Eradication of HCV and non–liver-related non–AIDS-related events in HIV/HCV coinfection

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List of abbreviations:

- HCV: hepatitis C virus
- HIV: human immunodeficiency virus.
- NLR-NAR: non–liver-related non–AIDS-related
- AIDS: acquired immunodeficiency syndrome
- 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).
- SEIMC: Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (Spanish Society of Infectious Diseases and Clinical Microbiology).
- RNA: ribonucleic acid
- CD4+: cluster of differentiation 4
- eGFR: estimated glomerular filtration rate
- CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration
- MDRD: Modification of Diet in Renal Disease

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Abstract

We assessed non–liver-related non–AIDS-related (NLR-NAR) events and mortality in a cohort of HIV/HCV-coinfected patients treated with interferon and ribavirin 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 non-responders. Fine and Gray regression analysis was conducted to determine the adjusted sub-hazard 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, prior 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 five-year follow-up, SVR was found to be associated with a significant decrease in the hazard of diabetes mellitus (sHR 0.57 [95% CI, 0.35 - 0.93] *P*= .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*=.075). Conclusion: Our data suggest that eradication of HCV in coinfected 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 coinfected patients regardless of fibrosis stage.

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, B-cell non-Hodgkin lymphoma, and neurocognitive dysfunction have been associated with HCV infection (1, 2).

In patients with chronic hepatitis C, sustained viral response 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 crosslinking 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 coinfected by human immunodeficiency virus (HIV) (5-7). In a recent systematic review and meta-analysis of the survival benefits of achieving sustained viral response, 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 coinfected 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-coinfected patients. The purpose of our study was to investigate the effect of sustained viral response in non–liver-related non–AIDS-related (NLR-NAR) events in a large cohort of HIV/HCV-coinfected patients treated with interferon plus ribavirin.

Patients and Methods

Design and patient selection

The patients were selected from the cohort of the "Grupo de Estudio del SIDA" (AIDS Study Group, GESIDA) of the "Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica" (Spanish Society of Infectious Diseases and Clinical Microbiology, SEIMC). This cohort was composed of patients who were naïve to anti-HCV therapy and who were treated with interferon and ribavirin. 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 interferon and ribavirin 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, since 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 interferon and ribavirin to coinfected patients was taken by infectious diseases physicians at each institution according to national and international guidelines. The eligibility criteria for interferon and ribavirin therapy included the absence of prior 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/μL, 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, prior 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 a sustained viral response; patients not fulfilling the criteria for a sustained viral response, including those who had a relapse after achieving an end-of-treatment response, were classified as non-responders. Safety was assessed by laboratory tests and evaluation of adverse clinical events during therapy.

Follow-up

Completion of treatment was followed by active monitoring (semi-annually until July 2010, and annually thereafter) to analyze clinical and laboratory parameters, including survival, the 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 interferon plus ribavirin 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 end points: liver-related events, AIDS-related events, NLR-NAR events, and mortality.

Liver-related events, 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 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] (Supplementary Material, Tables S1 and S2).

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 the category of treatment response 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) NLR-NAR deaths.

Statistics

Differences between groups were analyzed using the chi-square test, *t* test, or Mann-Whitney 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 non-responders. Unadjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) for events in non-responders 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 non-responders. Univariate and multivariate Fine and Gray regression analyses were performed as an alternative to Cox regression for comparison of the sub-hazard 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, prior 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.

As some patients experienced reinfections and several patients underwent retreatment with interferon plus ribavirin, we carried out various sensitivity analyses: a) the primary analysis, in which patients who achieved a sustained viral response with retreatment (after failure or after relapse) were included in the sustained viral response group; b) the second analysis, in which follow-up of retreated patients was censored on the same day of initiation of the second course of interferon plus ribavirin; c) the third analysis, in which patients who were retreated were excluded from the analysis; d) the fourth analysis, in which treatment response status was considered a time-dependent variable, that is, some patients could be considered both responders and non-responders 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 vs. FIB-4 <3.25); a) in the first analysis—limited to patients with liver-biopsy data—fibrosis was categorized as F0-F2 vs F3-F4; b) tin he second analysis, fibrosis was categorized as FIB-4 <3.25 or F0-F2 vs FIB ≥3.25 or F3-F4.

