Sustained Virological Response to Interferon Plus Ribavirin Reduces Liver-Related Complications and Mortality in Patients Coinfected with Human Immunodeficiency Virus and Hepatitis C Virus

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Human immunodeficiency virus (HIV) infection modifies the natural history of chronic hepatitis C, thus promoting more rapid progression to cirrhosis and end-stage liver disease. The objective of our study was to determine whether hepatitis C virus (HCV) clearance is associated with improved clinical outcomes in patients positive for HIV and HCV. It was an ambispective cohort study carried out in 11 HIV units in Spain and involved 711 consecutive patients positive for HIV/HCV who started interferon plus ribavirin therapy between 2000 and 2005. We measured sustained virologic response (SVR), i.e., undetectable HCV RNA at 24 weeks after the end of treatment, and clinical outcomes, defined as death (liver-related or non–liver-related), liver decompensation, hepatocellular carcinoma, and liver transplantation. Of 711 patients who were positive for HIV/HCV, 31% had SVR. During a mean follow-up of 20.8 months (interquartile range: 12.2-38.7), the incidence rates per 100 person-years of overall mortality, liver-related mortality, and liver decompensation were 0.46, 0.23, and 0.23 among patients with SVR and 3.12, 1.65, and 4.33 among those without SVR ($P = 0.003$, 0.028, and <0.001 by the log-rank test), respectively. Cox regression analysis adjusted for fibrosis, HCV genotype, HCV RNA viral load, Centers for Disease Control and Prevention clinical category, and nadir CD4+ cell count showed that the adjusted hazard ratio of liver-related events was 8.92 (95% confidence interval, 1.20; 66.11, $P = 0.032$) for nonresponders in comparison with responders and 4.96 (95% confidence interval, 2.27; 10.85, $P < 0.001$) for patients with fibrosis grade of F3-F4 versus those with F0-F2.Because this was not a prospective study, selection and survival biases may influence estimates of effect. *Conclusion:* Our results suggest that the achievement of an SVR after interferon-ribavirin therapy in patients coinfected with HIV/HCV reduces liver-related complications and mortality. (HEPATOLOGY 2009;50:407-413.)

Human immunodeficiency virus (HIV) infection modifies the natural history of chronic hepatitis C, thus promoting more rapid progression to fibrosis and development of cirrhosis and end-stage liver disease.[1-4] Despite a decline in morbidity and mortality from opportunistic infections since the introduction of highly active antiretroviral therapy (HAART), end-stage liver disease continues to be a frequent cause of hospital admission and death in populations coinfected with HIV and hepatitis C virus (HCV).[5,6] For this reason, all HIV-infected individuals with positive HCV RNA determinations should be considered as candidates for anti-

Abbreviations: APRICOT, AIDS Pegasys Ribavirin International Co-infection Trial; CDC, Centers for Disease Control and Prevention; CI, confidence interval; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; SVR, sustained virological response; OR, odds ratio.

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HCVtreatment, providing HIV infection is well-controlled and there are no contraindications to therapy with interferon or ribavirin.[7-10]

It is known that response to antiviral therapy appears to reduce liver complications in chronic hepatitis C[11,12]; however, little is known about the clinical consequences of achieving a sustained virological response (SVR) following therapy with interferon plus ribavirin in coinfected patients. Our objective was to determine the effect of achieving an SVR on clinical outcomes including mortality and liver-related complications in patients coinfected with HIV/HCV.

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 treated with interferon and ribavirin and was established in 2003 to follow patients coinfected with HIV/HCV who started therapy with these drugs after January 2000 at 11 institutions in Spain. The primary objective of this cohort study was to determine the effect of achieving an SVR after therapy with interferon and ribavirin on the long-term clinical outcomes, including liver-related complications and liver-related mortality, of coinfected patients. The study cohort received the approval of the ethics committees of the participating centers for the analysis of anonymous routine clinical data without written informed consent, with a view to scientific publication.

