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

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

Methods. An observational cohort study including consecutive HIV/HCV-coinfected patients treated with interferon plus ribavirin 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 nonresponders than in responders: AIDS-defining conditions (rate per 100 person years, 0.84 [95% confidence interval (CI), .59–1.10] vs 0.29 [.10–.48]; $P = .003$), non–liver-related deaths (0.65 [.42–.87] vs 0.16 [.02–.30]; $P = .002$), and non–liver-related, non–AIDS-related deaths (0.55 [.34–.75] vs 0.16 [.02–.30]; $P = .002$). Cox regression analysis showed that the adjusted hazard ratios of new AIDS-defining conditions, non–liver-related deaths, and non–liver-related, non–AIDS-related deaths for nonresponders compared with responders were 1.90 (95% CI, .89–4.10; $P = .095$), 3.19 (1.21–8.40; $P = .019$), and 2.85 (1.07–7.60; $P = .036$), respectively.

Conclusions. Our findings suggest that eradication of HCV after therapy with interferon plus ribavirin 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.

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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]. After 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, those making recommendations have considered HIV/HCV-coinfected patients as candidates for anti-HCV treatment [4].

Sustained virological response (SVR) to interferon plus ribavirin 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 a diagnosis of HCV infection 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 interferon plus ribavirin also improves fibrosis [10] and reduces liver-related complications and mortality, independently of the stage of fibrosis, as recently reported by our group [11]. Because 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 interferon plus ribavirin 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 interferon plus ribavirin between January 2000 and January 2008 at 19 institutions in Spain. All patients were naive 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 interferon plus ribavirin 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, $CD4^+$ T-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 levels at week 24 of treatment. Since 2002, anti-HCV was also stopped in patients with detectable HCV RNA levels at week 12 of treatment and a reduction of <2 log IU/mL in HCV RNA levels.

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 for 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 $CD4^+$ T-cell counts, and baseline HIV viral load. We also recorded information about cART, including type, date of initiation, and whether or not cART 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). The 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, 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 had a relapse after achieving end-of-treatment response, were classified as having no 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, $CD4^+$ T-cell count, HIV viral load, HCV RNA level, liver biopsy, aspartate aminotransferase–to–platelet ratio index [14], and anti-HCV therapy. The length of the study was calculated from the date interferon plus ribavirin was stopped to death or the last follow-up visit. The administrative censoring date was 12 July 2010.

End Points

We assessed the following end points: (1) liver-related complications, (2) progression of HIV infection, and (3) mortality.

Liver-related complications included 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 >1 event, only the first was included in the analyses of the association between SVR and "any event." Progression of HIV infection was defined as the occurrence of any new AIDS-defining conditions [16]. For mortality, all of the information related to death (death reports, autopsy reports, if available, and standard forms) was reviewed by 2 of the authors (J. B. and J. G. G.); both were blinded as to whether the patient reached an SVR or not and classified deaths in accordance 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 hepatocellular carcinoma; (2) AIDS-related death, when death was directly related to an AIDS-defining condition; and (3) non–liver-related, non–AIDS-related deaths.

Statistics

Differences between groups were analyzed using the χ^2 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) curves for the different end points. Multivariate analysis was performed using Cox regression analysis. The statistical analysis was performed using SPSS software, version 18.0 (SPSS Inc). Because several patients underwent retreatment with interferon plus ribavirin, those who achieved SVR after retreatment were included in the SVR group.

Table 1. Baseline Characteristics of 1599 HIV/Hepatitis C Virus–Coinfected Patients Treated With Interferon Plus Ribavirin at 19 Institutions in Spain Between 2000 and 2008

