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Improved Survival Among all Interferon-α-Treated Patients in HCV-002, a Veterans Affairs Hepatitis C Cohort of 2211 Patients, Despite Increased Cirrhosis Among Nonresponders

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Abstract

Background—As the era of interferon-alpha (IFN)-based therapy for hepatitis C ends, long-term treatment outcomes are now being evaluated.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest related to the data or interpretation of this study.

Aim—To more fully understand the natural history of hepatitis C infection by following a multisite cohort of patients.

Methods—Patients with chronic HCV were prospectively enrolled in 1999–2000 from 11 VA medical centers and followed through retrospective medical record review.

Results—A total of 2211 patients were followed for an average of 8.5 years after enrollment. Thirty-one percent of patients received HCV antiviral therapy, 15 % with standard IFN/ribavirin only, 16 % with pegylated IFN/ribavirin, and 26.7 % of treated patients achieved sustained virologic response (SVR). Cirrhosis developed in 25.8 % of patients. Treatment nonresponders had a greater than twofold increase in the hazard of cirrhosis and hepatocellular carcinoma, compared to untreated patients, whereas SVR patients were only marginally protected from cirrhosis. Nearly 6 % developed hepatocellular carcinoma, and 27.1 % died during the follow-up period. Treated patients, regardless of response, had a significant survival benefit compared to untreated patients (HR 0.58, CI 0.46–0.72). Improved survival was also associated with college education, younger age, lower levels of alcohol consumption, and longer duration of medical service follow-up—factors typically associated with treatment eligibility.

Conclusions—As more hepatitis C patients are now being assessed for all-oral combination therapy, these results highlight that patient compliance and limiting harmful behaviors contribute a significant proportion of the survival benefit in treated patients and that the long-term clinical benefits of SVR may be less profound than previously reported.

Keywords

Hepatitis C; Hepatitis C therapy; Cirrhosis; Hepatocellular carcinoma; Survival

Introduction

Chronic hepatitis C virus (HCV) infection is a major cause of hepatic cirrhosis, liver failure, and hepatocellular carcinoma (HCC), and is the leading indication for liver transplantation in the USA [1–3]. Until 2012, treatment for HCV consisted of interferon-α (IFNα) combined with ribavirin (RBV), which typically resulted in sustained virologic response (SVR) in a minority of patients with HCV genotypes 1 and 4 [4]. Unlike previous IFNα-containing treatments, current combination all-oral antiviral regimens are well tolerated and achieve SVR rates of over 90 % [5, 6]. Although nearly all patients can safely be treated with these combination antivirals, their high cost has led healthcare systems to prioritize their use in patients with cirrhosis or with significant liver disease (e.g., fibrosis stage F2 or greater) [7]. The clinical consequences of HCV are determined by a complex interplay of virus-specific, behavioral, and pharmacologic influences. We propose that current HCV treatment decisions are informed by comparing the long-term outcomes of treated and untreated HCV patients who have been followed during the preceding decades of IFNα-based therapy [8–10].

The long-term outcomes of patients treated with IFNα-based regimens and those who have remained untreated are now beginning to be understood. Numerous epidemiologic studies have shown that IFNα-based treatment regimens are associated with improved survival, even if SVR is not achieved [11, 12]. It had long been assumed that SVR largely protects patients

from the development of decom-pensated cirrhosis and that IFNα may have beneficial effects on hepatic fibrosis even if SVR is not achieved [3, 11, 13]. Recently published studies, however, have described new diagnoses of cirrhosis up to 8 years after IFNα-induced SVR and increased long-term incidence of cirrhosis among treatment nonresponders compared with untreated patients [14–17].

In order to gain additional insight into the contributions of antiviral treatment and other clinical factors to long-term HCV outcomes, we conducted a retrospective follow-up of HCV-001, a cohort of chronic HCV patients who were prospectively enrolled and assessed for treatment eligibility in 1999–2000. During the initial HCV-001 study, detailed clinical, demographic, and behavioral patient data were obtained, and their influences on IFNα/RBV treatment eligibility, treatment initiation, and therapeutic success were assessed [18, 19]. The present study, termed HCV-002, reports on the comprehensive medical record review of 2,211 original HCV-001 patients. We examined the influences of baseline risk profiles, treatment eligibility, treatment initiation, and treatment success on the long-term outcomes of cirrhosis, HCC, and death over an 11-year follow-up period.

Methods

Study Population and Design

The present study, HCV-002, is a follow-up to HCV-001, a cohort study of 4300 chronic HCV patients from 24 VA medical centers prospectively enrolled between December 1999 and December 2000 [8, 18, 19]. During that time, a nurse coordinator at each participating medical center performed comprehensive HCV counseling and administered an intake questionnaire to obtain detailed clinical and behavioral risk information including self-described race, psychiatric profiles, educational and socioeconomic histories, detailed histories of past and ongoing drug and alcohol abuse, and a likely date of first HCV exposure from a prioritized list of potential HCV transmission sources [18]. Clinical and laboratory assessments were also conducted to determine eligibility for treatment, including pre-consideration liver biopsy in many patients. A total of 40.7 % of HCV-001 patients were recommended for antiviral treatment, and 18 % underwent treatment with IFNα/RBV during the HCV-001 study [18]. Reasons for treatment ineligibility were recorded by the treating physician from a list of 13 factors considered at the time to be absolute or relative contraindications to IFNα. These included psychiatric comorbidity, decompensated cirrhosis, prior treatment failure, ongoing or recent substance abuse, inadequate social support, poor clinical compliance, and minimal liver disease [18]. During the treatment phase of the study, data were prospectively collected on treatment success [8, 18, 19].