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, New York, USA). The R package cmprsk (version 2.2) 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 40 years, 22.8% had prior AIDS-defining conditions, 1,366 (84.1%) were on cART, the median baseline CD4 cell count was 527 cells/mm^3, 69.4% had an undetectable HIV viral load, 62.4% were infected with genotypes 1 or 4, and 60.6% had an HCV RNA ≥500,000 IU/mL.

Baseline liver biopsy was performed in 1154 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 non-responders for qualitative or cumulative exposure to tenofovir disoproxil fumarate, a potentially nephrotoxic drug (19). However, significant differences were found between responders and non-responders in qualitative and/or cumulative exposure to didanosine, abacavir, indinavir, and lopinavir, all of which have been associated with cardiovascular disease (20) (Supplementary Material. Table S3).

Treatment Response

A total of 791 (48.7%) patients were treated with pegylated interferon α2a plus ribavirin, 615 (37.8%) were treated with pegylated interferon α2b plus ribavirin, and 219 (13.5%) were treated with the standard interferon α plus ribavirin regimen (three times weekly). The initial treatment response was categorized as sustained viral response in 592 (36%) patients and as no response in 1033 (64%) patients. During follow-up, six (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 six patients who experienced reinfections. A total of 42 retreated patients achieved sustained viral response, including one of the six reinfected patients. For the purpose of the primary analysis, there were 628 responders and 997 non-responders.

Clinical outcomes

The median (interquartile range) follow-up from the date interferon plus ribavirin was stopped for non-responders and responders was 65 (42 - 85) months and 65 (43 - 86) months, respectively. Loss to follow-up was recorded in 162 non-responders (16.2%) and 74 responders (11.8%) (*P*=.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 interferon plus ribavirin 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, hepatocellular carcinoma, and liver transplantation) were significantly higher in non-responders 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 non-responders than in responders. However, the rates of NLR-NAR cancers, cardiovascular events, and bone events were not significantly different between responders and non-responders.

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, sustained viral response 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*<.001), liver-related death (sub-hazard ratio [sHR]; 95% CI, 0.13 [0.06 - 0.28]; *P*<.001), new AIDS-defining events (sHR [95%CI], 0.37 [0.17 - 0.79]; *P*=.010), liver decompensation (sHR [95%CI], 0.10 [0.05 - 0.21]; *P*<.001), hepatocellular carcinoma (sHR [95%CI], 0.13 [0.03 - 0.50]; *P*=.003), and liver transplantation (sHR [95%CI], 0.12 [0.02 - 0.78]; *P*=.027). As for NLR-NAR events, sustained viral response was independently associated with a statistically significant reduced hazard of diabetes mellitus (sHR [95%CI], 0.57 [0.35 - 0.93]; *P*=.024), with a reduced hazard of renal events close to the threshold of significance (sHR [95%CI], 0.42 [0.17 – 1.09], *P*=.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*=.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 (Supplementary Material. Table 4).

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 non-responders are shown in **Figure 1**.

Discussion

We evaluated the clinical course of 1,625 HIV/HCV-coinfected patients who were followed up for a median of five years after the end of treatment with interferon plus ribavirin, 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 non-responders. 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 sustained viral response 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 insulin resistance and type 2 diabetes (22) and agrees with findings from previous studies in which sustained viral response caused a reduction in the risk of type 2 diabetes in HCV-monoinfected patients (11). It is also worth mentioning that insulin resistance and diabetes are associated with progression of liver disease, hepatic decompensation, and death in patients with chronic HCV (23-26) and with hepatocellular carcinoma in patients with HCV-related cirrhosis with or without HIV infection (27, 28). For these reasons, patients with chronic hepatitis C and insulin resistance or type 2 diabetes 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 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 end-stage renal disease (34). In addition, antiviral treatment for HCV has been associated with a lower risk of end-stage renal disease in large prospective cohorts in HCV-monoinfected individuals (12, 13). We found a significantly higher incidence of renal events in non-responders than in responders. However, with the stricter multivariate competing risk regression analyses, the lower hazard of chronic renal failure in responders than in non-responders 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 below 60 mL per minute per 1.73 m^2 (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 the 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 non-responders, competing risk regression analysis showed the adjusted hazard of cardiovascular events to be higher in responders than in non-responders, 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 authors 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 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 lipoviroparticles. Also noteworthy are the different effects of eradication of HCV on atherogenesis, namely, reversion 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 preclinical 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 combination antiretroviral therapy 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 coinfected patients, both HIV infection and HCV infection have been found to reduce bone mineral density through different pathophysiologic 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 non-responders 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 non-responders 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 coinfected 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 coinfected patients.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Figure legends