Anti-HCV therapy in Spain is provided by hospital pharmacies and is covered by the National Health System. The decision to administer anti-HCV therapy to coinfected patients was taken by infectious diseases physicians at each institution according to national and international guidelines. The eligibility criteria for anti-HCV therapy included absence of prior hepatic decompensation, CD4+ cell count $>$ 200 cells/μL, stable antiretroviral therapy or no need for antiretroviral therapy, absence of active opportunistic infections, and no active drug addiction. Patients were counseled against the use of alcohol. Anti-HCV therapy was stopped in all patients with detectable HCV RNA at week 24 of treatment. Since 2002, some institutions have been applying the so-called "2-log stopping rule," i.e., discontinuation of therapy in patients with detectable HCV RNA at week 12 of treatment with a reduction of $<$2 log IU/mL in HCV RNA.

Investigations. All the information was entered directly into a common database at each institution by trained personnel who used an ad hoc online application that satisfied local requirements of data confidentiality. This database included all demographic, clinical, virological (HIV and HCV), and laboratory data.

For each patient, we extracted the following data from the central database: age, sex, height and weight at the initiation of therapy with interferon plus ribavirin, HIV transmission category, prior acquired immunodeficiency syndrome (AIDS)-defining conditions, baseline and nadir CD4+ cell counts, and baseline HIV viral load. We also recorded information about HAART, including type, date of initiation, and whether it was maintained or changed during therapy. Information related to HCV infection included genotype, HCV RNA levels, and estimated year of HCV infection, which was estimated for injection drug users by assuming that it started the first year needles were unsafely shared. Duration of HCV infection was considered to be unknown for patients infected through sexual contact. 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[13] as follows: F0, no fibrosis; F1, portal fibrosis; F2, periportal fibrosis or rare portal-portal septa; F3, fibrous septa with architectural distortion and no obvious cirrhosis (bridging fibrosis); and F4, definite cirrhosis.

Assessment of Response to Interferon Plus Ribavirin. For each patient, we assessed the SVR, defined as an undetectable serum HCV RNA level 24 weeks after dis-

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continuation of therapy. Patients not fulfilling SVR criteria, including those who relapsed after achieving end-of-treatment response, were classified as non-SVR. Safety was assessed by laboratory tests and evaluation of clinical adverse events during therapy.

Follow-Up. Completion of treatment was followed by an active follow-up every 6 months. This analyzed clinical and laboratory parameters including survival, presence of liver decompensation, antiretroviral therapy, CD4+ cell count, HIV viral load, HCV RNA, liver biopsy, and anti-HCV therapy. The length of the study was calculated from the date response or nonresponse was confirmed and ended at death or at the last follow-up visit.

Endpoints. We assessed the following endpoints: (1) liver-related complications including ascites, hepatic encephalopathy, variceal bleeding, hepatocellular carcinoma, and liver transplantation; (2) HIV progression according to Centers for Disease Control and Prevention (CDC) criteria; and (3) mortality, including liver-related mortality. We also considered a composite end-point that included liver-related death, liver decompensation, hepatocellular carcinoma, and liver transplantation. Ascites was confirmed by paracentesis and/or ultrasound detection. Hepatic encephalopathy was established on clinical grounds after the reasonable exclusion of HIV-associated encephalopathy by clinical and laboratory parameters (i.e., CD4+ cell counts and HIV viral load) and neuroimaging techniques. The source of gastroesophageal bleeding was confirmed by endoscopy whenever possible. For patients who had more than one event, only the first was included in the analyses of the association between SVR and "any event".

Statistics. We calculated the frequencies, incidence rates, and estimates of the survival function (Kaplan-Meier) of the different endpoints. Differences between groups were analyzed using the chi-squared test, Student *t*-test, or Mann-Whitney U test, as appropriate. Logistic regression models were used to explore baseline factors predicting an SVR and discontinuation of therapy due to adverse events.

