

Eradication of Hepatitis C Virus and Non-Liver-Related Non-Acquired Immune Deficiency Syndrome-Related Events in Human Immunodeficiency Virus/Hepatitis C Virus Coinfection

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We assessed non-liver-related non-acquired immunodeficiency syndrome (AIDS)-related (NLR-NAR) events and mortality in a cohort of human immunodeficiency virus (HIV)/hepatitis C virus (HCV)-coinfected patients treated with interferon (IFN) and ribavirin (RBV), between 2000 and 2008. The censoring date was May 31, 2014. Cox regression analysis was performed to assess the adjusted hazard rate (HR) of overall death in responders and nonresponders. Fine and Gray regression analysis was conducted to determine the adjusted subhazard rate (sHR) of NLR deaths and NLR-NAR events considering death as the competing risk. The NLR-NAR events analyzed included diabetes mellitus, chronic renal failure, cardiovascular events, NLR-NAR cancer, bone events, and non-AIDS-related infections. The variables for adjustment were age, sex, past AIDS, HIV transmission category, nadir CD4⁺ T-cell count, antiretroviral therapy, HIV RNA, liver fibrosis, HCV genotype, and exposure to specific anti-HIV drugs. Of the 1,625 patients included, 592 (36%) had a sustained viral response (SVR). After a median 5-year follow-up, SVR was found to be associated with a significant decrease in the hazard of diabetes mellitus (sHR, 0.57; 95% confidence interval [CI], 0.35-0.93; $P = 0.024$) and decline in the hazard of chronic renal failure close to the threshold of significance (sHR, 0.43; 95% CI, 0.17-1.09; $P = 0.075$). **Conclusion:** Our data suggest that eradication of HCV in coinfecting patients is associated not only with a reduction in the frequency of death, HIV progression, and liver-related events, but also with a reduced hazard of diabetes mellitus and possibly of chronic renal failure. These findings argue for the prescription of HCV therapy in coinfecting patients regardless of fibrosis stage. (HEPATOLOGY 2017;66:344-356).

The liver is the key target of hepatitis C virus (HCV) infection; however, patients with HCV infection may have extrahepatic manifestations that are directly or indirectly related to the virus and may account for substantial morbidity and mortality.⁽¹⁾ The best documented of these complications is mixed cryoglobulinemia, although other conditions, such as cardiovascular disease, chronic renal failure, diabetes mellitus and insulin resistance (IR), B-cell non-Hodgkin's lymphoma, and neurocognitive dysfunction, have been associated with HCV infection.^(1,2)

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, combination antiretroviral therapy; CHC, chronic hepatitis C; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GESIDA, Grupo de Estudio del Sida de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (AIDS Study Group of the Spanish Society of Infectious Diseases and Clinical Microbiology); HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; HIV, human immunodeficiency virus; HR, hazard ratio; IFN, interferon; IQR, interquartile range; IR, insulin resistance; IRRs, incidence rate ratios; LDL, low-density lipoprotein; LT, liver transplantation; NLR-NAR, non-liver-related non-AIDS-related; Peg-IFN, pegylated interferon; RBV, ribavirin; SEIMC, Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (Spanish Society of Infectious Diseases and Clinical Microbiology); sHR, subhazard rate; SVR, sustained viral response; T2D, type 2 diabetes.

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In patients with chronic hepatitis C (CHC), sustained viral response (SVR) following anti-HCV therapy (i.e., eradication of HCV) significantly reduces progression of fibrosis and may reverse cirrhosis in some patients,⁽³⁾ although this process is limited by the extent of extracellular matrix cross-linking and angiogenesis.⁽⁴⁾ More remarkably, eradication of HCV has been found to reduce liver decompensation and increase survival in cohorts of patients infected by HCV alone and patients coinfecting by human immunodeficiency virus (HIV).⁽⁵⁻⁷⁾ In a recent systematic review and meta-analysis of the survival benefits of achieving SVR, viral clearance was found to be associated with a survival benefit in various HCV-infected populations, and survival was higher in patients with cirrhosis and those coinfecting with HIV.⁽⁸⁾

Many of the manifestations of HCV-related mixed cryoglobulinemia can resolve following successful HCV treatment, although patients with significant renal or neural injury may not recover fully after eradication of HCV infection.^(9,10) In the HCV-monoinfected population,

eradication of HCV following anti-HCV therapy may reduce the risk of developing type II diabetes mellitus,⁽¹¹⁾ renal and cardiovascular events,^(12,13) and neurocognitive dysfunction.⁽¹⁴⁾

To the best of our knowledge, the effect of eradication of HCV on extrahepatic manifestations of HCV has not been systematically studied in HIV/HCV-coinfecting patients. The purpose of our study was to investigate the effect of sustained viral response in non-liver-related non-acquired immunodeficiency syndrome (AIDS)-related (NLR-NAR) events in a large cohort of HIV/HCV-coinfecting patients treated with interferon (IFN) plus ribavirin (RBV).