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

APPENDIX: THE GESIDA HIV/HCV COHORT STUDY GROUP

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Table 1. Characteristics of 1,625 HIV/HCV-Coinfected Patients Stratified According to Response to Interferon Plus Ribavirin

Characteristic	No SVR (n=997)	SVR (n=628)	Total (N=1625)
Male sex, No. (%)	753 (75.5)	466 (74.2)	1219 (75.0)
Age, y, median (IQR) (baseline)	40 (37 - 43)	40 (37 - 43)	40 (37 - 43)
BMI (n=1332), 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)
Prior injection drug use, No. (%)	802 (80.4)	510 (81.2)	1,312 (80.7)
CDC disease category C, No. (%)[a]	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, yr., 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/d, No. (%)	58 (5.8)	19 (3) *	77 (4.7)

Diabetes mellitus	39 (3.9)	8 (1.3) *	47 (2.9)
Chronic renal failure[b]	3 (0.3)	1 (0.2)	4 (0.2)

Abbreviations: SVR, sustained viral response; IQR, interquartile range; BMI, body mass index; cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen.

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

[b]Confirmed eGFR <60 mL per minute per 1.73 m^2 at baseline.

*P<.05 compared with the No SVR group.

Table 2. Detailed description of non–liver-related non–AIDS-related events during follow-up in HIV/HCV-coinfected patients categorized according to response to therapy with interferon plus ribavirin

EVENT	No SVR (n=997)	SVR (n=628)	Total (N=1625)
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)
Non-melanoma skin cancer	5 (0.5)	0 (0)	5 (0.3)
Hodgkin 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 hematologic	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[1]	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[2]	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)

* $P<0.05$

[1]Including 958 Non-SVR and 620 SVR patients (patients with baseline diabetes mellitus were excluded)

[2]Including 994 Non-SVR and 627 SVR patients (patients with chronic renal failure at baseline were excluded)

Table 3. Frequency and rate of events during follow-up in 1,625 HIV/HCV–coinfected patients categorized according to response to interferon plus ribavirin therapy

EVENT	Frequency, No. (%)			Rate/100 person-years (95% CI)			
	No SVR N=997	SVR N=628	*P*[1]	No SVR	SVR	IRR (95%CI)	*P*[2]
Lost to follow-up	162 (16.2)	74 (11.8)	.013	3.19 (2.72 - 3.72)	2.33 (1.83 - 2.92)	1.37 (0.97 - 1.7)	.075
Overall mortality	145 (14.5)	30 (4.8)	<.001	2.75 (2.32 - 3.23)	0.93 (0.63 - 1.33)	2.95 (1.99 - 4.36)	<.001
Liver-related	83 (8.3)	6 (1.0)	<.001	1.57 (1.25 - 1.95)	0.19 (0.07 - 0.41)	8.43 (3.68 - 19.3)	<.001
Non-liver-related	62 (6.2)	24 (3.8)	.036	1.17 (0.90 - 1.50)	0.75 (0.48 - 1.11)	1.57 (0.98 - 2.52)	.059
AIDS-related	8 (0.8)	2 (0.3)	.224	0.15 (0.07 - 0.30)	0.06 (0.01 - 0.22)	2.44 (0.52 - 11.5)	.260
Non–liver-related non–AIDS-related	54 (5.4)	22 (3.5)	.075	1.02 (0.77 - 1.33)	0.68 (0.43 - 1.03)	1.50 (0.91 - 2.46)	.111
CDC category C disease	43 (4.3)	9 (1.4)	.001	0.81 (0.59 - 1.10)	0.28 (0.13 - 0.53)	2.91 (1.54 - 6.97)	.002
Liver decompensation	123 (12.3)	7 (1.1)	<.001	2.44 (2.03 - 2.91)	0.22 (0.09 - 0.45)	11.20 (5.14 - 23.6)	<.001
Hepatocellular carcinoma	29 (2.9)	3 (0.5)	.001	0.55 (0.37 - 0.79)	0.09 (0.02 - 0.27)	5.92 (2.04 - 36.0)	.003
Liver transplantation, No. (%)	16 (1.6)	1 (0.2)	.005	0.30 (0.17 - 0.49)	0.03 (0 - 0.17)	9.80 (1.30 - 73.9)	.027
NLR-NAR events							
Diabetes mellitus	72/958 (7.5)	23/620 (3.7)	.002	1.45 (1.13 - 1.82)	0.73 (0.46 - 1.09)	1.99 (1.24 - 3.18)	.004
NLR-NAR Cancer	67 (6.7)	33 (5.3)	.231	1.28 (0.99 - 1.63)	1.04 (0.72 - 1.46)	1.23 (0.81 - 1.87)	.329
Cardiovascular events	52 (5.2)	39 (6.2)	.396	0.99 (0.74 - 1.30)	1.24 (0.88 - 1.69)	0.80 (0.53 - 1.22)	.302
NAR-Infections	62 (6.2)	19 (3.0)	.004	1.19 (0.91 - 1.52)	0.59 (0.36 - 0.93)	2.01 (1.20 - 3.34)	.008
Bone events	33 (3.3)	24 (3.8)	.585	0.63 (0.44 - 0.89)	0.75 (0.48 - 1.12)	0.84 (0.48 - 1.38)	.447

