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

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Key points: We observed that eradication of HCV in HIV/HCV-coinfected patients was associated not only with a reduction in liver-related complications and mortality, but also with a reduction in HIV progression and mortality not related to liver disease.

ABSTRACT

Background: Sustained virological response (SVR) after therapy with interferon plus ribavirin (IFN-RBV) reduces liver-related complications and mortality in patients coinfected with HIV and hepatitis C virus (HIV/HCV). We assessed the effect of SVR on HIV progression and mortality not related to liver disease.

Methods: Observational cohort study including consecutive HIV/HCV-coinfected patients treated with IFN-RBV between 2000 and 2008 in 19 centers in Spain.

Results: Of 1599 patients, 626 (39%) had an SVR. After a median follow-up of approximately 5 years, we confirmed that failure to achieve an SVR was associated with an increased risk of liver-related events and liver-related death. We also observed higher rates of the following events in non-responders than in responders: AIDS-defining conditions (ADC) (x 100 person-years) (0.84 [0.59 - 1.10] vs 0.29 [0.10 - 0.48], *P*=.003), non–liver-related deaths (0.65 [0.42 - 0.87] vs 0.16 [0.02 - 0.30], *P*=.002), and non–liver-related non–AIDS-related deaths (0.55 [0.34 - 0.75] vs 0.16 [0.02 - 0.30], *P*=.002). Cox regression analysis, showed that the adjusted hazard ratio of new ADC, non–liver-related deaths, and non–liver-related non–AIDS-related deaths for non-responders in comparison with responders was 1.90 (95% CI, 0.89 - 4.10; *P*=.095), 3.19 (95% CI, 1.21 - 8.40; *P*=.019), and 2.85 (95% CI, 1.07 - 7.60; *P*=.036), respectively.

Conclusions: Our findings suggest that eradication of HCV after therapy with IFN-RBV in HIV/HCV-coinfected patients is associated not only with a reduction in liver-related events, but also with a reduction in HIV progression and mortality not related to liver disease.

INTRODUCTION

Human immunodeficiency virus (HIV) infection modifies the natural history of chronic hepatitis C, promoting more rapid progression to fibrosis and development of end-stage liver disease [1]. Following the decline in AIDS-related morbidity and mortality since the introduction of combination antiretroviral therapy (cART), end-stage liver disease emerged as a frequent cause of hospital admission and death in populations coinfected with HIV and hepatitis C virus (HCV) [2, 3]. For this reason, recommendations have considered HIV/HCV-coinfected patients as candidates for anti-HCV treatment [4].

Sustained virological response (SVR) to interferon plus ribavirin (IFN-RBV) enables a significant improvement in fibrosis in non–HIV-infected patients with chronic hepatitis C [5] and reduces liver-related complications and mortality in those with advanced fibrosis [6, 7]. One population-based cohort showed that alcohol consumption and an HCV diagnosis not made during systematic screening were significant determinants of poor outcome; interestingly, no deaths were observed among patients who achieved SVR [8]. A recent analysis found that SVR was associated with a reduction in all-cause mortality in US veterans monoinfected with HCV [9].

In HIV/HCV-coinfected patients, SVR to IFN-RBV also improves fibrosis [10] and reduces liver-related complications and mortality, independently of the stage of fibrosis, as recently reported by our group [11]. As HCV infection has been found to hasten HIV progression and mortality by some authors [12], we aimed to determine the effect of achieving an SVR after IFN-RBV on HIV progression and mortality not related to liver disease in HIV/HVC-coinfected patients.

METHODS

Design and patient selection

Our cohort was established in 2003 to follow HIV/HCV-coinfected patients who started therapy with IFN-RBV between January 2000 and January 2008 at 19 institutions in Spain. All patients were naïve to anti-HCV therapy. The primary objective of the study was to determine the effect of SVR on long-term clinical outcome, including liver-related complications, HIV progression, and mortality. The local ethics committees approved 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 IFN-RBV to coinfected patients was taken by physicians at each institution according to current guidelines. The eligibility criteria for anti-HCV therapy included absence of hepatic decompensation, CD4+ cell count > 200 cells/μL, stable cART or no need for cART, 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, anti-HCV was also stopped in patients with detectable HCV-RNA at week 12 of treatment and a reduction of < 2 log IU/mL in HCV-RNA.

Investigations

All the information was entered into a common database at each institution by trained personnel using an online electronic case report form that satisfied local requirements of data confidentiality. This database included all demographic, clinical, virological (HIV and HCV), and laboratory data. All the centers included in the cohort were monitored to verify that all the information in the database was consistent with the patient's medical history.