Patients and Methods

DESIGN AND PATIENT SELECTION

Patients were selected from the cohort of the “Grupo de Estudio del SIDA” (AIDS Study Group;

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**These authors contributed equally to this study.*

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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 naïve to anti-HCV therapy and who were treated with IFN and RBV. The cohort was established in 2003 to follow HIV/HCV-coinfected patients who started treatment with these drugs between January 2000 and January 2008 at 19 institutions in Spain. The primary objective of this cohort study was to determine the effect of response to IFN and RBV on long-term clinical outcomes, including liver-related complications, AIDS-related conditions, and mortality. The local ethics committees waived the requirement for written informed consent, because the study was based on anonymous routine clinical data intended for 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 and RBV to coinfected patients was taken by infectious diseases physicians at each institution according to national and international guidelines. The eligibility criteria for IFN and RBV therapy included the absence of previous hepatic decompensation, severe concurrent medical conditions (such as poorly controlled hypertension, heart failure, poorly controlled diabetes mellitus, and severely reduced renal function), $CD4^+$ T-cell count >200 cells/ μ L, stable antiretroviral therapy or no need for antiretroviral therapy, the absence of active opportunistic infections, and a ≥ 6 -month period of abstinence from heroin and cocaine in patients with a history of injection drug use. Patients were advised not to consume alcohol. Anti-HCV therapy was stopped in all patients with detectable HCV RNA at week 24 of treatment. Since 2002, anti-HCV therapy 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 data were entered directly into a shared database (created in 2003) by trained personnel at each institution using an online application that satisfied local requirements of data confidentiality. This database included all demographic, clinical, virological (HIV and HCV), and laboratory data. The database was modified in the first semester of 2014 to include variables related to NLR-NAR events during follow-up (see below), which were registered between June

and September 2014. All centers were monitored between October 2014 and April 2015 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; HIV transmission category; previous AIDS-defining conditions; baseline and nadir $CD4^+$ T-cell counts; and baseline HIV viral load. We also recorded information about combination antiretroviral therapy, 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 (assumed to be the first year needles were unsafely shared in the case of injection drug users). Duration of HCV infection was unknown for patients infected through sexual contact. Patients were asked about their current alcohol intake. A high intake of alcohol was defined as the consumption of more than 50 g of alcohol per day for at least 12 months.

Local pathologists scored liver biopsy samples following the criteria established by the METAVIR Cooperative Study Group⁽¹⁵⁾ 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. Staging of liver fibrosis was also estimated at baseline using the FIB-4 index⁽¹⁶⁾; advanced fibrosis was defined as a FIB-4 value ≥ 3.25 .

Patients with an undetectable serum HCV-RNA level 24 weeks after discontinuation of therapy were classified as having an SVR; patients not fulfilling the criteria for an SVR, including those who had a relapse after achieving an end-of-treatment response, were classified as nonresponders. Safety was assessed by laboratory tests and evaluation of adverse clinical events during therapy.

FOLLOW-UP

Completion of treatment was followed by active monitoring (semiannually until July 2010 and annually thereafter) to analyze clinical and laboratory parameters, including survival, presence of liver decompensation, antiretroviral therapy, $CD4^+$ T-cell count, HIV viral load, HCV RNA, and assessment of liver fibrosis. The length of the study was calculated from the date IFN plus RBV was stopped to death or the last follow-up visit. The administrative censoring date was May 31, 2014.

CLINICAL ENDPOINTS

We assessed the following incident endpoints: liver-related events; AIDS-related events; NLR-NAR events; and mortality.

Liver-related events included ascites, hepatic encephalopathy (HE), variceal bleeding, hepatocellular carcinoma (HCC), and liver transplantation (LT). Ascites was confirmed by paracentesis and/or ultrasound. HE was established on clinical grounds after the reasonable exclusion of HIV-associated encephalopathy based on clinical and laboratory parameters (i.e., CD4⁺ T-cell counts, 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 sustained viral response and “any event.”

AIDS-related events were defined as the occurrence of any new AIDS-defining conditions.⁽¹⁷⁾

NLR-NAR events included cardiovascular events (myocardial infarction, angina, stroke, peripheral artery disease, heart failure, ruptured aortic aneurysm, and mesenteric artery ischemia), renal events (chronic renal failure, dialysis, and renal transplantation), bone events (bone fractures and avascular bone necrosis), diabetes mellitus, NLR-NAR cancer (biopsy confirmed), and non-AIDS-related infections. As mentioned above, incident NLR-NAR events were collected retrospectively. For this purpose, all centers were provided with a structured electronic reporting form containing the list of NLR-NAR events and the precise definition of each of them based on a modified version of the Cohort of the Spanish AIDS Research Network criteria⁽¹⁹⁾ (Supporting Tables S1 and S2).

All the information related to death (death reports, autopsy reports [if available], and standard forms) was reviewed by J.B. and J.G.G. Both authors were blind to the category of treatment response and classified deaths in accord with the opinion of the attending clinician as follows: (1) liver-related death, when the train of events that ended in death was caused by liver decompensation or HCC; (2) AIDS-related death, when death was directly related to an AIDS-defining condition; and (3) NLR-NAR deaths.