Renal events	27/994 (2.7)	6/627 (.1)	.015	0.51 (0.34 - 0.75)	0.19 (0.07 - 0.41)	2.74 (1.13 - 6.65)	.025

Abbreviations: CI, confidence interval; SVR, sustained viral response; CDC, Centers for Disease Control and Prevention; CI, confidence interval; SVR, sustained virologic response; NLR, non–liver related; NAR, non–AIDS related. IRR, incidence risk ratio.

[a]Median follow-up times in months (interquartile range) for No-SVR and SVR were 59.3 (40.6-79.2), and 59.5 (42.8-81.8).

P^1: Pearson chi^2 test. P^2: Poisson regression

Table 4. Crude and adjusted hazards for events during follow-up for 997 non-responders to interferon plus ribavirin compared with 628 responders

	Univariate analysis[a]		Multivariate analysis[a,b]	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Overall deaths	0.35 (0.24 - 0.52)	<.001	0.36 (0.24 - 0.54)	<.001
	sHR (95% CI)	***P***	**sHR (95% CI)**	***P***
Cause-specific deaths				
Liver-related deaths	0.12 (0.05 - 0.28)	<.001	0.13 (0.06 - 0.28)	<.001
Non–liver-related deaths	0.69 (0.43 - 1.1)	.119	0.73 (0.44 - 1.20)	.214
AIDS-related deaths	0.45 (0.09 - 2.22)	.325	0.37 (0.09 - 1.43)	.148
NLR-NAR deaths	0.73 (0.44 - 1.19)	.204	0.79 (0.47 - 1.35)	.388
New AIDS-defining events	0.34 (0.16 - 0.72)	.004	0.37 (0.17 - 0.79)	.010
Liver-related events				
Liver decompensation	0.09 (0.04 - 0.2)	<.001	0.10 (0.05 - 0.21)	<.001
Hepatocellular carcinoma	0.12 (0.03 - 0.5)	.004	0.13 (0.03 - 0.50)	.003
Liver transplantation	0.10 (0.01 - 0.77)	.027	0.12 (0.02 - 0.78)	.027
NLR-NAR events				
Diabetes mellitus *	0.54 (0.34 - 0.87)	.011	0.57 (0.35 - 0.93)	.024
NLR-NAR Cancer	0.91 (0.6 - 1.38)	.650	0.91 (0.58 - 1.45)	.703
Cardiovascular events	1.41 (0.93 - 2.13)	.105	1.57 (0.99 - 2.50)	.056
NAR-Infections	0.55 (0.33 - 0.92)	.024	0.65 (0.37 - 1.14)	.131
Bone events	1.39 (0.82 - 2.35)	.225	1.28 (0.69 - 2.38)	.433
Renal events *	0.41 (0.17 - 0.99)	.049	0.43 (0.17 – 1.09)	.075

[a]Cox regression analysis was performed to compare the HR of overall death between responders and non-responders. Fine and Gray regression analysis was performed to compare the HR of events in the presence of competing risks.