For each patient, we extracted the following data from the central database: age, sex, height and weight at the initiation of therapy, HIV transmission category, prior AIDS-defining conditions, baseline and nadir CD4+ cell counts, and baseline HIV viral load. We also recorded information about cART; including type, date of initiation, and whether or not it was maintained or changed during therapy. Information related to HCV infection included genotype, HCV-RNA levels, and estimated year of HCV infection (assumed to start the first year needles were unsafely shared in the case of injection drug users). Duration of HCV infection was considered to be unknown for patients infected through sexual contact.

Local pathologists scored liver biopsy samples following the criteria established by the METAVIR Cooperative Study Group [13]. Diagnosis of liver fibrosis was also estimated using the aspartate aminotransferase to platelet ratio index (APRI) test, a noninvasive index developed in HCV-monoinfected patients [14] that has been validated in coinfected patients [15].

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 discontinuation 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 active monitoring every 6 months to analyze clinical and laboratory parameters, including survival, presence of liver decompensation, cART, CD4+ cell count, HIV viral load, HCV-RNA, liver biopsy, APRI [14], and anti-HCV

therapy. The length of the study was calculated from the date IFN-RBV was stopped to death or the last follow-up visit. The administrative censoring date was 12 July, 2010.

Endpoints

We assessed the following endpoints: a) Liver-related complications, including ascites, hepatic encephalopathy, variceal bleeding, hepatocellular carcinoma, and liver transplantation. Ascites was confirmed by paracentesis and/or ultrasound. Hepatic encephalopathy was established on clinical grounds after the reasonable exclusion of HIV-associated encephalopathy based on clinical findings, laboratory parameters, and neuroimaging techniques. The source of gastroesophageal bleeding was confirmed by endoscopy whenever possible. For patients who had more than 1 event, only the first was included in the analyses of the association between SVR and "any event"; b) HIV progression, defined as the occurrence of any new AIDS-defining conditions [16]; c) Mortality. All the information related to death (death reports, autopsy reports [if available], and standard forms) was reviewed by JB and JGG. Both authors were blind to whether the patient reached an SVR or not and classified deaths in accordance with the opinion of the attending clinician as follows: i) liver-related 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–liver-related non–AIDS-related deaths.

Statistics

Differences between groups were analyzed using the chi-square test, *t* test, or Mann-Whitney test, as appropriate. Analysis of normality was performed with the Kolmogorov–Smirnov test. Logistic regression models were used to explore baseline factors predicting an SVR and discontinuation of therapy due to adverse events. We calculated the

frequency, incidence rate, and survival function (Kaplan-Meier) for the different endpoints. Multivariate analysis was performed using Cox regression analysis. The statistical analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, Illinois, USA). As several patients underwent retreatment with IFN-RBV, those who achieved SVR after retreatment were included in the SVR group

RESULTS

Patient characteristics

Between January 2000 and January 2008, 1599 patients were included in the database. Their baseline characteristics are shown in **Table 1.** In brief, 75% were male, median age was 40 years, 23% had prior AIDS-defining conditions, median baseline CD4+ cell count was 527 cells/mm^3, 70% had an undetectable HIV viral load, median time since HCV infection was 18 years, 61% were infected by genotypes 1 or 4, and 61% had an HCV-RNA ≥ 500,000 IU/mL. Patients were asked about their alcohol intake at baseline, and 5% 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. Advanced fibrosis at baseline (F3-F4 in liver biopsy) was present in 448/1153 (39%) patients before anti-HCV therapy was started.

A total of 790 (49%) patients were treated with pegylated interferon-α2a plus RBV, 602 (38%) were treated with pegylated interferon-α2b plus RBV, and 207 (13%) were treated with standard thrice-weekly interferon-α plus. The median duration of anti-HCV therapy was 11.07 months in responders and 6.97 months in non-responders; P < 0.001. Scheduled therapy was completed by 555 (89%) responders and 352 (36%) non-responders; P < 0.001. Anti-HCV therapy was interrupted because of adverse events in 48 responders (8%) and 166 non-responders (17%); P < 0.001.

During treatment of hepatitis C, 1262 (79%) of the patients were on cART. The most common combinations were 2 nucleoside reverse transcriptase inhibitors (NRTI) plus 1 non-nucleoside reverse-transcriptase inhibitor (NNRTI) in 573 patients (45%), 2 NRTI plus 1 protease inhibitor (PI) in 176 (14%), 3 NRTI in 89 (7%), and other combinations in 424 (34%).