Characteristic	No SVR (n = 973; 61%)	SVR (n = 626; 39%)	Total (N = 1599)
Male sex, No. (%)	731 (75)	463 (74)	1194 (75)
Age, median (IQR), years	40 (37–43)	40 (37–43)	40 (37–43)
Prior injection drug use, No. (%)	774 (80)	513 (83)	1287 (81)
Prior AIDS-defining conditions, No. (%)	231 (24)	124 (20)	355 (23)
$CD4^+$ T-cell nadir, median (IQR), cells/mm^3	204 (109–321)	217 (117–333)	209 (110–326)
$CD4^+$ T-cell baseline, median (IQR), cells/mm^3	517 (374–714)	532 (404–730)	527 (391–723)
Time since HCV infection, median (IQR), years	18 (13–22)	19 (15–22)	18 (13–22)
Undetectable HIV RNA load at baseline, No. (%)[a]	643/960 (67.0)	448/612 (73.2)[b]	1091 (70)
HCV genotype, No. (%)			
1	574 (59)	213 (34)[b]	787 (49)
2	16 (2)	22 (4)[b]	38 (2)
3	196 (20)	338 (54)[b]	534 (34)
4	157 (16)	38 (6)[b]	195 (12)
Unknown	30 (3)	15 (2)	45 (3)
HCV RNA level, No. (%)			
<500 000 IU/mL	203 (21)	210 (34)[b]	413 (26)
≥500 000 IU/mL	627 (64)	352 (56)[b]	979 (61)
Unknown	143 (15)	64 (10)[b]	207 (13)
HBsAg positivity, No. (%)	37/925 (4)	18/609 (3)	55/1534 (4)
Stage of liver fibrosis F3–F4, No. (%)	324/724 (45)	124/429 (29)[b]	448/1153 (39)
Advanced fibrosis (F3–F4 or APRI >2), No. (%)	387/923 (42)	146/516 (28)[b]	533/1439 (37)
Alcohol intake >50 g/d, No. (%)	58 (7)	18 (3)[b]	76 (5)
cART during HCV treatment, No. (%)	810 (80)	452 (78)	1262 (79)

Abbreviations: APRI, aspartate aminotransferase–to–platelet ratio index; cART, combination antiretroviral therapy; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; SVR, sustained virological response.

[a] Baseline HIV viral load was determined in 1572 patients using commercial assays with different lower limits of detection: <500 (n = 1), <400 (n = 9), <200 (n = 124), <80 (n = 119), <50 (n = 1101), <40 (n = 70), and <20 (n = 148) HIV RNA copies/mL.

[b] $P < .05$.

Table 2. Frequency and Rate of Events During Follow-up in 1599 HIV/Hepatitis C Virus–Coinfected Patients With or Without Sustained Virological Response After Therapy With Interferon Plus Ribavirin

	Frequency of Events, No. (%)			Rate of Events/100 Person-Years (95% CI)		
Event	No SVR (n = 973)	SVR (n = 626)	*P*	No SVR	SVR	*P*[a]
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 (.12–.53)	<.001
Liver decompensation[b]	113 (11.6)	6 (1.0)	<.001	2.39 (1.95–2.83)	0.19 (.04–.35)	<.001
Hepatocellular carcinoma	28 (2.9)	3 (0.5)	.001	0.57 (.36–.78)	0.10 (.00–.21)	.001
Liver transplantation	21 (2.2)	4 (0.6)	.017	0.43 (.24–.61)	0.13 (.00–.26)	.024
HIV-related events						
New AIDS-defining conditions	41 (4.2)	9 (1.4)	.002	0.84 (.59–1.10)	0.29 (.10–.48)	.003
Mortality						
Deaths overall	90 (9.2)	8 (1.3)	<.001	1.82 (1.45–2.20)	0.26 (.08–.44)	<.001
Liver-related deaths	55 (5.7)	3 (0.5)	<.001	1.11 (.82–1.41)	0.10 (.00–.21)	<.001
Non–liver-related deaths	32 (3.3)	5 (.8)	.001	0.65 (.42–.87)	0.16 (.02–.30)	.002
AIDS-related	5 (0.5)	0 (0.0)	.072	0.10 (.01–.19)	0	.071
Non–liver-related, non–AIDS-related	27 (2.8)	5 (0.8)	.006	0.55 (.34–.75)	0.16 (.02–.30)	.002
Unknown	4 (0.4)	0 (0.0)	…	…	…	…

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; SVR, sustained virological response.

[a] Log-rank test.

[b] Ascites, variceal bleeding, hepatic encephalopathy.

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% of patients were male, their median age was 40 years, 23% had prior AIDS-defining conditions, the median baseline $CD4^+$ T-cell count was 527 cells/mm^3, 70% had an undetectable HIV viral load, the median time since HCV infection was 18 years, 61% were infected by genotypes 1 or 4, and 61% had an HCV RNA level ≥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 ≥50 g of alcohol per day for ≥12 months. Advanced fibrosis at baseline (F3–F4 at liver biopsy) was present in 448 of 1153 patients (39%) before anti-HCV therapy was started.