From the 24 original HCV-001 study sites, 11 opted to participate in HCV-002, which examined 2211 original patients from the VA hospitals in San Francisco, Palo Alto, Philadelphia, Minneapolis, Brooklyn, Manhattan, Bronx, Iowa City, Boston, Houston, and Long Beach. Data for the follow-up study were inclusive from HCV-001 enrollment date through December 31, 2011. All patients from the 11 sites were eligible for inclusion in HCV-002 as long as they had one or more VA medical service visits at least 1 year following the treatment eligibility assessment conducted in HCV-001. All HCV-001 patients provided written informed consent to participate in the original study, including long-term follow-up,

and both studies were approved by the local institutional review boards at each participating medical center. Permission for remote access to patient data at each HCV-002 site was obtained from the VHA Office of Health Data and Information (HDI) in Washington.

Data Acquisition and Development

The dataset for HCV-002 is derived from two sources: (1) data collected during the prospective phase of the HCV-001 study, previously described in detail, and (2) data retrospectively obtained from the web-based VA electronic medical record system (VistAWeb) [8, 18, 19]. A formal assessment of treatment eligibility during HCV-001 was made using two methods: exclusion criteria outlined above, and the treating physician's clinical judgment [8, 18]. Data derived from these assessments and from subsequent reports on treatment initiation and outcome from the HCV-001 study comprise the baseline dataset for the present study. All baseline data were manually validated during HCV-001 [18].

Follow-up data were obtained using automated processes for data extraction, data mining, and variable creation. Briefly, we used JavaScript software to develop tools to automatically extract content from the front end of the VistAWeb version of CPRS as text files from each of the 11 participating sites up to the end date of the study. The specific fields within the medical record from which data were extracted are listed in Supplemental Methods. Raw text files were stored initially on the local San Francisco VA research server then transferred to VINCI, the cloud-based storage and application workspace for the national VA. Two Visual Basic programs were used to convert raw content to Microsoft Excel files and then to compare the HCV-001 patient master list with the Excel list, checking for missing or incomplete data fields. Data extraction was repeated in cases where missing data fields were identified. This process was conducted in triplicate to ensure data completeness and quality. Excel files were then converted to SAS datasets, which were interrogated using an iteratively modified dictionary of search terms and text strings designed to capture clinically important variables and medical conditions as detailed in Supplemental Methods. A second algorithm was applied to exclude negative modifiers and negative assessments (such as "without cirrhosis"). Data from progress notes were primarily used to validate selected medical conditions, laboratory test results, treatment dates, and treatment outcomes. Corresponding dates of key diagnoses and antiviral treatment were obtained from outpatient medical encounters, including consults and procedures. Internal inconsistencies or ambiguities were resolved using manual data extraction from the medical record. During the HCV-002 study period, the therapeutic regimen, treatment date, and virologic response of each treated patient were also confirmed manually. ICD-9 codes were used to validate diagnoses, but not as a sole source to establish specific diagnoses as such coding might not always be complete.

Selected laboratory test results including HCV viral load, ALT, AST, and platelet counts taken from the date closest to, but preceding, the date of first treatment initiation.

Anatomic pathology reports and radiology reports were the primary sources of information used to establish the diagnoses of cirrhosis and HCC. Cirrhosis was defined as either (1) stage 4 fibrosis on biopsy or (2) a nodular liver contour plus at least one of three previously validated criteria: ascites, evidence of venous collateral vessels, or splenomegaly as visualized on abdominal CT scan, MRI, and/or ultrasound [20]. HCC was diagnosed by

imaging, pathology, and progress notes. For our HCV-002 cirrhosis assessment, a validation study on a randomly selected 5 % sample of the HCV-002 cohort found 86 % agreement with the results of the data mining process, a result that is competitive with other approaches [21]. Deaths were obtained from the medical record and confirmed by cross-reference with the national Social Security Death Index (SSDI). As cause of death is not available from the SSDI, only all-cause mortality was analyzed.

Outcome Measures, Predictors, and Confounders

Several outcome measures were defined for this study, including the number and proportion of patients who: (1) received IFNα-based treatment during the initial and follow-up phases; (2) achieved SVR (defined as undetectable HCV RNA at least 24 weeks after therapy); (3) developed cirrhosis; (4) developed HCC; and (5) died. Final treatment status was assessed as an independent risk factor for the development of cirrhosis, HCC, and overall survival.

Analytic models were developed to identify factors associated with treatment initiation, treatment outcome, cirrhosis and HCC development, and overall survival. Clinical parameters, including body mass index (BMI), ALT, and diabetes mellitus, were assessed for their independent influence on these outcomes. Viral factors ascertained included HIV and HBV infection status and HCV genotype. We also explored the effects of selected demographic and behavioral risk factors, including age, race/ ethnicity, alcohol consumption, other substance use, and psychiatric disorders. We evaluated the reliability of several alcohol consumption variables, including the metrics collected during the HCV-001 intake assessment and follow-up data obtained from the medical record, and found the data element obtained from the assessment of heavy alcohol use within 12 months prior to HCV-001 enrollment to be most consistently associated with other indicators of problem alcohol use. Therefore, we chose that variable for use in our analytic models. The substance abuse variable used in our analytic models is a compilation of self-reported data from the HCV-001 assessment and the data from HCV-001 clinician's final determination of treatment eligibility.