STATISTICAL ANALYSIS

Differences between groups were analyzed using the chi-square test, *t* test, or Mann-Whitney U test, as appropriate. Normality was analyzed using the

Kolmogorov–Smirnov test. We calculated the frequency and incidence rates of the different endpoints. The Pearson chi-square test was used to assess differences between the frequency of events between responders and nonresponders. Unadjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for events in nonresponders versus responders were estimated using Poisson regression. Univariate and multivariate Cox regression analyses were performed to compare the overall hazard of death between responders and nonresponders. Univariate and multivariate Fine and Gray regression analyses were performed as an alternative to Cox regression for comparison of the subhazard of survival data in the presence of competing risks. The dependent variables were cause-specific deaths, liver-related events, AIDS-related events, and NLR-NAR events. When factors associated with each cause-specific death were analyzed, the competing risk was the other causes of death as a whole. When factors associated with events were analyzed, the competing risk was overall death. In the multivariate analyses, the variables for adjustment were age, sex, previous AIDS-defining conditions (yes vs. no), HIV transmission category (injection drug users vs. non-injection drug users), nadir CD4⁺ T-cell count, combination antiretroviral therapy (yes vs. no), undetectable HIV-RNA at baseline (yes vs. no), FIB ≥ 3.25 (yes vs. no), genotype (3 vs. other genotypes), and cumulative exposure to selected antiretroviral drugs. We adjusted for FIB-4 instead of biopsy stage (METAVIR) in our multivariate analysis because we previously showed, in this same cohort, that FIB-4 outperforms liver biopsy in the assessment of prognosis (death and liver-related events) in HIV/HCV-coinfected patients.⁽¹⁸⁾ Patients who had diabetes mellitus or chronic renal failure according to our definitions at baseline were excluded from the analysis for these particular NLR-NAR events.

Because some patients experienced reinfections and several patients underwent retreatment with IFN plus RBV, we carried out various sensitivity analyses: (1) the primary analysis, in which patients who achieved an SVR with retreatment (after failure or after relapse) were included in the SVR group; (2) the second analysis, in which follow-up of retreated patients was censored on the same day of initiation of the second course of IFN plus RBV; (3) the third analysis, in which patients who were retreated were excluded from the analysis; and (4) the fourth analysis, in which treatment response status was considered a time-dependent variable, that is, some patients could be considered

TABLE 1. Characteristics of 1,625 HIV/HCV–Coinfected Patients Stratified According to Response to IFN Plus RBV

Characteristic	No SVR (n = 997)	SVR (n = 628)	Total (N = 1,625)
Male sex, no. (%)	753 (75.5)	466 (74.2)	1,219 (75.0)
Age, years, median (IQR) (baseline)	40 (37-43)	40 (37-43)	40 (37-43)
BMI (n = 1,332), median (IQR)	23.1 (21.1-25.3)	23.0 (21.3-25.6)	23.1 (21.2-25.4)
Follow-up months, median (IQR)	65 (42-85)	65 (43-86)	65 (43-85)
Past injection drug use, no. (%)	802 (80.4)	510 (81.2)	1,312 (80.7)
CDC disease category C, No. (%) [*]	245 (24.6)	125 (19.9) [‡]	370 (22.8)
CD4 ⁺ , nadir, cells/mm ³ , median (IQR)	200 (100-313)	212 (113-333)	204 (106-322)
cART during anti-HCV treatment, no. (%)	848 (85.1)	518 (82.5)	1,366 (84.1)
CD4 ⁺ , baseline, cells/mm ³ , median (IQR)	515 (374-718)	536 (404-729)	527 (391-724)
Undetectable HIV-RNA load at baseline, no. (%)	667 (66.9)	460 (73.2) [‡]	1,127 (69.4)
Duration of HCV infection, years, median (IQR)	18 (13-22)	19 (15-22)	19 (13-22)
HCV genotype, no. (%)			
1	581 (58.3)	224 (35.7) [‡]	805 (49.5)
2	13 (1.3)	24 (3.8) [‡]	37 (2.3)
3	214 (21.5)	332 (52.9) [‡]	546 (33.6)
4	170 (17.1)	40 (6.4) [‡]	210 (12.9)
Unknown	10 (1)	5 (0.8)	15 (0.9)
HCV RNA, no. (%)			
<500,000 IU/mL	282 (28.3)	258 (41.1) [‡]	540 (33.2)
≥500,000 IU/mL	644 (64.6)	340 (54.1) [‡]	984 (60.6)
Unknown	71 (7.1)	30 (4.8)	101 (6.2)
HBsAg positivity, no. (%)	39 (3.9)	16 (2.5)	55 (3.4)
METAVIR fibrosis score, no. (%)			
F0	44 (4.4)	31 (4.9)	75 (4.6)
F1	163 (16.3)	132 (21) [‡]	295 (18.2)
F2	200 (20.1)	139 (22.1)	339 (20.9)
F3	215 (21.6)	93 (14.8) [‡]	308 (19.0)
F4	109 (10.9)	28 (4.5) [‡]	137 (8.4)
Unknown	266 (26.7)	205 (32.6) [‡]	471 (29.0)
FIB-4 score, no. (%)			
<3.25	671 (67.3)	486 (77.4) [‡]	1,157 (71.2)
≥3.25	207 (20.8)	71 (11.3) [‡]	278 (17.1)
Unknown	119 (11.9)	71 (11.3)	190 (11.7)
Current alcohol intake >50 g/day, no. (%)	58 (5.8)	19 (3) [‡]	77 (4.7)
Diabetes mellitus	39 (3.9)	8 (1.3) [‡]	47 (2.9)
Chronic renal failure [†]	3 (0.3)	1 (0.2)	4 (0.2)

*A, asymptomatic acute HIV or persistent generalized lymphadenopathy; B, symptomatic non-C conditions; C, AIDS-defining conditions.