A total of 790 patients (49%) were treated with pegylated interferon-α2a plus ribavirin, 602 (38%) with pegylated interferon-α2b plus ribavirin, and 207 (13%) with standard thrice-weekly interferon-α plus ribavirin. The median duration of anti-HCV therapy was 11.07 months in responders and 6.97 months in nonresponders ($P < .001$). Scheduled therapy was completed by 555 responders (89%) and 352 nonresponders (36%; $P < .001$). Anti-HCV therapy was interrupted because of adverse events in 48 responders (8%) and 166 nonresponders (17%); $P < .001$.

During treatment of hepatitis C, 1262 (79%) of the patients were receiving cART. The most common combinations were 2 nucleoside reverse-transcriptase inhibitors (NRTIs) plus 1 nonnucleoside reverse-transcriptase inhibitor in 573 patients (45%), 2 NRTIs plus 1 protease inhibitor in 176 (14%), 3 NRTIs 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 who achieved SVR after the second course of interferon plus ribavirin. SVR was achieved in 251 of 982 patients (26%) with genotype 1 or 4 and 360 of 572 (63%) with genotype 2 or 3. We used multiple logistic regression analysis to identify pretreatment 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 $CD4^+$ T-cell count, HCV genotype, and HCV RNA level. It also included the type of interferon used (pegylated vs nonpegylated), the presence of advanced fibrosis, and alcohol intake >50 g/d. The final model identified 3 variables that were independently associated with increased probability of an SVR: HCV genotype 2–3 (odds ratio [OR], 4.82; 95% confidence interval [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; $P < .001$).

Table 3. New AIDS-Related Conditions and Non–Liver-Related Deaths in 1599 HIV/Hepatitis C Virus–Coinfected Patients With or Without Sustained Virological Response After Therapy With Interferon Plus Ribavirin

AIDS-Related Conditions and Non–Liver-Related Deaths	No SVR (n = 973)	SVR (n = 626)
New AIDS-related conditions	41	9
Recurrent pneumonia	11	4
Mycobacterium tuberculosis, any site	6	1
Esophageal candidiasis	5	2
Progressive multifocal leukoencephalopathy	5	0
Invasive cervical cancer	5	0
Pneumocystis jiroveci pneumonia	2	0
HIV wasting syndrome	2	0
Disseminated cryptococcosis	2	0
HIV encephalopathy	2	0
Recurrent *Salmonella* septicemia	0	1
Non-Hodgkin lymphoma	1	0
Disseminated *Mycobacterium avium* complex infection	0	1
Non–liver-related deaths	32	5
AIDS-related deaths		0
Progressive multifocal leukoencephalopathy	2	0
Cryptococcosis	1	0
Recurrent pneumonia	1	0
Invasive cervical cancer	1	0
Non–AIDS-related deaths		
Non–AIDS-related malignancy[a]	7	2
Cardiovascular event[b]	6	1
Bacterial infection[c]	6	0
Traumatic death[d]	3	0
Sudden death[e]	2	1
Suicide	1	1
Bleeding duodenal ulcer	1	0
Acute renal failure	1	0

Abbreviations: HIV, human immunodeficiency virus; SVR, sustained virological response.

[a] Non–AIDS-related malignancies included lung cancer (n = 2), anal carcinoma (n = 2), gastric carcinoma (n = 1), disseminated carcinoma of unknown origin (n = 1), and Hodgkin lymphoma (n = 1) in the patients without SVR, acute leukemia (n = 1) and pleuropulmonary sarcoma (n = 1) in the patients with SVR.

[b] No SVR: Cardiovascular events included acute myocardial infarction (n = 3), mesenteric ischemia (n = 2), and stroke (n = 1); SVR: acute myocardial infarction (n = 1).

[c] Bacterial infections included bacterial pneumonia (n = 3), bacterial meningitis (n = 1), urinary tract sepsis (n = 1), and bacterial endocarditis (n = 1).

[d] Causes of traumatic death included drowning (n = 1), abdominal trauma (n = 1), and a traffic accident (n = 1).

[e] One patient in the no-SVR group had a prior diagnosis of angina pectoris.

Outcomes

After a median follow-up of 62.0 months (interquartile range [IQR], 41.9–80.7) in nonresponders and 56.9 months (IQR, 41.6–79.9) 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 nonresponders than in responders (Table 2).

