findings from the main analysis. Another limitation of our study is that biopsy interpretation was not centralized and lacked quality control in terms of percentage of hepatic cylinders that were ≥2.5 cm in length. However, local pathologists at every

institution had extensive experience in scoring samples from patients with viral hepatitis, and staged liver biopsy samples following the criteria established by the METAVIR Cooperative Study Group. Finally, our study is also limited by missing data for variables such as educational level, adherence to treatment, lifestyle factors (exercise, diet, and smoking), and social support; therefore, we cannot rule out the possibility that differences in these variables could have affected the outcome.

In summary, our study shows that eradication of HCV in HIV/HCV-coinfected patients with nonadvanced liver fibrosis, and, more specifically, with moderate stages of liver fibrosis (F2), is associated with a reduction in the risk of complications of HCV-related liver disease, HIV progression, and mortality. These findings constitute a strong rationale for considering anti-HCV treatment in this population group, particularly treatment based on the newer and more effective direct antiviral agents.

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REFERENCES

1. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. *Hepatology*. 1999;30:1054–1058.
2. 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;33:562–569.
3. Tuyama AC, Hong F, Saiman Y, et al. Human immunodeficiency virus (HIV)-1 infects human hepatic stellate cells and promotes collagen I and monocyte chemoattractant protein-1 expression: implications for the pathogenesis of HIV/hepatitis C virus-induced liver fibrosis. *Hepatology*. 2010;52:612–622.
4. Lin W, Weinberg EM, Chung RT. Pathogenesis of accelerated fibrosis in HIV/HCV co-infection. *J Infect Dis.* 2013;207(suppl 1):S13–S18.
5. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med.* 2006;166:1632–1641.
6. Smith C, Sabin CA, Lundgren JD, et al. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. *AIDS.* 2010;24:1537–1548.
7. Operskalski EA, Kovacs A. HIV/HCV co-infection: pathogenesis, clinical complications, treatment, and new therapeutic technologies. *Curr HIV/AIDS Rep.* 2011;8:12–22.
8. Chen TY, Ding EL, Seage Iii GR, Kim AY. Meta-analysis: increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. *Clin Infect Dis.* 2009;49:1605–1615.
9. Branch AD, Van Natta ML, Vachon ML, et al. Mortality in hepatitis C virus-infected patients with a diagnosis of AIDS in the era of combination antiretroviral therapy. *Clin Infect Dis.* 2012;55:137–144.
10. Berenguer J, Alejos B, Hernando V, et al. Trends in mortality according to hepatitis C virus serostatus in the era of combination antiretroviral therapy. *AIDS.* 2012;26:2241–2246.
11. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med.* 2007;147:677–684.
12. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA*. 2012;308:2584–2593.
13. Berenguer J, Alvarez-Pellicer J, Martin PM, et al. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus. *Hepatology*. 2009;50:407–413.
14. Berenguer J, Rodriguez E, Miralles P, et al. Sustained virological response to interferon plus ribavirin reduces non-liver-related mortality in patients coinfected with HIV and hepatitis C virus. *Clin Infect Dis.* 2012;55:728–736.
15. Berenguer J, Alvarez-Pellicer J, Carrero A, et al. Clinical effects of viral relapse after interferon plus ribavirin in patients co-infected with human immunodeficiency virus and hepatitis C virus. *J Hepatol.* 2013;58:1104–1112.
16. The French METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology*. 1994;20:15–20.
17. Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. *J Hepatol.* 2008;48:835–847.
18. Shiffman ML, Diago M, Tran A, et al. Chronic hepatitis C in patients with persistently normal alanine transaminase levels. *Clin Gastroenterol Hepatol.* 2006;4:645–652.
19. Sanchez-Conde M, Montes-Ramirez ML, Miralles P, et al. Comparison of transient elastography and liver biopsy for the assessment of liver fibrosis in HIV/hepatitis C virus-coinfected patients and correlation with noninvasive serum markers. *J Viral Hepat.* 2010;17:280–286.
20. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. *J Hepatol.* 2011;55:245–264.
21. Macias J, Berenguer J, Japon MA, et al. Fast fibrosis progression between repeated liver biopsies in patients coinfected with human immunodeficiency virus/hepatitis C virus. *Hepatology*. 2009,50:1056–1063.
22. Qurishi N, Kreuzberg C, Luchters G, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. *Lancet*. 2003;362:1708–1713.
23. Limketkai BN, Mehta SH, Sutcliffe CG, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/HCV. *JAMA*. 2012;308:370–378.

APPENDIX. THE GESIDA HIV/HCV COHORT STUDY GROUP

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