Results

Patient Characteristics. Between January 2000 and December 2005, 711 patients were included in the database. Their baseline characteristics are shown in Table 1. In brief, 72% were male, the median age was 41 years, 21% had prior AIDS-defining conditions, the median baseline CD4+ cell count was 544 cells/mm^3, 52% had an undetectable HIV viral load, the median time since HCV infection was 18 years, 63% were infected by genotypes 1 or 4, and 70% had an HCV RNA $\geq$ 500,000 IU/mL. Patients were asked about their alcohol intake at baseline, and 34 (5.6%) were considered to have a high intake, defined as the consumption of at least 50 g of alcohol per day for at least 12 months. Liver biopsy was performed in 611 (86%) patients before anti-HCV therapy was started, and it revealed that 237 (39%) had bridging fibrosis or cirrhosis. A total of 311 (44%) patients were treated with pegylated interferon-α2a (PEG-IFN-α2a) plus ribavirin, 271 (38%) were treated with PEG-IFN-α2b plus ribavirin, and 129 (18%) were treated with standard thrice-weekly IFN-α plus ribavirin. During treatment of hepatitis C, 597 (84%) patients were on HAART. The most common combinations were two nucleoside reverse transcriptase inhibitor (NRTI) drugs plus one non-nucleoside reverse transcriptase inhibitor (NNRTI) drug in 252 patients (35%), two NRTI plus one protease inhibitor in 179 patients (25%), three NRTI in 120 patients (17%), and other combinations in 46 patients (7%).

Table 1. Patient Characteristics

Characteristic	Patients (N = 711)
Male sex-n (%)	507 (71.5)
Age-year, median (IQR)	40.9 (37.9–44.1)
Weight-kg, median (IQR)	67 (59–75)
Prior injection drug use-n (%)	567 (80.2)
CDC disease category C-n (%)	148 (21.2)
CD4+ cells baseline-n/mm^3	544 (396–721)
HIV RNA $<$ 50 copies/mL baseline-n (%)	313 (51.7)
Duration of HCV infection, median (IQR)	18 (13–22)
HCV genotype 1–4-n (%)	423 (62.9)
HCV RNA $\geq$ 500,000 IU/mL-n (%)	446 (69.5)
METAVIR fibrosis score 3–4-n (%)	237 (38.8)
HBsAg-positive	17 (2.4)
Alcohol intake $>$ 50 g/day-n (%)	34 (5.6)
Methadone use-n (%)	80 (12.4)

CDC, Centers for Disease Control and Prevention; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IQR, interquartile range.

Sustained Virological Response. Overall, 218 (31%) of the patients achieved an SVR. The response was 78 of 423 (18.4%) for genotypes 1 and 4, and 125 of 250 (50%) for genotypes 2 and 3. We used a multiple logistic regression analysis model to identify pretreatment factors that were predictive of an SVR. In the model, we included baseline factors that were associated with SVR by univariate regression analysis, such as CDC clinical category, nadir CD4+ cell count, HCV genotype, and HCV RNA level. We also included the type of interferon used (pegylated versus non-pegylated) and two variables of particular interest in this population, namely, presence of a fibrosis grade of F3-F4 in liver biopsy and an alcohol intake higher than 50 g/day. The final model identified

Table 2. Frequency and Rate of Events During Follow-Up in 711 Patients Positive for HIV/HCV Stratified According to Response to IFN-RBV

Event	Non-SVR (N = 493)	SVR (N = 218)	P	Rate/100 Person-Years (95% CI)		
				Non-SVR	SVR	P*
Follow-up-months, median (IQR)	22.1 (12.7-39.1)	18.7 (11.3-36.9)	0.071	–	–	–
Lost to follow-up-n (%)	25 (5)	13 (6)	0.955	2.3 (1.49-3.39)	2.97 (1.75-5.36)	0.413
Deaths-n (%)	34 (6.9)	2 (0.9)*	0.001	3.12 (2.16-4.37)	0.46 (0.06-1.65)	0.003
Liver-related-n (%)	18 (3.7)	1 (0.5)*	0.029	1.65 (0.98-2.61)	0.23 (0.01-1.27)	0.028
AIDS-related-n (%)	2 (0.4)	0 (0)	0.826	0.18 (0.02-0.66)	0 (0-0.84)	0.855
Other causes-n (%)	14 (2.8)	1 (0.5)	0.079	1.29 (0.7-2.17)	0.23 (0.01-1.27)	0.075
Liver decompensation-n (%)†	45 (9.1)	1 (0.5)*	<0.001	4.33 (3.16-5.8)	0.23 (0.01-1.27)	<0.001
Hepatocarcinoma–n (%)	9 (1.8)	0 (0)	0.100	0.83 (0.38-1.58)	0 (0-0.84)	0.099
Liver transplantation–n (%)	11 (2.2)	0 (0)	0.058	1.02 (0.50-1.82)	0 (0-0.84)	0.034

*By log-rank test.