We also found a significantly higher frequency and rate of new AIDS-defining conditions in nonresponders than in responders (Table 2). The different types of AIDS-defining conditions are listed in Table 3. There were 41 AIDS-defining conditions among nonresponders; the most frequent were recurrent pneumonia (n = 11), tuberculosis (n = 6), 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 nonresponders (83%) and 9 responders (100%) were receiving cART. HIV viral load and $CD4^+$ T-cell count were available for 40 of 41 nonresponders and all 9 responders. HIV viral load was detected in 23 nonresponders (57%) and 5 responders (56%). The median $CD4^+$ T-cell count was 341 cells/mm^3 (IQR, 170–571) for nonresponders and 400 cells/mm^3 (IQR, 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 nonresponders than in responders (Table 2 and Figure 1). Non–liver-related deaths are summarized in Table 3. Five deaths in nonresponders were caused by AIDS-defining conditions, compared with none in responders. There were 27 non–liver-related, non–AIDS-related deaths among nonresponders; 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 interferon plus ribavirin 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 $CD4^+$ T-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 end points was higher for nonresponders 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

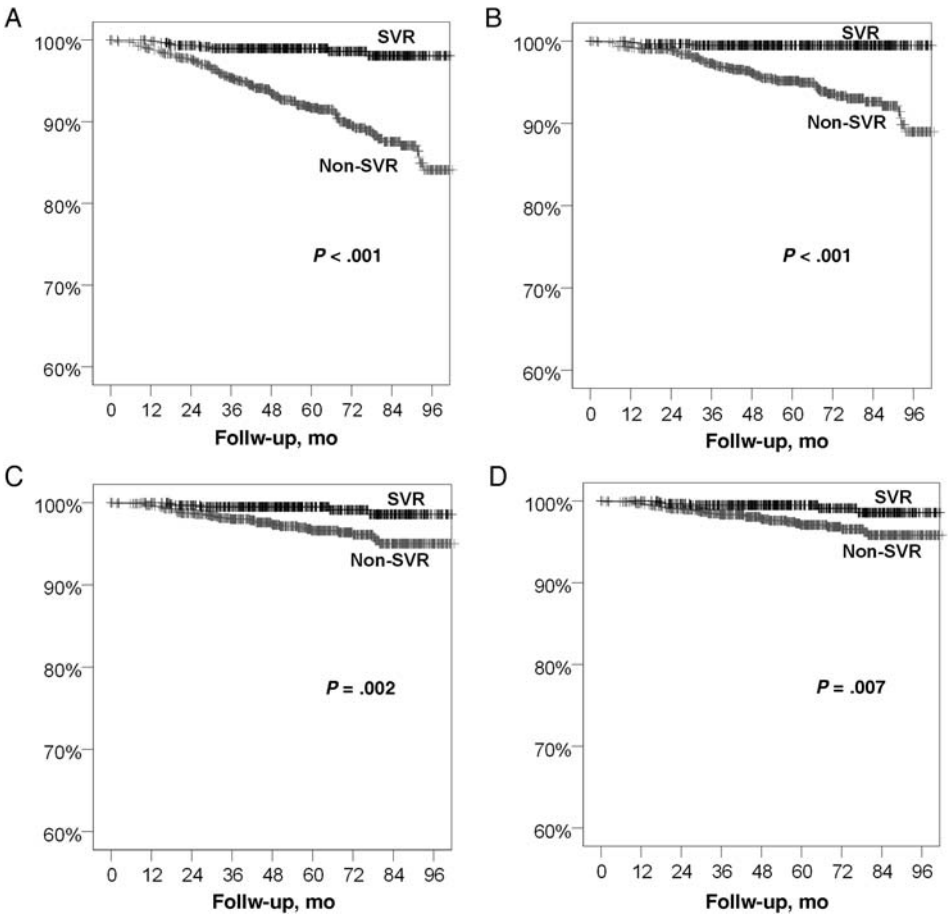

Figure 1. Kaplan-Meier curves showing the occurrence of overall deaths (*A*), liver-related deaths (*B*), non–liver related deaths (*C*), and non–liver-related, non–AIDS-related deaths (*D*) in 1599 patients coinfected with human immunodeficiency virus and hepatitis C virus, with or without sustained virological response after therapy with interferon plus ribavirin. Abbreviation: SVR, sustained virological response.

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 nonresponders 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 nonresponders at baseline and at the end of treatment with interferon plus ribavirin, 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 $CD4^+$ T-cell counts <200 cells/mL was not significantly different between responders and nonresponders at baseline and at the end of treatment, during the follow-up period we observed that a higher proportion of nonresponders than responders had $CD4^+$ T-cell counts <200 cells/mL, a statistically significant difference at 3, 6, and 9 months after discontinuation of therapy (Figure 2).