Patients were stratified based upon initial treatment eligibility and ultimate treatment status into four main analytic groups: (1) patients deemed eligible for treatment during HCV-001 and received treatment; (2) patients deemed eligible for treatment during HCV-001 but never treated; (3) patients ineligible for treatment during HCV-001 who received treatment during the HCV-002 follow-up period; and (4) patients ineligible during HCV-001 who were never treated. In each treated group, treatment success (SVR vs. non-SVR) was assessed separately as a risk factor for the development of cirrhosis, HCC, and death.

Statistical Analysis

All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). Chi-square tests were conducted for categorical data analysis, and the Student's *t* test or Wilcoxon rank sum test was used to assess the association of continuous predictors on categorical dependent variables. Hierarchical univariate and multivariate logistic regression models were used to assess the influence of selected predictors and confounders on binary outcomes, including treatment eligibility, treatment initiation, and SVR. For hierarchical or

mixed effects modeling, the 11 participating VA medical centers were stratified into three levels corresponding to average annual HCV caseload size during the follow-up period (<2000 patients, 2000–2999 patients, and ≥3000 patients) in order to reduce the degrees of freedom in multivariate models and because caseload volume can influence treatment practices and outcomes [22]. Cox proportional hazards models were used to analyze the effects of risk factors and confounders on time-to-event, including cirrhosis, HCC, and death.

Results

In total, 2211 patients were eligible for follow-up. Their demographic and clinical characteristics stratified by treatment status are presented in Tables 1 and Table S1. The mean length of follow-up after enrollment in HCV-001 was 8.5 years, and nearly 98 % of patients were male. The majority of patients were White (52.2 %), and a significant proportion (30.4 %) was Black. The mean age at HCV-001 enrollment (1999–2000) was 51.4 years. A total of 298 patients (13.5 %) were coinfected with HIV and HCV, and 87 patients (4.1 %) were HBsAg positive, indicating likely chronic coinfection with HBV. Only 25.4 % of patients underwent a pretreatment liver biopsy. Of these, 42.4 % had Batts–Ludwig fibrosis stage 2–3, indicating moderate liver disease, while 33.7 % had stage 4 fibrosis (cirrhosis).

Treatment Eligibility, Initiation, and Outcome

Clinical characteristics of patients were stratified by treatment eligibility status at the prospective HCV-001 assessment and ultimate treatment status by the end of HCV-002 follow-up (Table 2). A total of 462 (20.9 %) patients received antiviral therapy during the HCV-001 study period. An additional 230 (10.4 %) patients received antiviral therapy during HCV-002 follow-up. Only 185 of the 692 treated patients (26.7 %) achieved SVR, and SVR rates were equivalent in those deemed eligible and ineligible at the HCV-001 assessment. A total of 1519 patients never received hepatitis C therapy, including 371 (16.8 %) who were categorized as treatment-eligible, and 1148 (51.9 %) who were deemed ineligible during HCV-001. At enrollment in HCV-001, the baseline prevalence of cirrhosis was 8.5 % after a mean of 26 years of chronic infection. An additional 17.4 % of cohort patients developed cirrhosis during the 11-year HCV-002 period of follow-up. Nearly 6 % of the cohort developed HCC during the course of the study, and 27.1 % died (Table 1).

Compared to untreated patients, treated patients were significantly younger, more likely to be White, have a higher baseline ALT, and were less likely to have a history of alcohol abuse, drug abuse, serious psychiatric condition, HIV coinfection, or diabetes. Patients with cirrhosis during the HCV-001 assessment were significantly more likely to be treated. A total of 57 % percent of patients with cirrhosis at baseline were eventually treated compared to 30 % of patients who developed cirrhosis during follow-up and 29 % of patients without cirrhosis ($P<0.0001$). Among patients with pretreatment biopsies, 64.7 % were treated. Those with fibrosis stages 2–3 were significantly more likely to be treated than those with milder disease or cirrhosis ($P = 0.0002$). Demographic and clinical characteristics of cohort patients stratified by treatment status and facility caseload volume are presented in Table S2.

The 185 patients who achieved SVR were less likely to have genotype 1 or 4 infection (OR 0.30, CI 0.18–0.51 compared to GT 2 or 3) and less likely to be Black compared to another race (OR 0.34, CI 0.12–0.99) in univariate analyses (Table 3). These factors remained independently significant in multivariable modeling. The use of standard rather than pegylated IFNα was also independently associated with SVR. This was unexpected, as pegylated IFNα typically leads to higher SVR rates compared with standard IFNα [23, 24]. A detailed analysis, however, revealed that 33.9 % of patients who were treated with pegylated IFNα were prior treatment failures, compared with only 8.5 % receiving standard IFNα ($P < 0.0001$, Table S3). Pre-treatment cirrhosis was also present in 18.8 % of pegylated IFNα recipients, compared to 11.8 % receiving standard IFNα ($P = 0.03$, Table S3). Prior treatment and advanced disease likely account for the observed lower efficacy of pegylated IFNα in HCV-002 study patients [25, 26].