[†]Confirmed eGFR <60 mL per minute per 1.73 m² at baseline.

[‡]P < 0.05 compared to the no SVR group.

Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention; HBsAg, hepatitis B surface antigen.

both responders and nonresponders during follow-up. We also performed two sensitivity analyses according to the classification of liver fibrosis in addition to the primary analysis, in which fibrosis was categorized as FIB ≥3.25 versus FIB-4 <3.25; (1) in the first analysis—limited to patients with liver-biopsy data—fibrosis was categorized as F0-F2 versus F3-F4; and (2) in the second analysis, fibrosis was categorized as FIB-4 <3.25 or F0-F2 versus FIB ≥3.25 or F3-F4.

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 21.0; IBM Corp., Armonk, NY). The R package, cmprsk (version 2.2; R Foundation for Statistical Computing), was used to plot the cumulative incidence curves and

conduct competing risks regression analysis. The cmprsk package can be downloaded from the Comprehensive R Archive Network (<http://cran.r-project.org>) and run within R.

Results

PATIENT CHARACTERISTICS

Data from the 1,625 patients who started treatment between January 2000 and January 2008 were included in the database. Baseline characteristics are shown in Table 1. In brief, 75.0% were men, the median age was

TABLE 2. Detailed Description of NLR-NAR Events During Follow-up in HIV/HCV–Coinfected Patients Categorized According to Response to Therapy With IFN Plus RBV

Event	No SVR (n = 997)	SVR (n = 628)	Total (N = 1,625)
Cancer (non-AIDS non-liver-related)	67 (6.7)	33 (5.3)	100 (6.2)
Lung	7 (0.7)	6 (1.0)	13 (0.8)
Anus	7 (0.7)	2 (0.3)	9 (0.6)
Head and neck	4 (0.4)	4 (0.6)	8 (0.5)
Vagina/vulva	6 (0.6)	1 (0.2)	7 (0.4)
Colorectal	6 (0.6)	0 (0)	6 (0.4)
Breast	5 (0.5)	0 (0)	5 (0.3)
Nonmelanoma skin cancer	5 (0.5)	0 (0)	5 (0.3)
Hodgkin's lymphoma	2 (0.2)	2 (0.3)	4 (0.2)
Brain	3 (0.3)	0 (0)	3 (0.2)
Sarcoma	1 (0.1)	2 (0.3)	3 (0.2)
Penis	2 (0.2)	1 (0.2)	3 (0.2)
Esophagus	1 (0.1)	1 (0.2)	2 (0.1)
Stomach	2 (0.2)	0 (0)	2 (0.1)
Other hematological	1 (0.1)	1 (0.2)	2 (0.1)
Prostate	1 (0.1)	1 (0.2)	2 (0.1)
Other	14 (1.4)	12 (1.9)	26 (1.6)
Diabetes mellitus*	72 (7.5) [‡]	23 (3.7) [‡]	95 (6.0)
Cardiovascular events	52 (5.2)	39 (6.2)	91 (5.6)
Coronary acute myocardial infarction	19 (1.9)	23 (3.7)	42 (2.6)
Coronary angina	8 (0.8)	3 (0.5)	11 (0.7)
Cerebrovascular transient ischemic attack	2 (0.2)	4 (0.6)	6 (0.4)
Cerebrovascular reversible ischemic deficit	2 (0.2)	0 (0)	2 (0.1)
Cerebrovascular established stroke	3 (0.3)	4 (0.6)	7 (0.4)
Cerebrovascular asymptomatic cerebrovascular disease	0 (0)	1 (0.2)	1 (0.1)
Peripheral arterial disease	7 (0.7)	2 (0.3)	9 (0.6)
Congestive heart failure	4 (0.4)	1 (0.2)	5 (0.3)
Pulmonary hypertension	5 (0.5)	1 (0.2)	6 (0.4)
Mesenteric ischemia	1 (0.1)	0 (0)	1 (0.1)
Aortic dissection	1 (0.1)	0 (0)	1 (0.1)
Non-AIDS-related sepsis requiring hospital admission	62 (6.2) [‡]	19 (3.0) [‡]	81 (5.0)
Bone-related events	33 (3.3)	24 (3.8)	57 (3.5)
Large bone fracture	23 (2.3)	19 (3.0)	42 (2.6)
Avascular necrosis of bone	5 (0.5)	5 (0.8)	10 (0.6)
Vertebral fracture	5 (0.5)	0 (0)	5 (0.3)
Renal events [†]	27 (2.7) [‡]	6 (1.0) [‡]	33 (2.0)
Chronic renal failure not requiring dialysis	24 (2.4) [‡]	5 (0.8) [‡]	29 (1.8)
Chronic renal failure requiring dialysis	3 (0.3)	1 (0.2)	4 (0.2)

*Including 958 non-SVR and 620 SVR patients (patients with baseline diabetes mellitus were excluded).

[†]Including 994 non-SVR and 627 SVR patients (patients with chronic renal failure at baseline were excluded).

[‡] $P < 0.05$.