DISCUSSION

We evaluated the clinical course in 1599 HIV/HCV-coinfected patients who were followed up for a median period of approximately 5 years after therapy with interferon plus ribavirin. 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, the risks of both non–liver-related deaths and non–liver-related, non–AIDS-related deaths were significantly higher for nonresponders than for responders after adjustment for important baseline variables, such as age, sex, HIV transmission category, nadir $CD4^+$ T-cell count, cART,

Table 4. Crude and Adjusted Hazard Ratios for Non–Liver-Related Events During Follow-up for Nonresponders to Interferon Plus Ribavirin Compared With Responders (Cox Regression Analysis)

Event	Crude HR (95% CI)	*P*	Adjusted[a] HR (95% CI)	*P*
New AIDS-defining conditions	2.86 (1.39–5.9)	.004	1.90 (.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

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Adjusted for age, sex, human immunodeficiency virus (HIV) transmission category (injection drug users vs non–injection drug users), $CD4^+$ T-cell nadir, advanced fibrosis (F3–F4 at biopsy or aspartate aminotransferase–to–platelet ratio >2), baseline HIV RNA levels <50 copies/mL, and combination antiretroviral therapy.

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 interferon plus ribavirin was higher in nonresponders 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 recovery of $CD4^+$ T cells in patients with fully suppressed HIV after cART [18]. Our findings, however, support the notion that HCV has a negative effect 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 the recovery of $CD4^+$ T cells, even after years of exposure to cART [20].

The increased risk of non–liver-related death and non–liver-related, non–AIDS-related death found in our study among nonresponders, compared with responders, 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 of not only HCV disease complications but also progression of HIV infection [23]. In addition, in HIV/HCV-coinfected patients

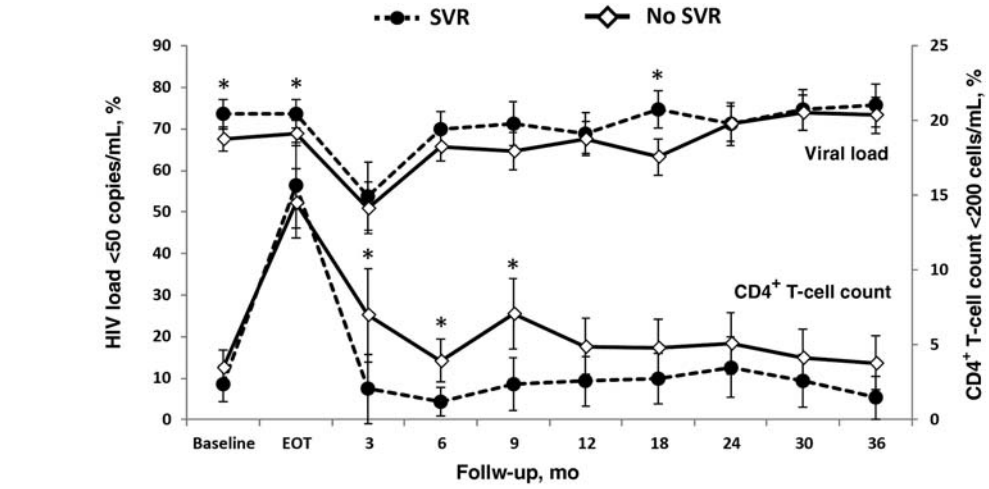

Figure 2. Immunovirological status at baseline, at the end of anti–hepatitis C virus (HCV) treatment (EOT) and during follow-up in 1599 patients coinfected with human immunodeficiency virus (HIV) and HCV, with or without sustained virological response (SVR) after therapy with interferon plus ribavirin. Viral load: proportion of patients with undetectable HIV viral load; dashed line: patients with SVR; solid line: patients with no SVR. $CD4^+$ T-cell count: Proportion of patients with $CD4^+$ T-cell counts <200 cells/mL; dashed line: patients with SVR; solid line: patients with with no SVR.

with liver cirrhosis, microbial translocation has been correlated with markers of systemic immune activation [24].

After adjustment for standard 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 soluble intercellular adhesion molecule 1 and soluble vascular cell adhesion molecule 1 (sVCAM-1), and SVR after therapy with interferon plus ribavirin 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 nonresponders in our study, particularly in the case of bacterial pneumonia. This is because progression of liver disease was more common in nonresponders 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 nonresponders 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 comorbid conditions (smoking, diabetes, standard 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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Potential conflicts of interest. All authors: No reported conflicts.

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