Liver Disease in Treated and Untreated Patients

At the time of HCV-001 enrollment, the prevalence of cirrhosis in the HCV-002 cohort was 8.5 %. An additional 17.4 % of patients developed cirrhosis during follow-up. Among untreated patients, cirrhosis was present in 80 (5.3 %) at baseline, and developed in 267 (17.6 %) during follow-up. Among treated patients, 109 (15.7 %) had cirrhosis at baseline, and 115 (16.6 %) developed cirrhosis during follow-up. Patients who ultimately achieved SVR had 10.3 % cirrhosis prevalence ($n = 19$) at baseline, and 9.7 % ($n = 18$) developed cirrhosis during follow-up. In treatment failures (including nonresponders and relapsers), 90 (17.8 %) had cirrhosis at baseline and 97 (19.1 %) developed cirrhosis during follow-up (Table 2).

In Cox proportional hazards analysis, treatment nonresponders had a greater than twofold increased risk of cirrhosis compared to untreated patients in both univariate (HR 2.14, CI 1.67–2.76) and multivariate models (HR 2.11, CI 1.61–2.76, Table 4). Other independent predictors of cirrhosis included diabetes (HR 1.41, CI 1.17–1.71) and higher baseline ALT (HR 1.03, 95 % CI 1.02–1.04, per 10 unit increment). Black race was protective against the development of cirrhosis (HR 0.62, 95 % CI 0.50–0.78), consistent with prior studies [13, 27]. While Latinos had a marginally significant increase in cirrhosis in univariate analysis, this effect did not persist in multivariate models. SVR was only marginally protective against cirrhosis in multivariate modeling (HR 0.61, CI 0.35–1.04). Treatment eligibility during HCV-001 (as a binary variable) had no clear effect on the development of cirrhosis (Table 2).

Figure 1 depicts the age-adjusted cumulative incidence of cirrhosis stratified by treatment group for patients without cirrhosis at baseline. Patients achieving SVR had a significantly lower incidence of cirrhosis than untreated patients ($P < 0.009$), while nonresponders had significantly more cirrhosis than untreated patients ($P = 0.009$). Very similar relationships were found when HCV-001 enrollment was taken as time zero (Figure S1).

Nearly 6 % of the cohort developed HCC during the course of the study, and 27.1 % died. The risk of HCC was highly correlated with cirrhosis, but did not differ significantly between treated and untreated patients. In proportional hazards analysis, patients with cirrhosis had a highly significant sevenfold increase in HCC (HR 7.66, CI 4.89–12.01, Table S4). Other factors independently associated with HCC included treatment nonresponse (HR

2.03, CI 1.15–3.56), older age (HR 1.02, CI 1.00–1.05), diabetes mellitus (HR 1.60, CI 1.08–2.36), and baseline ALT (HR 1.03, CI 1.02–1.05, per 10 unit increment). There was no significant difference in the incidence of HCC between untreated patients and treated patients (including all treatment response groups). SVR was not significantly protective against HCC among patients overall, nor did it confer protection among treated patients with preexisting cirrhosis (Table S4).

Improved Survival in Patients Who Received HCV Therapy

The age-adjusted death rate for the cohort overall was 7.57 per 1000 person years. For patients achieving SVR, the death rate was 3.10, while for untreated patients it was 9.01. Treated patients, regardless of outcome, experienced a significant survival benefit compared to untreated patients (HR for dying 0.58, CI 0.46–0.72, overall, and HR 0.37, CI 0.22–0.64; HR 0.21, CI 0.05–0.84; and HR 0.69, CI 0.51–0.94 for SVR, relapsers, and nonresponders, respectively) in multivariate models (Table 5). These relationships are shown in Figs. 2 and S2. Other factors significantly associated with improved survival include Latino or Black ethnicity, college education, younger age, and years of clinical follow-up. By contrast, an increased hazard for death during follow-up was seen with: HIV coinfection, cirrhosis, HCC, HCV genotypes 1 or 4 (independent predictors of treatment nonresponse), and heavy drinking in the 12 months prior to HCV-001 enrollment.

The independent effects of treatment eligibility and treatment initiation on the major outcomes (cirrhosis, HCC and death) were analyzed in subgroup analyses (Table 6). Among untreated patients, treatment eligibility compared to ineligibility conferred a survival benefit (HR 0.73, CI 0.58–0.91, Table 6). Within the group of treatment-eligible patients, receipt of antiviral treatment significantly increased the risk of cirrhosis, compared to remaining untreated (HR for cirrhosis 1.52, CI 1.17–1.98); however, treatment combined with treatment eligibility afforded a significant survival advantage over treatment-eligible but untreated patients (HR 0.72, CI 0.53–0.97, Table 6). Patients who were ineligible for treatment in HCV-001 and were never treated had the worst survival (HR for death 2.07, CI 1.63–2.62, compared to eligible and treated).