Sustained virological response

Overall, 626 (39%) of the patients achieved an SVR; this figure includes 42 of 174 retreated patients that achieved SVR after the second course of IFN-RBV. The response was 251/982 (26%) for genotypes 1 and 4 and 360/572 (63%) for genotypes 2 and 3. We used multiple logistic regression analysis to identify pre-treatment factors that were predictive of an SVR. The model included baseline factors that were associated with SVR by univariate regression analysis, for example, prior AIDS-defining conditions, nadir CD4+ cell count, HCV genotype, and HCV-RNA level. It also included the type of interferon used (pegylated vs. non-pegylated), the presence of advanced fibrosis, and alcohol intake higher than 50 g per day. The final model identified 3 variables that were independently associated with increased probability of an SVR: HCV genotype 2-3 (OR, 4.82; 95% CI, 3.53-6.58; *P*<.001), HCV-RNA level < 500,000 IU/mL (OR, 1.60; 95% CI, 1.17-2.19; *P*=.003), and absence of advanced fibrosis (OR, 1.91; 95% CI, 1.40-2.62; *P*<.001).

Outcomes

After a median follow-up of 62.0 (IQR, 41.9 - 80.7) months in non-responders and 56.9 (IQR, 41.6 - 79.9) months in responders (*P*=.204), we found a significantly higher frequency and rate (per 100 persons-years) of liver decompensation, hepatocellular carcinoma, and liver transplantation in non-responders than in responders (**Table 2**).

We also found a significantly higher frequency and rate of new AIDS-defining conditions in non-responders than in responders (**Table 2**). The different types of AIDS-defining conditions are listed in **Table 3**. There were 41 AIDS-defining conditions among non-responders; the most frequent were recurrent pneumonia (n=11), tuberculosis (n=6), and esophageal candidiasis (n=5), progressive multifocal leukoencephalopathy (n=5), and invasive cervical cancer (n=5). There were only 9 AIDS-defining conditions among responders; the most frequent was recurrent pneumonia (n=4) (**Table 3**). At the time of the first new AIDS-defining condition, 34 non-responders (83%) and 9 responders (100%) were receiving cART. HIV viral load and CD4+ cell count were available for 40/41 non-responders and 9/9 responders. HIV viral load was detected in 23 non-responders (57%) and in 5 responders (56%). The median (IQR) CD4+ cell count was 341 cells/mm^3 (170 - 571) for non-responders and 400 cells/mm^3 (159 - 466) for responders.

We also found a significantly higher frequency and rate of overall deaths, liver-related deaths, non-liver related deaths, and non–liver-related non–AIDS-related deaths in non-responders than in responders (**Table 2 and Figure 1**). Non–liver-related deaths are summarized in **Table 3**. Five deaths in non-responders were caused by AIDS-defining conditions compared with none in responders. There were 27 non–liver-related non–AIDS-related deaths among non-responders; the most frequent causes were non–AIDS-defining cancers (n=7), cardiovascular events (n=6), and bacterial infections (n=6). There were 5 non–AIDS-related deaths among responders, including 2 due to non–AIDS-defining cancers.

We applied Cox regression analysis to investigate the association between response to IFN-RBV and the development of new AIDS-defining conditions, non–liver-related death, and non–liver-related non–AIDS-related death. When we adjusted for age, sex, HIV transmission category, nadir CD4+ cell count, cART, HIV-RNA level below the limit of

detection, and liver fibrosis, we found that the adjusted hazard ratio of each of these clinical endpoints was higher for non-responders than for responders, although it reached statistical significance only for non–liver-related death and non–liver-related non–AIDS-related death (**Table 4**). We carried out 2 sensitivity analyses. In the first, we excluded those patients with recurrent pneumonia as a new AIDS-defining condition and those who died of bacterial pneumonia. In the second, we did not exclude patients with recurrent pneumonia as a new AIDS-defining condition or those who died of bacterial pneumonia, although we did censor their follow-up until these events occurred. Interestingly, the results of these analyses did not change the main observation that the risk of HIV progression, non–liver-related death, and non–liver-related non–AIDS-related death were significantly higher for non-responders than for responders after adjustment for important baseline variables (data not shown).

The percentage of patients with HIV viral load below the limit of detection was higher in responders than in non-responders at baseline and at the end of treatment with IFN-RBV, although it did not differ among the groups during follow-up except at a single time-point in month 18 (**Figure 2**). Although the percentage of patients with CD4+ cell counts < 200 cells/mL was not significantly different between responders and non-responders at baseline and at the end of treatment, during the follow-up period we observed that a higher proportion of non-responders than responders had CD4+ cell counts < 200 cells/mL, reaching statistical significance at 3, 6, and 9 months after discontinuation of therapy (**Figure 2**)

DISCUSSION

We evaluated the clinical course of 1599 HIV/HCV-coinfected patients who were followed up for a median period of approximately 5 years after therapy with IFN-RBV. We found that failure to achieve an SVR was associated with increased risk of liver decompensation,

hepatocellular carcinoma, liver transplantation, and liver-related death; findings consistent with our previous observations [11]. Interestingly, we also found that failure to achieve an SVR was associated with an increased risk of HIV progression and non–liver-related mortality. Most non–liver-related deaths were due to non–AIDS-defining cancers, cardiovascular events, and bacterial infections. Of note, both the risk of non–liver-related death, and non–liver-related non–AIDS-related death was significantly higher for non-responders than for responders after adjustment for important baseline variables such as age, sex, HIV transmission category, nadir CD4+ cell count, cART, HIV-RNA level below the limit of detection, and liver fibrosis. The frequency of severe immunodeficiency—defined as a CD4+ T-lymphocyte count < 200 cells/mm^3—after discontinuation of IFN-RBV was higher in non-responders than in responders; this finding could not be explained by differences in suppression of HIV replication between the groups.