†Ascites, upper gastrointestinal bleeding, hepatic encephalopathy.

CI, confidence interval; HCV, hepatitis C virus; IFN, interferon; IQR, interquartile range; RBV, ribavirin; SVR, sustained virological response.

three variables that were independently associated with increased odds of an SVR: HCV genotype 2-3 (odds ratio [OR], 3.81; 95% confidence interval [CI], 2.55-5.69; $P < 0.0001$), HCV-RNA level < 500,000 IU/mL (OR, 1.71; 95% CI, 1.13-2.58; $P = 0.011$), and nadir CD4+ cell count (OR, 1.01; 95% CI, 1.00-1.03; $P = 0.026$).

Outcomes. After a median follow-up of 22.1 (interquartile range, 12.7-39.1) months in nonresponders and 18.7 (interquartile range, 11.3-36.9) months in responders, we found a significantly higher frequency of the following events in nonresponders than in responders: overall death (6.9% versus 0.9%), liver-related death (3.7% versus 0.5%), and liver decompensation (9.1% versus 0.5%) (Table 2). Likewise, we found that the incidence rates (per 100 person-years) of the following events were significantly higher in nonresponders than in responders: death, liver-related death, liver decompensation, and liver transplantation (Table 2). Kaplan-Meier estimates of the survival function showed that death, liver-related death, and liver decompensation were significantly lower in responders than in nonresponders (Fig. 1). We also found that the composite endpoint that included liver-related death, liver decompensation, hepatocellular carcinoma, and liver transplantation was significantly lower in responders than in nonresponders (Fig. 2). Finally, we performed a multivariate analysis of factors associated with the composite endpoint by Cox regression analysis. When we adjusted for fibrosis, HCV genotype, HCV RNA viral load, CDC clinical category, and nadir CD4+ cell count, we found that the adjusted hazard ratio of liver-related events was 8.92 (95% CI, 1.20-66.11; $P = 0.032$) for nonresponders in comparison with responders and 4.96 (95% CI, 2.27-10.85; $P < 0.001$) for patients with F3-F4 versus those with F0-F2 (Table 3).

Discussion

In the present study, we evaluated the clinical course of a large cohort of patients coinfected with HIV/HCV who were followed-up for a median of approximately 20 months after therapy with interferon plus ribavirin. The dropout rate was low (5.3%). We found that patients who achieved an SVR had a significantly lower rate of all-cause death, liver-related death, and decompensated liver disease than those who did not.

The effectiveness of treatment for chronic hepatitis C is usually evaluated according to the number of patients who reach SVR, which is a surrogate marker. However, available evidence suggests that SVR is associated with improvements in liver damage as well as with reductions in long-term morbidity and mortality related to hepatitis C.

Studies that have analyzed pretreatment and posttreatment liver biopsies from randomized clinical trials have shown that successful treatment with IFN with or without ribavirin may halt and even reverse hepatic fibrosis.[14-16] The clinical consequences of achievement of SVR have been addressed in a few studies in patients monoinfected with HCV. In a cohort of 455 patients with chronic hepatitis C followed prospectively for a median of 9 years, response to interferon was a significant predictor of complications by univariate analysis. However, after adjustment for the fibrosis score, serum albumin concentration, and mode of transmission in a multivariate model, treatment response failed to reach significance ($P = 0.058$) as a predictor of outcome.[11] Another multinational cohort study analyzed 479 consecutive patients with chronic hepatitis C with advanced fibrosis or cirrhosis that was treated with IFN or PEG-IFN with or without ribavirin. The authors found that SVR was associated