Discussion

The current HCV-002 study, a retrospective medical records review of 2,211 VA HCV patients who were prospectively enrolled and evaluated in 1999–2000, provides a long-term view of the IFNα-based antiviral treatment era. All patients underwent a formal assessment for IFNα/RBV treatment, and those who remained viremic after 2002 were often reconsidered for pegylated IFNα/ RBV. As our follow-up period closed in 2011, this cohort was not affected by the approval of combination therapy using first-generation protease inhibitors or later generations of combination oral antivirals. HCV-002 patients were more likely to undergo antiviral therapy (31.3 %) than the overall VA HCV population (21.5 %) followed during this time [13]. This finding was not unexpected since HCV treatment is highly correlated with receipt of specialty care [3, 28], and cohort patients were recruited from specialty clinics. Cohort patients also had lower age-adjusted death rates than VA HCV patients overall (3.1 and 9.0 per 1000 person years for SVR and untreated patients,

respectively), despite having been recruited from clinics which typically see patients with more significant liver disease than primary care [3].

The current study confirms and extends a number of important findings. We, and others, previously described two unexpected long-term effects of IFNα-based HCV regimens [13, 17]. First, SVR may not guarantee protection from cirrhosis, which can be diagnosed up to 8 years after viral clearance [13–15, 17]. Second, compared to untreated controls, IFNα treatment without SVR was associated with more cirrhosis. Since patients with advanced fibrosis are more likely to be treated and advanced disease is associated nonresponse, this finding could be an artifact of selection bias and unmeasured confounding. However, the association between nonresponse and cirrhosis persisted in multivariate models that included behavioral risk factors, and has been found in other studies that were able to adjust for pretreatment fibrosis stage [17]. The largest similar study to date of 110,000 VA HCV registry patients also found a twofold increase in the hazard of cirrhosis among treatment failures, after adjustment for other risk factors [13]. These results are somewhat counterintuitive, since untreated patients were more likely to have behavioral risk profiles linked to cirrhosis and HCC such as older age, recent heavy alcohol use, and HIV/HCV coinfection [13, 17]. It is possible that immune responses post-IFNα among relapsers or nonresponders have changes which place patients at risk of accelerated fibrosis progression, as is seen in post-liver transplant or HIV–HCV coinfected patients [29–31], but such mechanisms are not able to be identified in the current study.

Fewer than 27 % of treated patients achieved SVR, which conferred only a marginally significant 39 % protective effect on the long-term development of cirrhosis. These results corroborate studies of the national VA HCV registry and a recent study of San Francisco HCV cohorts, in which SVR reduced cirrhosis by only 26 and 32 %, respectively [13, 17]. Previous studies have described short-term improvements in hepatic fibrosis and a 75–85 % long-term reduction in cirrhosis after SVR when compared to treatment failures [31–33]. These studies, however, compared outcomes in SVR patients to those who failed treatment, rather than to untreated patients, a more appropriate comparison group [34–36]. In the present study, we adjust for factors differentiating treated from untreated patients; nevertheless, unmeasured social, medical, and psychiatric disease may account for some of the remaining differences. A cautious interpretation of these findings, however, suggests that the protective effects of SVR may be more modest and less enduring than is commonly accepted, since nonresponders may be more at risk for cirrhosis than untreated patients overall [34, 35, 37–40].

Whereas treatment failure had some association with cirrhosis, it was also associated with improved survival. All treated patients, including treatment failures, had improved survival compared to untreated patients. Heavy alcohol drinking and being HIV+ contributed to this relationship, as both factors were associated with lower treatment rates and also independently associated with mortality. Better survival was strongly correlated with variables that predicted HCV therapy eligibility and initiation: Latino ethnicity, college education, younger age, and a longer duration of follow-up in subspecialty clinics. Data on liver-related death could not reliably be captured in HCV-002, but robust data on cirrhosis and HCC were available. No improvements in overall survival could be attributed directly to

treatment-related reductions in cirrhosis or HCC, as liver disease was more prevalent in treated patients compared to untreated controls. Rather, improved survival in treated patients appeared to be associated with beneficial clinical and behavioral risk profiles in treatment-eligible patients. These findings suggest that avoidance of risky health behaviors and compliance with medical care may account for a significant proportion of the survival benefits associated with antiviral treatment in VA patients.

This study was limited by several factors. As a retrospective review, we used preexisting medical records to obtain outcome data. Ascertainment of cirrhosis was difficult. Only half of the study patients had liver imaging or biopsy, the principal means used for diagnosing cirrhosis. Therefore, we likely underestimated the true incidence of cirrhosis in this population. Only 8.5 % of HCV-001 patients had baseline cirrhosis, despite long duration of infection. Although lower than frequently cited 30-year cirrhosis rates of 20–40 %, these numbers are consistent with prospective HCV cohort studies [38–43]. Validation studies conducted on a sample of patient records indicated a high level of reliability for major outcomes, including HCV treatment response, cirrhosis, HCC, and death. Although unmeasured confounding may have biased the results, rigorous data collection, robust statistical methods, and the congruence of our findings with those of two previous published studies suggest that our results reflect the true experience of this cohort [13, 17]. Use of a time-dependent variable to correct for variations in time from estimated infection to treatment initiation strengthens our estimates to more closely approximate a true population hazard rate. Nevertheless, these results reflect the experience of a select group of patients and are not generalizable to the majority of VA HCV patients, who are not followed by hepatology or infectious disease specialists [3, 13].