The findings of reports on the effect of HCV on the progression of HIV infection are conflicting. One study found no evidence that HCV infection increases the risk of progression or death or affects the immune response to cART [17]; another reported that HCV serostatus did not affect the CD4 recovery in patients with fully suppressed HIV after cART [18]. Our findings, however, support the notion that HCV has a negative impact on HIV infection, an observation shared by other authors who found an association between HCV infection and increased risk of developing AIDS-defining conditions [12, 19]. Recent works have also shown that active HCV infection impairs CD4 recovery, even after years of exposure to cART [20].

The increased risk of non–liver-related death and non–liver-related non–AIDS-related death among non-responders than responders found in our study may be explained by several factors, including immune activation, defective immunity, systemic inflammation, and liver disease itself.

In HIV-infected patients, those who were coinfected with HCV had higher grades of immune activation than those not coinfected with HCV [21, 22], and this elevated immune activation may place these individuals at increased risk not only of HCV disease complications, but also of HIV progression [23]. In addition, in HIV/HCV-coinfected patients with liver cirrhosis, microbial translocation has been correlated with markers of systemic immune activation [24].

After adjustment for traditional risk factors, HCV infection was associated with increased carotid intima-media thickness [25], as well as with increased cardiovascular mortality among blood donors [26]. However, Weber et al found no association between HBV or HCV coinfection and development of myocardial infarction in a prospective cohort study of HIV-infected patients [27].

Interestingly, just as cART causes a decline in the high levels of inflammation and hypercoagulation that are characteristically associated with untreated HIV infection [28], eradication of HCV may have similar effects. In this regard, HIV/HCV coinfection has been found to increase serum levels of soluble adhesion molecules sICAM-1 and sVCAM-1, and SVR after therapy with IFN-RBV significantly reduces these cardiovascular markers [29]. This observation is of interest, because soluble adhesion molecules, especially sVCAM-1, are associated with cardiovascular death among patients with coronary artery disease [30].

Finally, liver disease could also have contributed to non–liver-related mortality among non-responders in our study, particularly in the case of bacterial pneumonia. This is because progression of liver disease was more common in non-responders than in responders [31] and because mortality from infections such as pneumococcal pneumonia is high in patients with cirrhosis [32]. To address this issue, we carried out 2 sensitivity analyses, the results of which did not change the main observation that both the risk of HIV progression

and non–liver-related death were significantly higher for non-responders than for responders.

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 have been obtained in an entirely prospective study. This is because follow-up was by the same physicians in the same reference hospitals throughout the course of their disease, with standard clinical and laboratory parameters. Furthermore, all the information in the database was monitored to verify that it was consistent with the patient's medical history. Another limitation is the lack of information about adherence to cART during follow-up; however, the absence of differences in suppression of HIV replication between the groups during follow-up suggests that adherence to cART probably had little impact on the differences found in outcomes. Our study is also limited by the lack of information about pneumococcal vaccination and other baseline comorbidities (smoking, diabetes, traditional cardiovascular risk factors); therefore, we cannot rule out the possibility that differences in these variables could have affected outcome.

Although the study design precluded determination of causality, our results suggest that eradication of HCV in HIV/HCV-coinfected patients is associated not only with a reduction in liver-related complications and mortality, but also with a reduction in HIV progression and mortality not related to liver disease. These findings support an increasingly strong rationale for earlier evaluation of new direct-acting antivirals against HCV in coinfected patients, a subgroup with a hugely unmet need for treatment [33].

NOTES

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CONFLICTS OF INTEREST

All authors no conflicts

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REFERENCES

1. 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** Aug 15;33(4):562-9.

2. Soriano V, Garcia-Samaniego J, Valencia E, Rodriguez-Rosado R, Munoz F, Gonzalez-Lahoz J. Impact of chronic liver disease due to hepatitis viruses as cause of hospital admission and death in HIV-infected drug users. Eur J Epidemiol **1999** Jan;15(1):1-4.

3. Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis **2001** Feb 1;32(3):492-7.

4. Soriano V, Puoti M, Sulkowski M, et al. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. Aids **2007** May 31;21(9):1073-89.