[b]Adjusted for age, sex, prior 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 vs higher than the median cumulative exposure.

*Excluding 47 and 4 patients with diabetes mellitus and chronic renal failure at baseline, respectively

Abbreviations: HR, hazard ratio; CI, confidence interval; sHR, sub-hazard ratio; NLR, non-liver related; NAR, non-AIDS related.

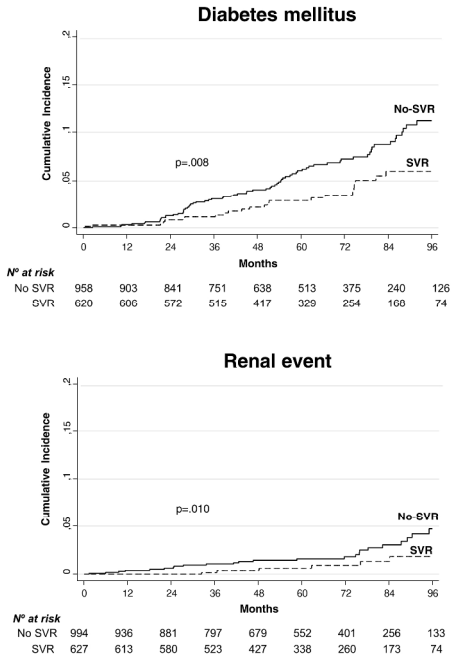

Figure 1. Cumulative probabilities of renal events and diabetes mellitus in responders and non-responders. Responders and non-responders were compared using Gray's test.

254x190mm (300 x 300 DPI)

Table S1. Types of non–liver-related non–AIDS-related events

Cardiovascular events

- Coronary
  - Acute myocardial infarction
  - Angina
  - Sudden death from possible coronary etiology
- Cerebrovascular
  - Transient ischemic attack
  - Reversible ischemic deficit
  - Established stroke
  - Asymptomatic cerebrovascular disease
- Peripheral arterial disease
- Congestive heart failure
- Primary pulmonary hypertension

Renal events

- Chronic renal failure
- Initiation of dialysis
- Kidney transplantation

Bone-related events

- Vertebral fracture
- Large bone fracture
- Osteonecrosis (avascular necrosis of bone)

Metabolic events

- Diabetes mellitus

Cancer (non–liver-related non–AIDS-related)

- Anus
- Brain
- Breast
- Colorectal
- Esophagus
- Head and neck
- Hodgkin lymphoma
- Kidney
- Lung
- Melanoma
- Non-melanoma skin
- Other hematologic non–AIDS-related
- Penis
- Prostate
- Sarcoma
- Stomach
- Testicle
- Vagina/vulva
- Other

Non–AIDS-related infections

- Sepsis requiring hospitalization

Table S2. Definitions of non–liver-related non–AIDS-related events

1) Cardiovascular Events

A) Coronary

Acute myocardial infarction:

Acute myocardial infarction is defined as the presence of any of the following criteria:

1. ECG diagnosis or
2. Symptoms + probable ECG + elevated levels of cardiac biomarkers
3. Typical symptoms + elevated levels of cardiac biomarkers + ECG with signs of ischemia, or ECG not classifiable or not available.
4. Fatal cases with the macroscopic appearance of recent myocardial infarction and/or recent coronary occlusion in autopsy

ECG changes:

- Diagnostic ECG: (a) appearance of unambiguous Q waves; if the Q wave is ambiguous, it must be accompanied by alterations in the ST segment or T wave; all these changes must be accompanied by a progression in the T wave in 3 or more leads; (b) ST-segment elevation that lasts more than 24 hours with T-wave progression in 3 or more leads.
- Probable ECG: (a) Non-significant drop in the T segment in a recording accompanied by significant drop in another recording; or (b) Non-significant ST elevation in a recording accompanied by significant elevation in another recording; or (c) Non-significant T wave reversal in a recording accompanied by significant reversal in another recording.
- ECG with signs of ischemia: corresponds to ECG abnormalities that have not progressed.
- ECG not coded: for technical reasons or intrinsic conduction disturbances/arrhythmias.