These studies raise the question of whether IFNα treatment without SVR can lead to persistent liver injury and draw attention to the fact that even SVR itself does not offer complete protection [15, 39]. It is possible that immunostimulatory pharmacologic effects of IFNα may trigger fibrosis progression, even if HCV is eventually cleared. Alternatively, liver damage “may have been done” by many years of chronic infection, and some patients may be destined to progress to cirrhosis even if the virus is eradicated. If the latter is true, SVR in response to new IFNα-free combination treatments may not prove to be as beneficial as anticipated. As the birth cohort with prevalent HCV in the USA ages, patients will also have more liver disease and thus likely be closer to cirrhosis when they achieve SVR after 2015. These findings overall suggest that patients who previously failed IFNα-based treatment may be candidates for enhanced surveillance and should be actively considered for retreatment with new combination antivirals.

Now that the IFNα therapeutic era has largely ended, combination oral antivirals have changed HCV from a condition managed with toxic, poorly effective therapies to one that can often be cured without bad side effects. Long-term outcomes of current therapies, however, have yet to be recorded or examined. Given the national HCV burden and the current costs of therapy, it will be important to quantify the long-term hazards and benefits of these medications in high-risk populations in order to inform future treatment decisions during this transformative era in HCV therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

VA	U.S. Department of Veterans Affairs
VHA	Veterans Health Administration
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IFNα	Interferon-α
RBV	Ribavirin
SVR	Sustained virologic response
HCC	Hepatocellular carcinoma
HDI	Health data and information

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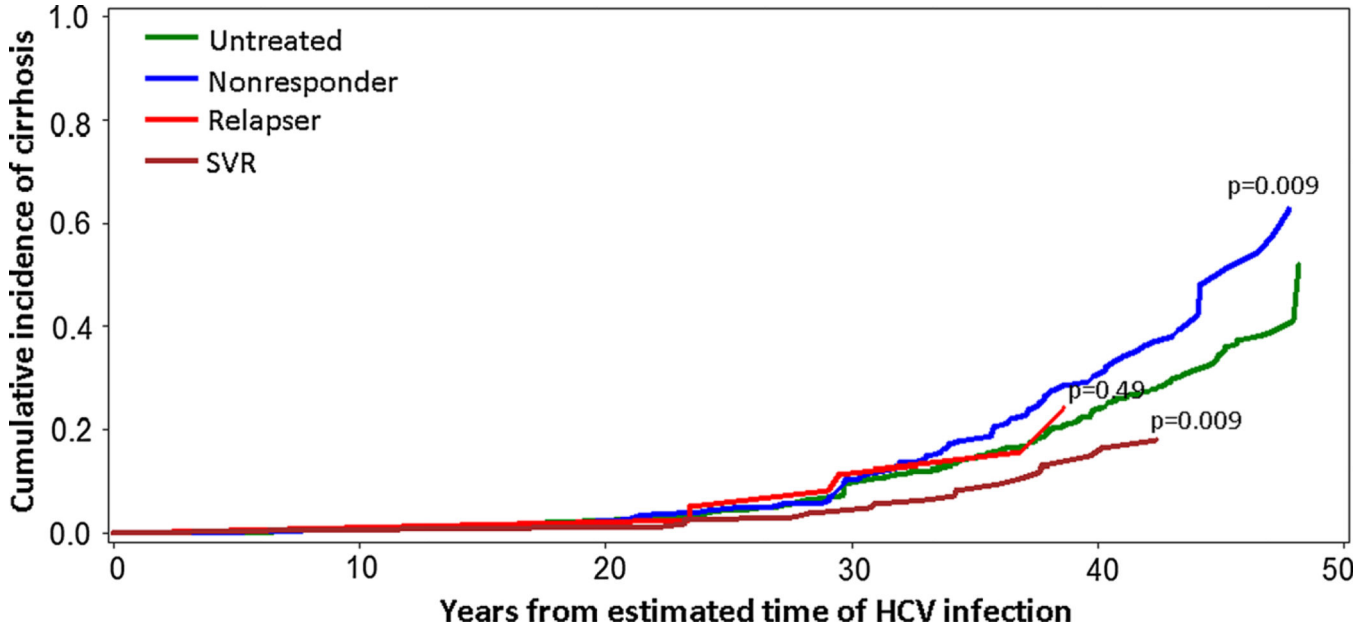

Fig. 1.

Kaplan–Meier curves showing age-adjusted cumulative incidence of cirrhosis with respect to hepatitis C treatment status and response. Treatment nonresponse is associated with a higher incidence of cirrhosis. Age-adjusted cumulative incidence of cirrhosis by treatment group, for patients without cirrhosis at baseline (patients with cirrhosis prior to treatment are included in the untreated group, which is the referent group). Nonresponders were significantly more likely to develop cirrhosis during follow-up than untreated patients. Conversely, SVR patients appeared to be significantly protected from cirrhosis