5. Camma C, Di Bona D, Schepis F, et al. Effect of peginterferon alfa-2a on liver histology in chronic hepatitis C: a meta-analysis of individual patient data. Hepatology **2004** Feb;39(2):333-42.

6. Coverdale SA, Khan MH, Byth K, et al. Effects of interferon treatment response on liver complications of chronic hepatitis C: 9-year follow-up study. Am J Gastroenterol **2004** Apr;99(4):636-44.

7. 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** Nov 20;147(10):677-84.

8. Di Martino V, Crouzet J, Hillon P, Thevenot T, Minello A, Monnet E. Long-term outcome of chronic hepatitis C in a population-based cohort and impact of antiviral therapy: a propensity-adjusted analysis. J Viral Hepat **2011** Jul;18(7):493-505.

9. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol **2011** Jun;9(6):509-16 e1.

10. Lissen E, Clumeck N, Sola R, et al. Histological response to pegIFNalpha-2a (40KD) plus ribavirin in HIV-hepatitis C virus co-infection. Aids **2006** Nov 14;20(17):2175-81.

11. 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** Aug;50(2):407-13.

12. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. Lancet **2000** Nov 25;356(9244):1800-5.

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** Jul;20(1 Pt 1):15-20.

14. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology **2003** Aug;38(2):518-26.

15. Moreno S, Garcia-Samaniego J, Moreno A, et al. Noninvasive diagnosis of liver fibrosis in patients with HIV infection and HCV/HBV co-infection. J Viral Hepat **2009** Apr;16(4):249-58.

16. Centers for Disease Control and Prevention (U.S.). 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep **1992** Dec 18;41(RR-17):1-19.

17. Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. JAMA **2002** Jul 10;288(2):199-206.

18. Peters L, Mocroft A, Soriano V, et al. Hepatitis C virus coinfection does not influence the CD4 cell recovery in HIV-1-infected patients with maximum virologic suppression. J Acquir Immune Defic Syndr **2009** Apr 15;50(5):457-63.

19. d'Arminio Monforte A, Cozzi-Lepri A, Castagna A, et al. Risk of developing specific AIDS-defining illnesses in patients coinfected with HIV and hepatitis C virus with or without liver cirrhosis. Clin Infect Dis **2009** Aug 15;49(4):612-22.

20. Potter M, Odueyungbo A, Yang H, Saeed S, Klein MB. Impact of hepatitis C viral replication on CD4+ T-lymphocyte progression in HIV-HCV coinfection before and after antiretroviral therapy. AIDS **2010** Jul 31;24(12):1857-65.

21. Kovacs A, Al-Harthi L, Christensen S, Mack W, Cohen M, Landay A. CD8(+) T cell activation in women coinfected with human immunodeficiency virus type 1 and hepatitis C virus. J Infect Dis **2008** May 15;197(10):1402-7.

22. Rempel H, Sun B, Monto A, Calosing C, Pulliam L. HCV Stimulates HIV Immune Activation in HIV/HCV Co-infected Subjects on HAART (Paper # 672). In: 17th Conference on Retroviruses and Opportunistic Infections San Francisco, California, **2010**.

23. Kovacs A, Karim R, Mack WJ, et al. Activation of CD8 T cells predicts progression of HIV infection in women coinfected with hepatitis C virus. J Infect Dis **2010** Mar 15;201(6):823-34.

24. de Oca Arjona MM, Marquez M, Soto MJ, et al. Bacterial translocation in HIV-infected patients with HCV cirrhosis: implication in hemodynamic alterations and mortality. J Acquir Immune Defic Syndr **2011** Apr 15;56(5):420-7.

25. Mostafa A, Mohamed MK, Saeed M, et al. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors. Gut **2010** Aug;59(8):1135-40.

26. Guiltinan AM, Kaidarova Z, Custer B, et al. Increased all-cause, liver, and cardiac mortality among hepatitis C virus-seropositive blood donors. Am J Epidemiol **2008** Mar 15;167(6):743-50.

27. Weber R, Sabin C, Reiss P, et al. HBV or HCV coinfections and risk of myocardial infarction in HIV-infected individuals: the D:A:D Cohort Study. Antivir Ther **2010**;15(8):1077-86.

28. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. Annu Rev Med **2011** Feb 18;62:141-55.

29. de Castro IF, Micheloud D, Berenguer J, et al. Hepatitis C virus infection is associated with endothelial dysfunction in HIV/hepatitis C virus coinfected patients. AIDS **2010** Aug 24;24(13):2059-67.

30. Blankenberg S, Rupprecht HJ, Bickel C, et al. Circulating cell adhesion molecules and death in patients with coronary artery disease. Circulation **2001** Sep 18;104(12):1336-42.

31. 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** Oct;50(4):1056-63.