40 years, 22.8% had previous AIDS-defining conditions, 1,366 (84.1%) were on combination antiretroviral therapy (cART), the median baseline CD4 cell count was 527 cells/mm³, 69.4% had an undetectable HIV viral load, 62.4% were infected with genotypes 1 or 4, and 60.6% had an HCV RNA $\geq 500,000$ IU/mL. Baseline liver biopsy was performed in 1,154 patients, of whom 445 (38.6%) had bridging fibrosis or cirrhosis. At baseline, 77 (4.7%) patients reported a high intake of alcohol, 47 (2.9%) had diabetes mellitus, and 4 (0.2%) had chronic renal failure.

During the study period, no significant differences were found between responders and nonresponders for qualitative or cumulative exposure to tenofovir

disoproxil fumarate, a potentially nephrotoxic drug.⁽¹⁹⁾ However, significant differences were found between responders and nonresponders in qualitative and/or cumulative exposure to didanosine, abacavir, indinavir, and lopinavir, all of which have been associated with cardiovascular disease⁽²⁰⁾ (Supporting Table S3).

TREATMENT RESPONSE

A total of 791 (48.7%) patients were treated with pegylated interferon (Peg-IFN) $\alpha 2a$ plus RBV, 615 (37.8%) were treated with Peg-IFN $\alpha 2b$ plus ribavirin, and 219 (13.5%) were treated with the standard IFN α plus RBV regimen (three times weekly). The initial

TABLE 3. Frequency and Rate of Events During Follow-up in 1,625 HIV/HCV-Coinfected Patients Categorized According to Response to IFN Plus RBV Therapy

Event	Frequency, No. (%)		P ¹	Rate/100 Person-Years (95% CI)		IRR (95% CI)	P ²
	No SVR (N = 997)	SVR (N = 628)		No SVR	SVR		
Lost to follow-up	162 (16.2)	74 (11.8)	0.013	3.19 (2.72-3.72)	2.33 (1.83-2.92)	1.37 (0.97-1.7)	0.075
Overall mortality	145 (14.5)	30 (4.8)	<0.001	2.75 (2.32-3.23)	0.93 (0.63-1.33)	2.95 (1.99-4.36)	<0.001
Liver-related	83 (8.3)	6 (1.0)	<0.001	1.57 (1.25-1.95)	0.19 (0.07-0.41)	8.43 (3.68-19.3)	<0.001
Non-liver-related	62 (6.2)	24 (3.8)	0.036	1.17 (0.90-1.50)	0.75 (0.48-1.11)	1.57 (0.98-2.52)	0.059
AIDS-related	8 (0.8)	2 (0.3)	0.224	0.15 (0.07-0.30)	0.06 (0.01-0.22)	2.44 (0.52-11.5)	0.260
Non-liver-related non-AIDS-related	54 (5.4)	22 (3.5)	0.075	1.02 (0.77-1.33)	0.68 (0.43-1.03)	1.50 (0.91-2.46)	0.111
CDC category C disease	43 (4.3)	9 (1.4)	0.001	0.81 (0.59-1.10)	0.28 (0.13-0.53)	2.91 (1.54-6.97)	0.002
Liver decompensation	123 (12.3)	7 (1.1)	<0.001	2.44 (2.03-2.91)	0.22 (0.09-0.45)	11.20 (5.14-23.6)	<0.001
HCC	29 (2.9)	3 (0.5)	0.001	0.55 (0.37-0.79)	0.09 (0.02-0.27)	5.92 (2.04-36.0)	0.003
LT, no. (%)	16 (1.6)	1 (0.2)	0.005	0.30 (0.17-0.49)	0.03 (0-0.17)	9.80 (1.30-73.9)	0.027
NLR-NAR events							
Diabetes mellitus	72/958 (7.5)	23/620 (3.7)	0.002	1.45 (1.13-1.82)	0.73 (0.46-1.09)	1.99 (1.24-3.18)	0.004
NLR-NAR cancer	67 (6.7)	33 (5.3)	0.231	1.28 (0.99-1.63)	1.04 (0.72-1.46)	1.23 (0.81-1.87)	0.329
Cardiovascular events	52 (5.2)	39 (6.2)	0.396	0.99 (0.74-1.30)	1.24 (0.88-1.69)	0.80 (0.53-1.22)	0.302
NAR infections	62 (6.2)	19 (3.0)	0.004	1.19 (0.91-1.52)	0.59 (0.36-0.93)	2.01 (1.20-3.34)	0.008
Bone events	33 (3.3)	24 (3.8)	0.585	0.63 (0.44-0.89)	0.75 (0.48-1.12)	0.84 (0.48-1.38)	0.447
Renal events	27/994 (2.7)	6/627 (0.1)	0.015	0.51 (0.34-0.75)	0.19 (0.07-0.41)	2.74 (1.13-6.65)	0.025

P¹ = Pearson chi² test; P² = Poisson regression.

*Median follow-up times in months (IQR) for no-SVR and SVR were 59.3 (40.6-79.2) and 59.5 (42.8-81.8).

Abbreviation: CDC, Centers for Disease Control and Prevention.