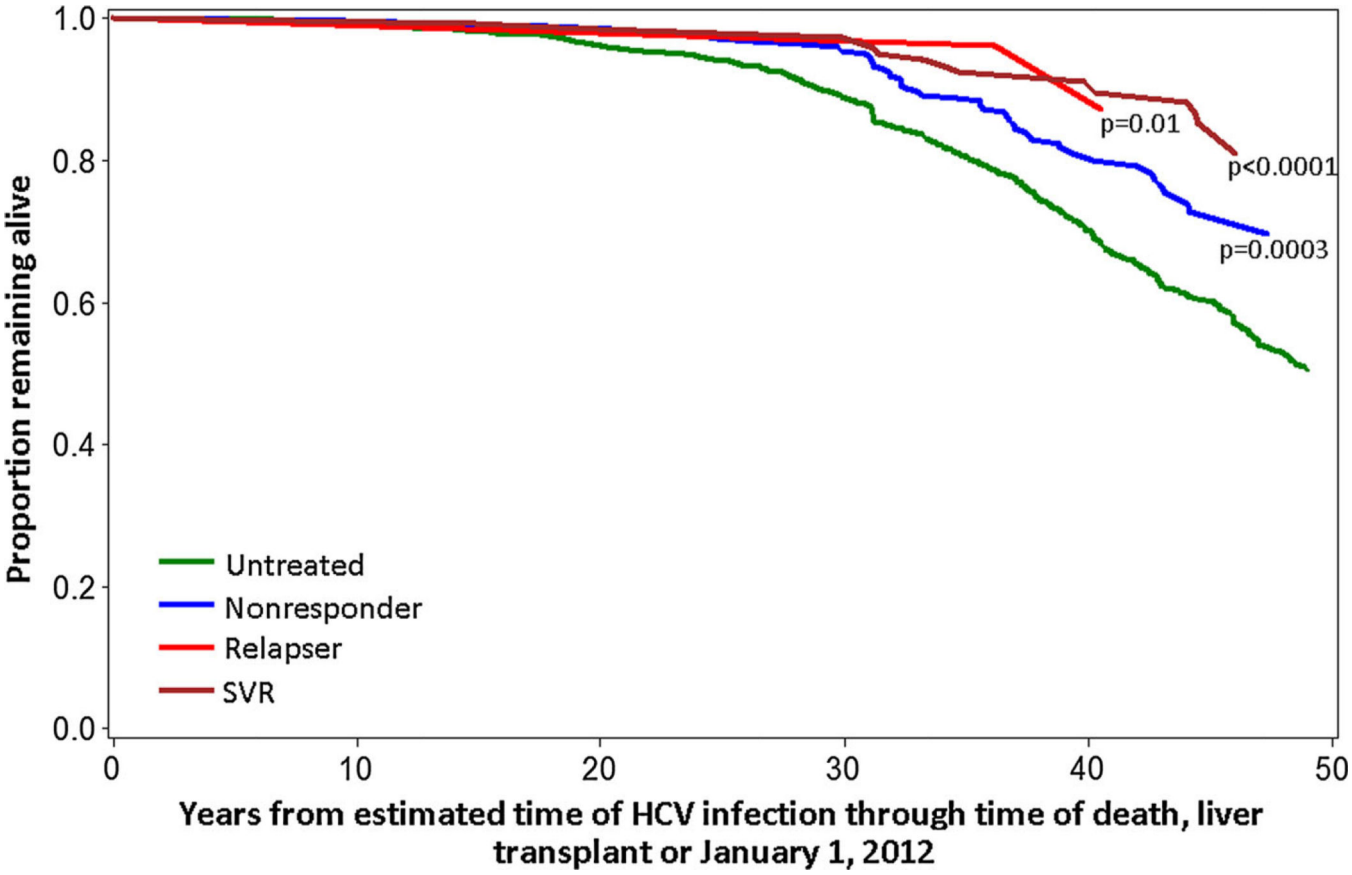

Fig. 2.

Kaplan–Meier curves showing age-adjusted survival with respect to hepatitis C treatment status and response. Survival is improved across all treatment groups (patients with cirrhosis prior to treatment are included in the untreated group, which is the referent group). All subcategories of treated patients were significantly less likely to die during follow-up than untreated patients

Table 1

Demographic and clinical characteristics of the cohort by hepatitis C treatment status at study end