Elevation of cardiac enzymes:

Including creatine kinase (CK) (and the MB isoenzyme of CK), LDH, cardiac-specific troponin T and cardiac-specific troponin I. Documented elevations of aminotransferases are also accepted.

Symptoms:

Typical:

- Crushing chest pain or angina pectoris (any synonym for pain is acceptable e.g., "pressure", "discomfort")
- Duration of more than 20 minutes
- Absence of non-atherosclerotic cardiac or non-cardiac causes.

Atypical:

- Atypical pain (short duration or intermittent), episode lasting less than 20 minutes, or at an unusual location (upper abdomen, arms, jaw, neck).
- Acute left ventricular failure
- Shock
- Syncope
- No underlying disease other than ischemic heart disease
- No definitive non-atherosclerotic cardiac or non-cardiac cause

Angina

Symptoms suggestive of myocardial ischemia, such as chest tightness and pain or pain in the jaw or arm. The pain usually lasts less than 20 minutes. ECG changes (e.g., depression of at least 0.5 mm of the ST segment or T-wave inversion of at least 1 mm in 2 or more contiguous leads) must objectively confirm myocardial ischemia.

Stable angina:

- Angina that has not changed its frequency or characteristics during the last 6 weeks. It is controlled with rest or treatment.

Unstable angina:

- Angina during inactivity, usually lasting more than 20 minutes.
- Angina of recent onset.
- Recent progression of angina reflected by an increase in severity.

B) Cerebrovascular

The diagnosis of cerebral hemorrhage is established with CT or MRI; ischemic episodes are confirmed based on clinical and radiological data: onset of neurological deficit in which other causes (space-occupying lesions in the brain, meningoencephalitis) are ruled out and monitoring during the following hours confirmed signs of cerebral ischemia in the imaging tests.

Transient ischemic attack

Episode of focal neurologic dysfunction caused by ischemia of a brain area that lasts less than 24 hours.

Reversible ischemic deficit

Episode of focal neurologic dysfunction of more than 24 hours' duration with subsequent recovery.

Established stroke

Neurological deficit that does not change during the first 24-72 hours of observation.

Asymptomatic cerebrovascular disease

Neuroimaging studies showing ischemic brain lesions that have not produced clinical manifestations (silent infarcts) in patients with risk factors.

C) Peripheral arterial disease

Peripheral arterial disease is defined as the presence of atherosclerosis in the arteries of the lower extremities. It is characterized by intermittent claudication or other clinical manifestations that indicate a more advanced stage, such as ischemic pain at rest, blue toe syndrome, non-healing ulcers or focal gangrene, with objective evidence of peripheral arterial disease, i.e., an ankle-brachial index (ABI) at rest of <0.9. In addition to ABI, the test results considered accepted as objective evidence of peripheral arterial disease included the following: Doppler ultrasound, MRI angiography, and CT angiography. Also included in this group are patients undergoing arterial revascularization or amputation.

D) Heart failure

Heart failure is defined as compatible symptoms that correspond to functional classes II to IV of the New York Heart Association (NYHA): class II (mild), slight limitation to ordinary physical activities, such as those arising from palpitations or dyspnea, without dyspnea at rest; class III (moderate), marked limitation to ordinary physical activities without dyspnea at rest; class IV (severe), inability to perform any physical activity, dyspnea at rest.

The aforementioned symptoms are accompanied by a ventricular ejection fraction ≤0.40 on echocardiography (Hjalmarson A, JAMA 2000; 283: 1295-302).

E) Pulmonary hypertension

Pulmonary arterial hypertension was defined as a mean pulmonary artery pressure of ≥25 mmHg and a pulmonary capillary wedge pressure of ≤ 15 mmHg at rest (Galiè N, N Engl J Med 2005; 353: 2148-57).

2) Renal events

A) Chronic renal failure

Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 for more than 3 months. eGFR can be calculated using the CKD-EPI or MDRD formulas.

B) Initiation of hemodialysis or peritoneal dialysis

C) Kidney transplantation

3) Bone events

A) Osteonecrosis (avascular necrosis of bone)

A diagnosis of osteonecrosis is confirmed when definite or probable criteria are met

Definite osteonecrosis

- Histological confirmation
- When 2 of the following criteria are met:
    1) Compatible findings in a plain radiograph: i) line of subchondral fracture or depression of the femoral head and/or ii) band sclerosis of the femoral head.
    2) Compatible bone scan findings: area of low uptake surrounded by an area of high uptake (known as the "cold in hot" pattern).
    3) Typical MRI findings: a high-intensity region of bone marrow edema accompanied by a peripheral band of low signal intensity on both T1- and T2-weighted images separating the osteonecrosis from the surrounding healthy bone marrow.