TABLE 4. Crude and Adjusted Hazards for Events During Follow-up for 997 Nonresponders to IFN plus RBV Compared With 628 Responders

	Univariate Analysis*		Multivariate Analysis* [†]	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Overall deaths	0.35 (0.24-0.52)	<0.001	0.36 (0.24-0.54)	<0.001
	sHR (95% CI)	P Value	sHR (95% CI)	P Value
Cause-specific deaths				
Liver-related deaths	0.12 (0.05-0.28)	<0.001	0.13 (0.06-0.28)	<0.001
Non-liver-related deaths	0.69 (0.43-1.1)	0.119	0.73 (0.44-1.20)	0.214
AIDS-related deaths	0.45 (0.09-2.22)	0.325	0.37 (0.09-1.43)	0.148
NLR-NAR deaths	0.73 (0.44-1.19)	0.204	0.79 (0.47-1.35)	0.388
New AIDS-defining events	0.34 (0.16-0.72)	0.004	0.37 (0.17-0.79)	0.010
Liver-related events				
Liver decompensation	0.09 (0.04-0.2)	<0.001	0.10 (0.05-0.21)	<0.001
HCC	0.12 (0.03-0.5)	0.004	0.13 (0.03-0.50)	0.003
LT	0.10 (0.01-0.77)	0.027	0.12 (0.02-0.78)	0.027
NLR-NAR events				
Diabetes mellitus [‡]	0.54 (0.34-0.87)	0.011	0.57 (0.35-0.93)	0.024
NLR-NAR cancer	0.91 (0.6-1.38)	0.650	0.91 (0.58-1.45)	0.703
Cardiovascular events	1.41 (0.93-2.13)	0.105	1.57 (0.99-2.50)	0.056
NAR infections	0.55 (0.33-0.92)	0.024	0.65 (0.37-1.14)	0.131
Bone events	1.39 (0.82-2.35)	0.225	1.28 (0.69-2.38)	0.433
Renal events [‡]	0.41 (0.17-0.99)	0.049	0.43 (0.17-1.09)	0.075

*Cox regression analysis was performed to compare the HR of overall death between responders and nonresponders. Fine and Gray regression analysis was performed to compare the HR of events in the presence of competing risks.

[†]Adjusted for age, sex, previous AIDS-defining conditions (yes vs. no), HIV transmission category (injection drug users vs. non-injection drug users), nadir CD4⁺ cell count, cART (yes vs. no), undetectable HIV RNA at baseline (yes vs. no), FIB4 ≥ 3.25 (yes vs. no), genotype (3 vs. other genotypes), and exposure to abacavir, didanosine, indinavir, and lopinavir: lower than or equal to the median cumulative exposure in years versus higher than the median cumulative exposure.

[‡]Excluding 47 and 4 patients with diabetes mellitus and chronic renal failure at baseline, respectively.

treatment response was categorized as SVR in 592 (36%) patients and as no response in 1,033 (64%). During follow-up, 6 (1%) of 592 responders developed HCV reinfection a median of 49 months after discontinuing anti-HCV therapy (minimum, 22 months; maximum, 87 months). A total of 198 patients were retreated during follow-up: 192 patients whose first course of anti-HCV therapy failed and the 6 patients who experienced reinfections. A total of 42 retreated patients achieved SVR, including 1 of the 6 reinfected patients. For the purpose of the primary analysis, there were 628 responders and 997 nonresponders.

CLINICAL OUTCOMES

The median (interquartile range; IQR) follow-up from the date IFN plus RBV was stopped for nonresponders and responders was 65 (42-85) and 65 (43-86) months, respectively. Loss to follow-up was recorded in 162 nonresponders (16.2%) and 74 responders (11.8%; $P = 0.013$).

A detailed description of incident NLR-NAR events during follow-up is shown in Table 2. By order of frequency, these were cancer ($n = 100$ [6.2%]), diabetes mellitus ($n = 95$ [6.0%]), cardiovascular events

($n = 91$ [5.6%]), non-AIDS-related infections ($n = 81$ [5.0%]), bone-related events ($n = 57$ [3.5%]), and renal events ($n = 33$ [2.0%]).

The frequencies and rates of events during follow-up stratified by response to IFN plus RBV are shown in Table 3. The rates of overall death, liver-related death, new AIDS-defining conditions, and all types of liver-related events (decompensation, HCC, and LT) were significantly higher in nonresponders than in responders. As for NLR-NAR events, we found that the rates of diabetes mellitus, non-AIDS-related infections, and renal events were significantly higher in nonresponders than in responders. However, the rates of NLR-NAR cancers, cardiovascular events, and bone events were not significantly different between responders and nonresponders.

The results of the univariate and multivariate proportional hazards regression analyses of factors associated with clinical outcomes are shown in Table 4. In comparison with no response, SVR was associated with a statistically significant reduced adjusted hazard of overall death (hazard ratio [HR] and 95% CI, 0.36 [0.24-0.54]; $P < 0.001$), liver-related death (subhazard ratio [sHR] and 95% CI, 0.13 [0.06-0.28]; $P < 0.001$), new AIDS-defining events (sHR [95% CI],