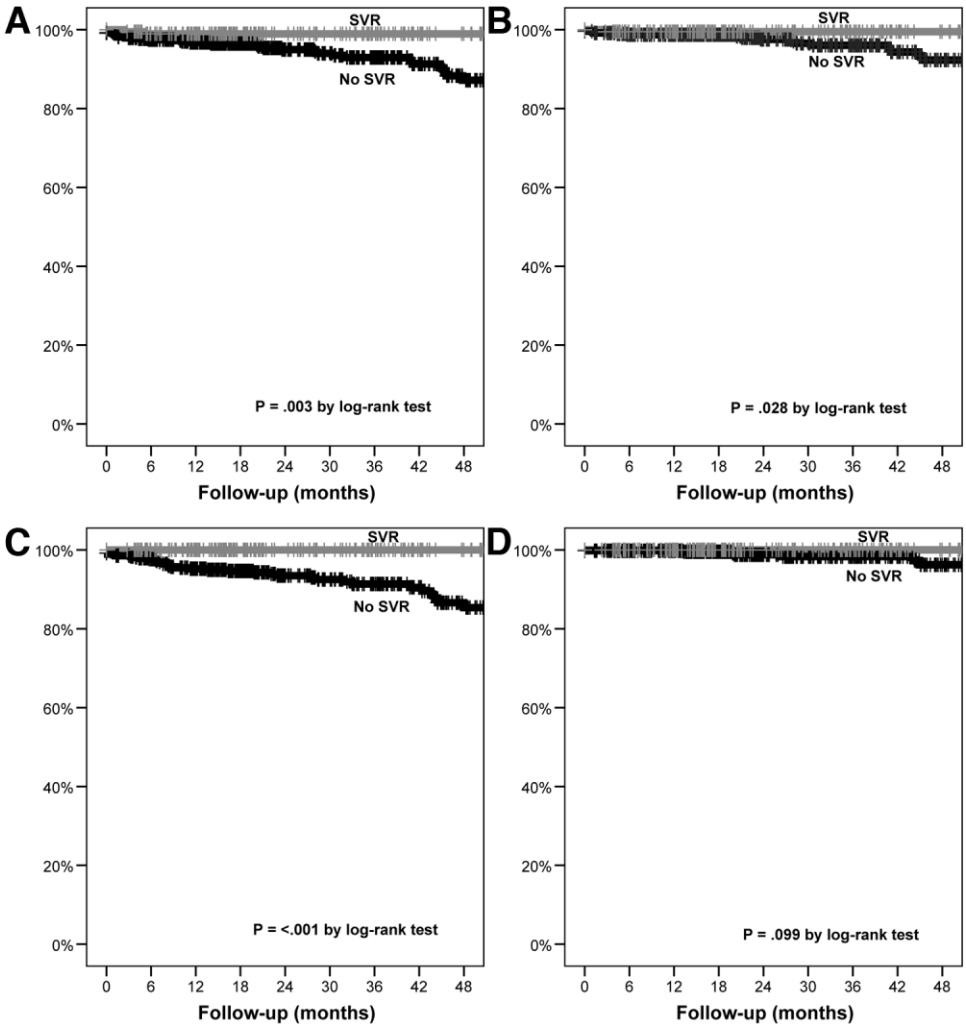

Fig. 1. Kaplan-Meier curves showing the occurrence of clinical events in 711 patients positive for HIV/HCV with and without SVR following therapy with interferon plus ribavirin: (A) overall mortality; (B) liver-related mortality; (C) liver decompensation; and (D) hepatocellular carcinoma.

with a statistically significant reduction in the hazard of clinical events, mainly liver failure.[12] In a retrospective study from the United Kingdom, patients with advanced liver fibrosis who underwent a liver biopsy before 2002 were followed for a median of 51 months. Of the 131 patients with no previous history of decompensated disease, 25% died or received a transplant after a median interval of 42 months. In a multivariate analysis, combination therapy with IFN and ribavirin was associated with improved survival, most notably among sustained responders.[17] Available evidence also suggests that even patients with compensated liver cirrhosis who achieve SVR may experience beneficial alterations of their disease course. For example, in a multicenter cohort of 920 Italian patients with histologically proven HCV-derived cirrhosis treated with IFN monotherapy, a significant reduction in the rates of liver-related complications, hepatocellular carcinoma, and liver-related mortality was found in patients who achieved an SVR compared with those who did not.[18]