Probable osteonecrosis

Clinical and radiological suspicion, but 2 of the above criteria are not met

B) Spinal fracture

The diagnosis is clinical and radiological. The presence of fracture is defined as a visual estimation of a reduction in the vertebral height (anterior, middle, or posterior) ≥20% in a plain radiograph of the spine in lateral projection (Genant HKJ Bone Miner Res 1993).

C) Long-bone fracture

The diagnosis is clinical and radiological. Long-bone fracture is defined as a break in the continuity of bone with or without separation of the fragments on a plain radiograph.

4) Metabolic events

A) Diabetes mellitus

- Fasting plasma glucose (FPG) >126 mg/dL (7.0 mmol/L) on at least 2 separate consecutive occasions, no evidence of glucose levels in the normal range.
- In the absence of information on FPG levels, diagnosis can be established in either of the following circumstances:
    - Symptoms of diabetes + blood glucose concentration >200 mg/dL (11.1 mmol/L), or
    - Plasma glucose 2 hours after a glucose tolerance test >200 mg/dL (11.1 mmol/L), or
    - The diagnosis was made elsewhere, and the patient was started on antidiabetic therapy

5) Cancer (non–AIDS-related non–liver-related)

The diagnosis requires histopathological confirmation.

6) Non–AIDS-related infections

A) Sepsis requiring hospitalization

Sepsis is defined as systemic inflammatory response syndrome (SIRS) caused by an infectious process at any location

- SIRS is defined by the presence of at least 2 of the following criteria
    1. Fever (>38°C) or hypothermia (<36°C)
    2. Increased heart rate (>90/min)
    3. Tachypnea (>20/min) or hyperventilation ($PaCO_2$ <32 mmHg)
    4. WBC >12,000/mm^3 or <4,000/mm^3 or the presence of >10% neutrophils.
- Infection can be established based on the presence of positive blood cultures or a compatible clinical picture without positive blood cultures.

Table S3. Exposure to antiretroviral drugs that have been associated with chronic renal failure or cardiovascular disease during the study period

Antiretroviral drug	No SVR (n=997)	SVR (n=628)	Total (N=1625)	*P*
Tenofovir disoproxil fumarate				
Ever exposed, No. (%)	609 (61.1)	376 (59.9)	985 (60.6)	.627
Cumulative exposure, years, median (IQR)	3.32 (1.84 - 4.80)	3.46 (2.01 - 5.05)	3.42 (1.91 - 4.92)	.192
Didanosine				
Ever exposed, No. (%)	186 (18.7)	78 (12.4)	264 (16.2)	.001
Cumulative exposure, years, median (IQR)	2.85 (1.56 - 4.77)	3.52 (1.98 - 5.69)	3.15 (1.72 - 4.96)	.036
Abacavir				
Ever exposed, No. (%)	269 (27.0)	141 (22.5)	410 (25.2)	.041
Cumulative exposure, years, median (IQR)	3.23 (1.68 - 4.83)	3.93 (2.49 - 5.42)	3.62 (1.89 – 5.00)	.002
Indinavir				
Ever exposed, No. (%)	24 (2.4)	19 (3.0)	43 (2.6)	.450
Cumulative exposure, years, median (IQR)	2.16 (1.78 - 2.63)	2.78 (2.17 - 4.32)	2.34 (1.85 - 3.19)	.035
Lopinavir				
Ever exposed, No. (%)	279 (28.0)	137 (21.8)	416 (25.6)	.006
Cumulative exposure, years, median (IQR)	2.97 (1.46 - 4.81)	3.61 (2.01 - 5.18)	3.22 (1.72 - 4.9)	.038

Table S4. Sensitivity analysis with patients classified according to reinfections and retreatments

Adjusted hazards for events during follow-up for 997 non-responders to interferon plus ribavirin compared with 628 responders according to the type of analysis [a,b]