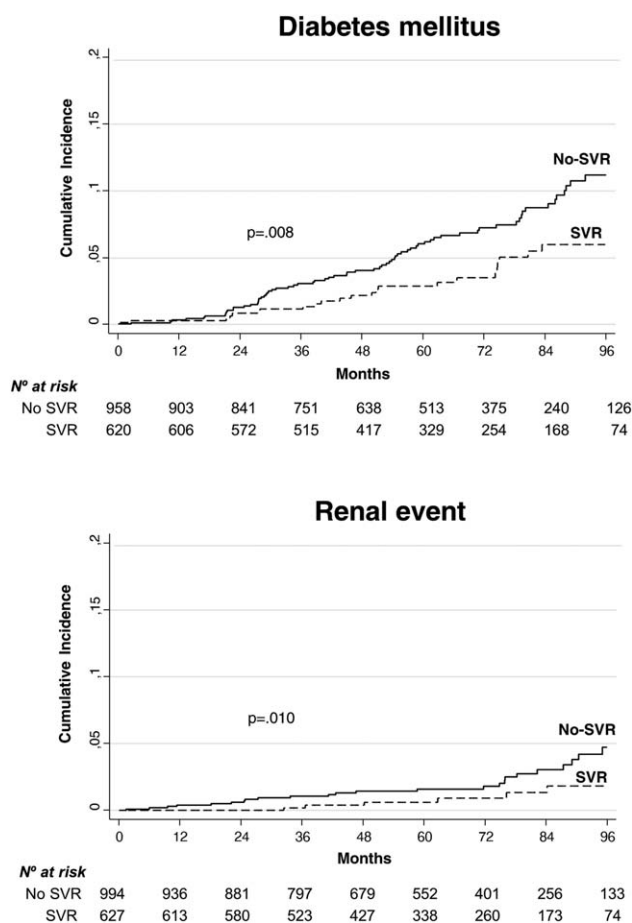


FIG. 1. Cumulative probabilities of renal events and diabetes mellitus in responders and non-responders. Responders and non-responders were compared using Gray's test.

0.37 [0.17-0.79]; $P = 0.010$), liver decompensation (sHR [95%CI], 0.10 [0.05 - 0.21]; $P < 0.001$), HCC (sHR [95% CI], 0.13 [0.03-0.50]; $P = 0.003$), and LT (sHR [95% CI], 0.12 [0.02-0.78]; $P = 0.027$). As for NLR-NAR events, SVR was independently associated with a statistically significant reduced hazard of diabetes mellitus (sHR [95% CI], 0.57 [0.35-0.93]; $P = 0.024$), with a reduced hazard of renal events close to the threshold of significance (sHR [95% CI], 0.42 [0.17-1.09]; $P = 0.074$), and with a higher hazard of cardiovascular events also close to the threshold of significance (sHR [95% CI], 1.57 [0.99-2.50]; $P = 0.056$). The results of the primary analysis were confirmed in the sensitivity analyses based on the definitions of treatment response, although in the third subanalysis, the reduced adjusted hazard of renal events following eradication of HCV was statistically

significant (Supporting Table S4). The results of the primary analysis also remained unchanged after the different sensitivity analyses based on the different definitions of advanced fibrosis (data not shown).

The cumulative probabilities of diabetes mellitus and renal events in responders and nonresponders are shown in Fig. 1.

Discussion

We evaluated the clinical course of 1,625 HIV/HCV-coinfected patients who were followed up for a median of 5 years after the end of treatment with IFN plus RBV, with the primary objective of evaluating the effect of treatment response on incident NLR-NAR events. We found that during follow-up, the incidence rates of diabetes mellitus, renal events, and non-AIDS-related infections were significantly lower in responders than in nonresponders. However, no significant differences were found between the groups in the rates of NLR-NAR cancers, cardiovascular events, and bone events. When we carried out regression analysis after adjusting for clinically significant covariates and considering death as a competitive risk, we found that SVR was associated with a significant decrease in the hazard of diabetes mellitus. However, the decrease in the hazard of renal events almost reached statistical significance. In agreement with previous reports from this cohort, we found that treatment response was associated with a decreased hazard of overall and liver-related death, all types of liver-related events, and new AIDS-related conditions.^(7,21)

Our finding that treatment response in HIV/HCV-coinfected patients was associated with a significant decrease in the hazard of diabetes mellitus lends further support to the causative role of HCV infection in IR and type 2 diabetes (T2D)⁽²²⁾ and agrees with findings from previous studies in which SVR caused a reduction in the risk of T2D in HCV-monoinfected patients.⁽¹¹⁾ It is also worth mentioning that IR and diabetes are associated with progression of liver disease, hepatic decompensation, and death in patients with chronic HCV⁽²³⁻²⁶⁾ and with HCC in patients with HCV-related cirrhosis with or without HIV infection.^(27,28) For these reasons, patients with CHC and IR or T2D might benefit from antiviral therapy irrespective of their stage of fibrosis.⁽²⁹⁾

HCV infection has been associated with an increased risk of end-stage renal disease (ESRD) in HCV-monoinfected individuals^(30,31) and HIV/

HCV-coinfected individuals.^(32,33) HCV infection has also been found to increase the mortality of patients with ESRD.⁽³⁴⁾ In addition, antiviral treatment for HCV has been associated with a lower risk of ESRD in large, prospective cohorts in HCV-monoinfected individuals.^(12,13) We found a significantly higher incidence of renal events in nonresponders than in responders. However, with the stricter multivariate competing risk regression analyses, the lower hazard of chronic renal failure in responders than in nonresponders did not reach the conventional threshold for significance ($P = 0.075$). The clinical and public health repercussions of this finding are relevant because the risk of death, cardiovascular events, and hospitalization increases proportionally with reductions in estimated glomerular filtration rates (eGFRs) below 60 mL per minute per 1.73 m².⁽³⁵⁾