32. Propst-Graham KL, Preheim LC, Vander Top EA, Snitily MU, Gentry-Nielsen MJ. Cirrhosis-induced defects in innate pulmonary defenses against Streptococcus pneumoniae. BMC Microbiol **2007**;7:94.

33. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology **2011** Oct;54(4):1433-44.

Table 1. Baseline characteristics of 1599 HIV/HCV-coinfected patients treated with interferon plus ribavirin at 19 institutions in Spain between 2000 and 2008.

Characteristic	Non-SVR N=973 (61%)	SVR N=626 (39%)	Total 1599
N			
Male sex-n (%)	731 (75)	463 (74)	1194 (75)
Age-yr, median (IQR)	40 (37- 43)	40 (37- 43)	40 (37- 43)
Prior injection drug use-n (%)	774 (80)	513 (83)	1287 (81)
Prior AIDS-defining conditions-n (%)	231 (24)	124 (20)	355 (23)
CD4+ cells nadir-n/mm^3, median (IQR)	204 (109- 321)	217 (117- 333)	209 (110- 326)
CD4+ cells baseline-n/mm^3, median (IQR)	517 (374- 714)	532 (404- 730)	527 (391- 723)
Time since HCV infection (yr), median (IQR)	18 (13- 22)	19 (15- 22)	18 (13- 22)
Undetectable HIV RNA load at baseline-n (%)*	643/960 (67.0)	448/612 (73.2) #	1091 (70)
HCV genotype-n (%)			
1	574 (59)	213 (34) #	787 (49)
2	16 (2)	22 (4) #	38 (2)
3	196 (20)	338 (54) #	534 (34)
4	157 (16)	38 (6) #	195 (12)
Unknown	30 (3)	15 (2)	45 (3)

HCV RNA-n (%)			
< 500,000 IU/mL	203 (21)	210 (34) #	413 (26)
≥ 500,000 IU/mL	627 (64)	352 (56) #	979 (61)
Unknown	143 (15)	64 (10) #	207 (13)
HBsAg positivity-n (%)	37/925 (4)	18/609 (3)	55/1534 (4)
Stage of liver fibrosis F3-F4-n (%)	324/724 (45)	124/429 (29) #	448/1153 (39)
Advanced fibrosis (F3-F4 or APRI > 2)-n (%)	387/923 (42)	146/516 (28) #	533/1439 (37)
Alcohol intake > 50 g/day-n (%)	58 (7)	18 (3) #	76 (5)
cART during HCV treatment-n (%)	810 (80)	452 (78)	1262 (79)

*Baseline HIV viral load was determined in 1572 patients using commercial assays with different lower limits of detection in HIV-RNA copies/mL: <500 (n=1), <400 (n=9), <200 (n=124), <80 (n =119), < 50 (n=1101), <40 (n=70), and <20 (n=148).
# p<0.05
Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; CDC, Centers for Disease Control and Prevention; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IQR, interquartile range; cART, combination antiretroviral therapy.

Table 2. Frequency and rate of events during follow-up in 1599 HIV/HCV-coinfected patients with and without sustained virological response after therapy with interferon plus ribavirin.

	Frequency of events N (%)			Rate of events/100 person-years (95% CI)		
Event	**Non-SVR (n=973)**	**SVR (n=626)**	***P***	**Non-SVR**	**SVR**	***P* ***
Loss to follow-up	114 (11.7)	56 (8.9)	.079	2.32 (1.89 - 2.75)	1.82 (1.35 - 2.3)	.139
Liver-related events						
Any event	135 (13.9)	10 (1.6)	<.001	2.87 (2.39 - 3.36)	0.32 (0.12 - 0.53)	<.001
Liver decompensation#	113 (11.6)	6 (1.0)	<.001	2.39 (1.95 - 2.83)	0.19 (0.04 - 0.35)	<.001
Hepatocellular carcinoma	28 (2.9)	3 (0.5)	.001	0.57 (0.36 - 0.78)	0.10 (0.00 - 0.21)	.001
Liver transplantation	21 (2.2)	4 (0.6)	.017	0.43 (0.24 - 0.61)	0.13 (0.00 - 0.26)	.024
HIV-related events						
New AIDS-defining conditions	41 (4.2)	9 (1.4)	.002	0.84 (0.59 - 1.10)	0.29 (0.10 - 0.48)	.003
Mortality						
Deaths overall	90 (9.2)	8 (1.3)	<.001	1.82 (1.45 - 2.20)	0.26 (0.08 - 0.44)	<.001
Liver-related deaths	55 (5.7)	3 (0.5)	<.001	1.11 (0.82 - 1.41)	0.10 (0.00 - 0.21)	<.001
Non–liver-related deaths	32 (3.3)	5 (0.8)	.001	0.65 (0.42 - 0.87)	0.16 (0.02 - 0.30)	.002
AIDS-related	5 (0.5)	0 (0.0)	.072	0.10 (0.01 - 0.19)	0	.071
Non–liver-related non–AIDS-related	27 (2.8)	5 (0.8)	.006	0.55 (0.34 - 0.75)	0.16 (0.02 - 0.30)	.002

Unknown	4 (0.4)	0 (0.0)	-	-	-	-

* Log-rank test.