Little is known about the consequences of achieving SVR in patients coinfected with HIV/HCV. In a subanalysis from the multinational AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT), paired liver biopsies obtained from 401 patients were analyzed to investigate a possible correlation between virological and histological responses. Histological response was defined as a two-point or greater reduction in the Ishak-modified histological activity index score. The investigators found that histological response was correlated with virological response, although a substantial proportion of patients who did not achieve an SVR experienced histological improvement.[19] Likewise, in a subanalysis from the ANRS HC02 RIBAVIC trial, paired liver biopsies from 198 patients were analyzed. In the multivariate analysis, the authors found that didanosine and failure to achieve SVR were significantly associated with worsening of liver fibrosis.[20] In a study that assessed liver fibrosis using elastography in 103 patients coinfected with HIV/HCV, the 34 pa-

tients who achieved SVR improved their liver disease stage compared with the 69 patients who did not.[21]

The results of our study, which is the largest to date to assess the natural history of hepatitis C after therapy with interferon and ribavirin, suggest that treatment and clearance of HCV can reduce the incidence of liver complications and death in patients coinfected with HIV/HCV. Interestingly, these benefits could be shown in a relatively short follow-up time of approximately 20 months and were mainly due to a significant reduction in the rate of liver decompensation events (ascites, upper gastrointestinal bleeding, and hepatic encephalopathy) and in the rate of liver transplantation. We could not demonstrate a reduction in the incidence of hepatocellular carcinoma. This highlights the importance of continued surveillance of these patients, particularly those with advanced fibrosis and cirrhosis.

Our study has several limitations, the most important being that it is not entirely prospective. We believe, however, that its characteristics make it unlikely that the results differ considerably from those that would be obtained in a prospective study. This is because patients were followed closely by the same physicians in the same reference hospitals throughout the course of their disease, with a follow-up that included determination of standard clinical and laboratory parameters every 6 months. Furthermore, there is an important potential source of selection bias, because patients who did not achieve SVR may also have had unfavorable factors such as higher frequencies of advanced liver fibrosis or cirrhosis. Therefore, by selecting patients who did not achieve SVR, we may also be selecting those patients who have more advanced disease and, therefore, will be more likely to develop hepatic complications. In order to clarify this point, we carried out an adjusted multivariate analysis and found that the presence of bridging fibrosis or cirrhosis in baseline biopsies was an independent factor associated with poorer clinical outcome; however, this same analysis showed that the achievement of SVR was also independently associated with a beneficial alteration of the disease course. In the multivariate model, we did not adjust for markers of advanced liver disease (e.g., albumin, bilirubin, platelet count, international normalized ratio, or prothrombin time).

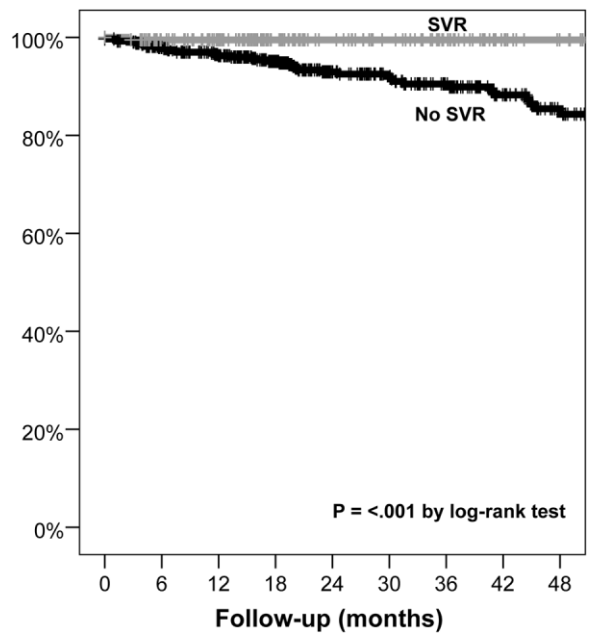

Fig. 2. Kaplan-Meier curves showing the occurrence of liver-related events (liver-related death, liver decompensation, hepatocellular carcinoma, and liver transplantation) in 711 patients positive for HIV/HCV with and without SVR following therapy with interferon plus ribavirin.

Table 3. Multivariate Analysis of Factors Associated with Liver-Related Events by Cox Regression Analysis

Factor	Adjusted HR	95% CI	*P*
Non-SVR versus SVR	8.92	(1.20–66.11)	0.032
F3-F4 vs F0-F2	4.96	(2.27–10.85)	0.000
Genotype 1-4 versus 2-3	1.35	(0.63–2.88)	0.443
HCV RNA < 500,000 IU/mL	0.73	(0.33–1.62)	0.444
CDC category C versus A/B	0.95	(0.49–1.87)	0.327
Nadir CD4+cells	0.99	(0.99–1.00)	0.319

Liver-related events include: liver-related death, liver decompensation, hepatocellular carcinoma, and liver transplantation.