In our study, NLR-NAR cancer was the most common NLR-NAR event during follow-up; however, the hazard of this event was not found to be modified by eradication of HCV. Despite advances in HIV therapy, cancer rates are still higher among HIV-infected individuals than among matched non-HIV-infected individuals,⁽³⁶⁾ probably owing to the high prevalence of traditional cancer risk factors, coinfection with other oncogenic viruses, and associated immunodeficiency among HIV-infected individuals.⁽³⁷⁾ In addition, non-AIDS-related cancer is currently the leading non-AIDS cause of death among people with HIV in high-income settings.⁽³⁸⁾ For all the above reasons, evidence-based cancer screening must be considered an essential component in the care of HIV-infected individuals.

Intriguingly, although the crude incidence of cardiovascular events was not significantly different between responders and nonresponders, competing risk regression analysis showed the adjusted hazard of cardiovascular events to be higher in responders than in nonresponders, although, once again, on the very threshold of statistical significance ($P = 0.056$). This finding contrasts with those other studies in which HCV clearance following anti-HCV therapy has been found to reduce the risk of stroke.^(39,40) The association between HCV infection and cardiovascular events is a contentious issue. Several observational studies have found that in the general population, HCV is an independent factor associated with coronary artery disease,⁽⁴¹⁻⁴⁵⁾ stroke,^(39,46,47) and peripheral artery disease.⁽⁴⁸⁾ HCV infection has also been found to increase the likelihood of cardiovascular disease among HIV-infected individuals.^(49,50) However, other

researchers have not found an association between HCV infection and angiographic coronary artery disease^(51,52) or myocardial infarction.⁽⁵³⁾ Meta-analyses have demonstrated an increased risk of cardiovascular events associated with HCV infection in some patients,^(54,55) but not in others.⁽⁵⁶⁾ It is important to note that HCV infection has opposing effects on the pathophysiology of atherosclerosis. On the one hand, HCV induces an alteration in markers of inflammation and endothelial dysfunction that could potentially stimulate atherogenesis.⁽⁵⁷⁻⁵⁹⁾ On the other hand, HCV infection is associated with lower total cholesterol and low-density lipoprotein (LDL) cholesterol levels,^(60,61) probably owing to increased deposition of lipids in hepatocytes, where the lipids are used to promote HCV replication and secretion of lipovirions. Also noteworthy are the different effects of eradication of HCV on atherogenesis, namely, reversal of inflammation and endothelial dysfunction⁽⁶²⁾ and rebound of LDL and total cholesterol to levels associated with increased risk of coronary disease.^(60,63) The above findings indicate that further work is needed to assess the effects of eradication of HCV on pre-clinical atherosclerosis and cardiovascular events.

Both injection drug use and liver cirrhosis can contribute to bacterial infections among HCV-infected individuals. As for liver cirrhosis, the only identified factor for bacterial infections is advanced liver disease.⁽⁶⁴⁾ In the cART era, HCV infection has been shown to predispose to severe bacterial infections associated with hospitalization or death in HIV-infected individuals.⁽⁶⁵⁾ However, we did not find a significant association between response to anti-HCV treatment and the hazard of non-AIDS-related infections.

Chronic HCV infection is associated with low bone mineral density, even in the absence of cirrhosis⁽⁶⁶⁾; in coinfecting patients, both HIV infection and HCV infection have been found to reduce bone mineral density through different pathophysiological mechanisms.⁽⁶⁷⁾ Furthermore, HCV has been found to increase the risk of osteoporotic fractures among HIV-infected patients, a risk that is explained, only in part, by the severity of liver disease.⁽⁶⁸⁾ We did not find an association between eradication of HCV and the hazard of bone fractures; however, it has yet to be determined whether successful treatment of HCV will significantly improve bone mineral density in HIV/HCV-coinfected patients.

The main limitation of our study is that its design was 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: patients were followed by the same infectious diseases physicians in the same reference hospitals throughout the course of the disease, with standard clinical and laboratory parameters assessed at least every 6 months. In addition, the frequency of loss to follow-up was higher among nonresponders than among responders. However, we believe that the potential bias caused by this difference would tend to minimize the frequency and rates of events among nonresponders rather than increase them. Our study is also limited by the lack of information about pneumococcal vaccination, smoking, alcohol and drug use during follow-up, and cardiovascular risk factors; therefore, we cannot rule out the possibility that differences in these variables could have affected outcome. The strengths of our study include the high number of patients included and the long follow-up period. We also emphasize the use of multivariate Fine and Gray regression as an alternative to Cox regression for survival data in the presence of competing risks and the performance of sensitivity analyses that confirmed the findings of the primary analysis. Finally, in our study, all the information in the database was monitored to verify that it was consistent with the patient's medical records.

Although the study design precludes determination of causality, our results suggest that eradication of HCV in coinfecting patients is associated not only with a reduction in overall death, liver-related death, new AIDS-related events, and all types of liver-related events, but also with a statistically significant reduced hazard of diabetes mellitus and a decline in the hazard of chronic renal failure very close to the threshold of significance. These findings argue for the prescription of HCV therapy regardless of liver fibrosis stage in coinfecting patients.

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Appendix

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