Ascites, variceal bleeding, hepatic encephalopathy

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

Table 3. New AIDS-related conditions and non–liver-related deaths in 1599 HIV/HCV-coinfected patients with and without sustained virological response after therapy with interferon plus ribavirin.

	Non-SVR (n=973)	SVR (n=626)
New AIDS-related conditions	**N=41**	**N=9**
Recurrent pneumonia	11	4
Mycobacterium tuberculosis, any site	6	1
Esophageal candidiasis	5	2
Progressive multifocal leukoencephalopathy	5	-
Invasive cervical cancer	5	-
Pneumocystis jiroveci pneumonia	2	-
HIV wasting syndrome	2	-
Disseminated cryptococcosis	2	-
HIV encephalopathy	2	-
Recurrent *Salmonella* septicemia	-	1
Non-Hodgkin lymphoma	1	-
Disseminated *Mycobacterium avium* complex infection	0	1
Non–liver-related deaths	**N=32**	**N=5**
AIDS-related		-
Progressive multifocal leukoencephalopathy	2	-
Cryptococcosis	1	-
Recurrent pneumonia	1	-
Invasive cervical cancer	1	-
Non–AIDS-related		
Non–AIDS-related malignancy[1]	7	2
Cardiovascular event[2]	6	1
Bacterial infection[3]	6	-
Traumatic death[4]	3	-
Sudden death[5]	2	1
Suicide	1	1
Bleeding duodenal ulcer	1	-
Acute renal failure	1	-

[1] Non-SVR: lung cancer (n=2), anal carcinoma (n=2), gastric carcinoma (n=1), disseminated carcinoma of unknown origin (n=1), Hodgkin lymphoma (n=1). SVR: acute leukemia (n=1), pleuropulmonary sarcoma (n=1).

[2] Non-SVR: acute myocardial infarction (n=3), mesenteric ischemia (n=2), stroke (n=1). SVR: acute myocardial infarction (n=1)

[3] Bacterial pneumonia (n=3), bacterial meningitis (n=1), urinary tract sepsis (n=1), bacterial endocarditis (n=1)

[4] Drowning (n=1), abdominal trauma (n=1), traffic accident (n=1)

[5] One of the patients in the Non-SVR group had a prior diagnosis of angina pectoris

Table 4. Crude and adjusted hazard ratios (95% confidence intervals) of non–liver-related events during follow-up for non-responders to interferon plus ribavirin in comparison with responders (Cox regression analysis).

	Crude			Adjusted*		
Event	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
New AIDS-defining conditions	2.86	1.39 - 5.9	.004	1.90	(0.89 - 4.1)	.095
Non–liver-related deaths	4.08	1.59 - 10.5	.003	3.19	(1.21 - 8.4)	.019
Non–liver-related non–AIDS-related deaths	3.42	1.32 - 8.9	.012	2.85	(1.07 - 7.6)	.036