CDC, Centers for Disease Control and Prevention; CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; SVR, sustained viral response.

In summary, our study shows that SVR to treatment for hepatitis C is associated with improved clinical outcomes in patients coinfected with HIV/HCV. These findings emphasize the need to prioritize adequate management of chronic HCV infection, one of the most clinically relevant comorbid conditions in the HIV-infected population.

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References

1. Eyster ME, Diamondstone LS, Lien JM, Ehmann WC, Quan S, Goedert JJ. Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immunodeficiency virus. The Multicenter Hemophilia Cohort Study. J Acquir Immune Defic Syndr 1993;6:602-610.
2. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, 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. Soto B, Sanchez-Quijano A, Rodrigo L, del Olmo JA, Garcia-Bengoechea M, Hernandez-Quero J, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol 1997;26:1-5.
4. Telfer P, Sabin C, Devereux H, Scott F, Dusheiko G, Lee C. The progression of HCV-associated liver disease in a cohort of haemophilic patients. Br J Haematol 1994;87:555-561.
5. Bica I, McGovern B, Dhar R, Stone D, McGowan K, Scheib R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis 2001;32:492-497.
6. Cacoub P, Geffray L, Rosenthal E, Perronne C, Veyssier P, Raguin G. Mortality among human immunodeficiency virus-infected patients with cirrhosis or hepatocellular carcinoma due to hepatitis C virus in French Departments of Internal Medicine/Infectious Diseases, in 1995 and 1997. Clin Infect Dis 2001;32:1207-1214.
7. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med 2004;351:438-450.
8. Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, et al. Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med 2004;351:451-459.
9. Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA 2004;292:2839-2848.
10. Laguno M, Murillas J, Blanco JL, Martinez E, Miquel R, Sanchez-Tapias JM, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. AIDS 2004;18:F27-F36.
11. Coverdale SA, Khan MH, Byth K, Lin R, Weltman M, George J, et al. Effects of interferon treatment response on liver complications of chronic hepatitis C: 9-year follow-up study. Am J Gastroenterol 2004;99:636-644.
12. Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med 2007;147:677-684.
13. 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.
14. Camma C, Giunta M, Andreone P, Craxi A. Interferon and prevention of hepatocellular carcinoma in viral cirrhosis: an evidence-based approach. J Hepatol 2001;34:593-602.
15. Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002;122:1303-1313.
16. Camma C, Di Bona D, Schepis F, Heathcote EJ, Zeuzem S, Pockros PJ, et al. Effect of peginterferon alfa-2a on liver histology in chronic hepatitis C: a meta-analysis of individual patient data. HEPATOLOGY 2004;39:333-342.
17. Lawson A, Hagan S, Rye K, Taguri N, Ratib S, Zaitoun AM, et al. The natural history of hepatitis C with severe hepatic fibrosis. J Hepatol 2007;47:37-45.
18. Bruno S, Stroffolini T, Colombo M, Bollani S, Benvegnu L, Mazzella G, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. HEPATOLOGY 2007;45:579-587.
19. Lissen E, Clumeck N, Sola R, Mendes-Correa M, Montaner J, Nelson M, et al. Histological response to pegIFNalpha-2a (40KD) plus ribavirin in HIV-hepatitis C virus co-infection. AIDS 2006;20:2175-2181.
20. Bani-Sadr F, Lapidus N, Bedossa P, De Boever CM, Perronne C, Halfon P, et al. Progression of fibrosis in HIV and hepatitis C virus-coinfected patients treated with interferon plus ribavirin-based therapy: analysis of risk factors. Clin Infect Dis 2008;46:768-774.
21. Barreiro P, Labarga P, Martin-Carbonero L, Amor A, Ruiz-Sancho A, Castellares C, et al. Sustained virological response following HCV therapy is associated with non-progression of liver fibrosis in HCV/HIV-co-infected patients. Antivir Ther 2006;11:869-877.