	Primary analysis		Second analysis		Third analysis		Fourth analysis	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Overall deaths	0.36 (0.24 - 0.54)	<.001	0.35 (0.23 - 0.53)	<.001	0.32 (0.21 - 0.49)	<.001	0.35 (0.23 - 0.52)	<.001
	sHR (95% CI)	***P***	**sHR (95% CI)**	***P***	**sHR (95% CI)**	***P***	**sHR (95% CI)**	***P***
Cause-specific deaths								
LR	0.13 (0.06 - 0.28)	<.001	0.13 (0.06 - 0.29)	<.001	0.12 (0.05 - 0.27)	<.001	0.12 (0.05 - 0.27)	<.001
NLR	0.73 (0.44 - 1.20)	.214	0.70 (0.42 - 1.18)	.180	0.65 (0.38 - 1.12)	.117	0.70 (0.42 - 1.15)	.161
AR	0.37 (0.09 - 1.43)	.148	0.37 (0.10 - 1.46)	.155	0.39 (0.11 - 1.42)	.153	0.36 (0.09 - 1.41)	.144
NLR NAR	0.79 (0.47 - 1.35)	.388	0.76 (0.44 - 1.32)	.330	0.69 (0.39 - 1.25)	.223	0.76 (0.45 - 1.29)	.305
New AR events	0.37 (0.17 - 0.79)	.010	0.38 (0.17 - 0.85)	.019	0.25 (0.1 - 0.64)	.004	0.34 (0.16 - 0.72)	.005
LR events								
Decompensation	0.10 (0.05 - 0.21)	<.001	0.06 (0.02 - 0.15)	<.001	0.06 (0.02 - 0.17)	<.001	0.07 (0.03 - 0.17)	<.001
HCC	0.13 (0.03 - 0.50)	.003	0.06 (0.01 - 0.43)	.005	0.09 (0.01 - 0.65)	.017	0.06 (0.01 - 0.42)	.005
Transplantation	0.12 (0.02 - 0.78)	.027	NA	NA	NA	NA	NA	NA
NLR NAR events								
Diabetes mellitus *	0.57 (0.35 - 0.93)	.024	0.49 (0.29 - 0.83)	.007	0.52 (0.30 - 0.91)	.021	0.48 (0.29 - 0.80)	.005
NLR-NAR cancer	0.91 (0.58 - 1.45)	.703	0.93 (0.59 - 1.49)	.771	0.80 (0.49 - 1.30)	.370	0.87 (0.55 - 1.37)	.538
Cardiovascular	1.57 (0.99 - 2.50)	.056	1.49 (0.92 - 2.39)	.103	1.58 (0.96 - 2.62)	.075	1.47 (0.93 - 2.33)	.100
NAR infections	0.65 (0.37 - 1.14)	.131	0.63 (0.35 - 1.11)	.111	0.64 (0.35 - 1.16)	.142	0.62 (0.35 - 1.09)	.094
Bone events	1.28 (0.69 - 2.38)	.433	1.38 (0.75 - 2.53)	.303	1.46 (0.74 - 2.91)	.276	1.32 (0.72 - 2.43)	.368
Renal events *	0.43 (0.17 - 1.09)	.075	0.44 (0.17 - 1.11)	.082	0.38 (0.14 - 0.99)	.047	0.40 (0.16 - 1.02)	.055

[a]Cox regression analysis was performed for comparison of the HR of overall death between responders and non-responders. Fine and Gray regression analysis was performed for comparison of the HR of events in the presence of competing risks.
[b]*Adjusted for age, sex, prior 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 vs higher than the median cumulative exposure).*

* Excluding 47 and 4 patients with diabetes mellitus and chronic renal failure at baseline, respectively

Abbreviations: HR, hazard ratio; CI, confidence interval; sHR, subhazard ratio; LR, liver-related; NLR, non–liver-related; AR, AIDS-related; NAR, non–AIDS-related; HCC, hepatocellular carcinoma.

Description of the 4 types of analysis

- **Primary analysis**: those who achieved sustained viral response with retreatment were included in the sustained viral response group
- **Second analysis**: the follow-up of retreated patients was censored on the same day as the initiation of the second course with interferon plus ribavirin.
- **Third analysis**: patients who were retreated were excluded from the analysis.
- **Fourth analysis**: treatment response status was considered a time-dependent variable