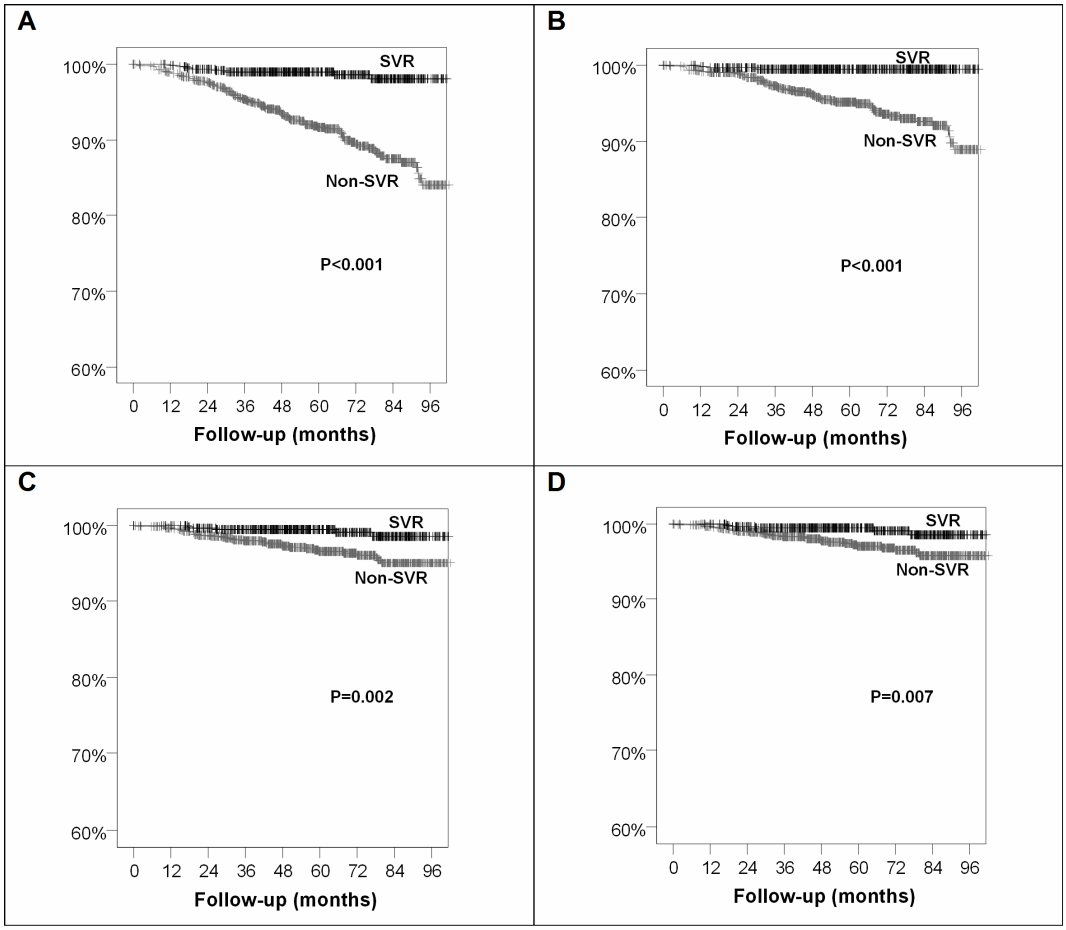
*Adjusted for age, sex, HIV-transmission category (injection drug users vs non–injection drug users), CD4+ cells nadir, advanced fibrosis (F3-F4 on biopsy or aspartate aminotransferase to platelet ratio >2), HIV-RNA < 50 copies/mL baseline and cART

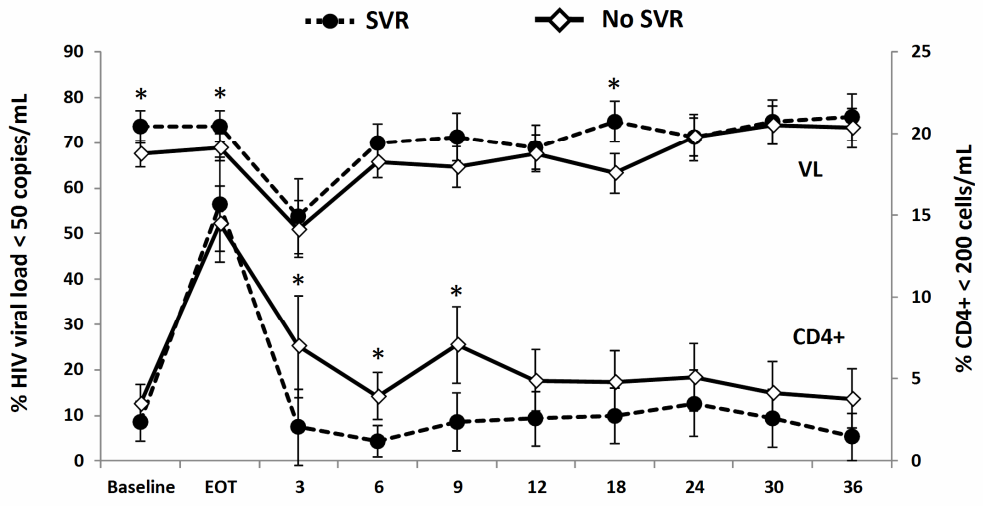
Figure 1.

Kaplan–Meier curves showing the occurrence of overall deaths (1A), liver-related deaths (1B), non-liver related deaths (1C), and non–liver-related non–AIDS-related deaths (1D) in 1599 HIV/HCV-coinfected patients with and without sustained virologic response (SVR) following therapy with interferon plus ribavirin.

Figure 2.

Immunovirological status at baseline, at the end of anti-HCV treatment (EOT), and during follow-up in 1599 HIV/HCV-coinfected patients with and without sustained virological response (SVR) after therapy with interferon plus ribavirin. Solid line, proportion of patients with CD4+ < 200 cells/mL; dotted line, proportion of patients with HIV viral load < 50 copies/mL. * *P*<.05





Studied										
Viral Load	1560	1480	388	1175	723	841	828	744	719	682
CD4+	1591	1511	403	1204	748	861	842	765	739	693