Variable	Treated (*N* = 692)	Untreated (*N* = 1519)	*P* value*
Age at study entry (mean ± SD)	49.64 ± 6.29	52.20 ± 8.64	<0.0001
Gender			
Male	676 (97.7 %)	1488 (98.0 %)	0.68
Race/ethnicity			
White	395 (59.2 %)	704 (49.1 %)	0.0003
Black	166 (24.9 %)	473 (33.0 %)	
Latino	89 (13.3 %)	193 (13.5 %)	
Asian	1 (0.1 %)	8 (0.6 %)	
Native American	9 (1.3 %)	29 (2.0 %)	
Others	7 (1.0 %)	27 (1.9 %)	
Completed some college or higher	347 (55.8 %)	631 (46.2 %)	<0.0001
History of incarceration	358 (51.7 %)	799 (52.6 %)	0.71
HCV genotype			
1 or 4	484 (71.5 %)	932 (71.6 %)	<0.0001
2 or 3	181 (26.7 %)	277 (21.3 %)	
Mixed	12 (1.8 %)	92 (7.1 %)	
HIV+	73 (10.5 %)	225 (14.8 %)	0.006
Baseline BMI (mean ± SD)	28.78 ± 4.93	28.13 ± 5.20	0.005
Baseline ALT (mean ± SD)	105.82 ± 104.79	74.02 ± 64.48	<0.0001
Diabetes mellitus ever	186 (26.9 %)	440 (29.0 %)	0.31
History of heavy alcohol use at any time prior to HCV-001 (>80 g/day)	369 (53.3 %)	835 (55.0 %)	0.47
Heavy alcohol use (>80 g/day) within 12 months prior to HCV-001	51 (7.4 %)	192 (12.6 %)	0.0002
Ever injected drugs	396 (57.2 %)	829 (54.6 %)	0.25
Substance abuse contraindicating treatment during HCV-001	59 (8.5 %)	271 (17.8 %)	<0.0001
Psychiatric condition contraindicating treatment during HCV-001	56 (8.1 %)	236 (15.5 %)	<0.0001
Liver biopsy (at least one)	585 (84.5 %)	647 (42.6 %)	<0.0001
Liver imaging (at least one)	370 (53.5 %)	649 (42.7 %)	<0.0001
Cirrhosis at baseline (HCV-001)	109 (15.8 %)	80 (5.3 %)	<0.0001
Cirrhosis ever (baseline through end of HCV-002 follow-up)	224 (32.4 %)	347 (22.8 %)	<0.0001
HCC ever	43 (6.2 %)	84 (5.5 %)	0.52
Liver transplant ever	11 (1.6 %)	17 (1.1 %)	0.36
Death during follow-up	112 (16.2 %)	488 (32.1 %)	<0.0001
Years of follow-up (mean ± SD)	9.41 ± 2.23	8.08 ± 3.24	<0.0001

**P* values were calculated from Chi-square or Fisher's exact test for categorical variables and Student's *t* test or Wilcoxon rank sum test for continuous variables

Table 2

Demographic and clinical characteristics by treatment eligibility in HCV-001 and treatment status at study end

Variable	Eligible in HCV-001 and SVR (*N* = 122)	Eligible in HCV-001 and non-SVR (*N* = 340)	Eligible in HCV-001 and untreated (*N* = 371)	Ineligible in HCV-001 and SVR (*N* = 63)	Ineligible in HCV-001 and non-SVR (*N* = 167)	Ineligible in HCV-001 and untreated (*N* = 1148)	P value*
Age at study entry (mean ± STD)	49.64 ± 7.24	49.98 ± 6.18	50.89 ± 7.09	49.40 ± 7.06	49.03 ± 5.39	52.62 ± 9.05	<0.0001
Years of infection at study entry (mean ± STD)	25.32 ± 9.50	26.25 ± 8.49	26.51 ± 8.49	26.16 ± 8.16	24.76 ± 8.71	26.34 ± 8.69	0.15
Race ethnicity							
White	97 (80.2 %)	177 (53.0 %)	170 (47.0 %)	43 (75.4 %)	78 (50.3 %)	534 (49.8 %)	<0.0001
Black	14 (11.6 %)	100 (29.9 %)	126 (34.8 %)	8 (14.0 %)	44 (28.4 %)	347 (32.4 %)	
Latino	8 (6.6 %)	51 (15.3 %)	56 (15.5 %)	4 (7.0 %)	26 (16.8 %)	137 (12.8 %)	
Others	2 (1.7 %)	6 (1.8 %)	10 (2.8 %)	2 (3.5 %)	7 (4.5 %)	54 (5.0 %)	
Cirrhosis							
Never had cirrhosis	94 (77.0 %)	210 (61.8 %)	284 (76.5 %)	54 (85.7 %)	110 (65.9 %)	888 (77.4 %)	<0.0001
Cirrhosis before treatment/start date for untreated	11 (9.0 %)	55 (16.2 %)	23 (6.2 %)	8 (12.7 %)	35 (21.0 %)	57 (5.0 %)	
Developed cirrhosis after treatment/start date for untreated	17 (13.9 %)	75 (22.1 %)	64 (17.3 %)	1 (1.6 %)	22 (13.2 %)	203 (17.7 %)	
History of heavy alcohol use within 12 months prior to HCV-001 ([80 g/day)	4 (3.3 %)	19 (5.6 %)	32 (8.6 %)	8 (12.7 %)	20 (12.0 %)	160 (13.9 %)	<0.0001
Substance abuse contraindicating treatment during HCV-001	0 (0.0 %)	9 (2.6 %)	6 (1.6 %)	10 (15.9 %)	40 (24.0 %)	265 (23.1 %)	<0.0001
Psychiatric condition contraindicating treatment during HCV-001	2 (1.6 %)	7 (2.1 %)	13 (3.5 %)	10 (15.9 %)	37 (22.2 %)	223 (19.4 %)	<0.0001
Diabetes Mellitus ever	25 (20.5 %)	102 (30.0 %)	100 (27.0 %)	14 (22.2 %)	45 (26.9 %)	340 (29.6 %)	0.24
HCC ever	1 (0.8 %)	30 (8.8 %)	22 (5.9 %)	1 (1.6 %)	11 (6.6 %)	62 (5.4 %)	0.02
Death during follow-up	18 (14.8 %)	67 (19.7 %)	95 (25.6 %)	3 (4.8 %)	24 (14.4 %)	393 (34.2 %)	<0.0001

**P* values were calculated from Chi-square or Fisher's exact test for categorical variables and Student's *t* test or Wilcoxon rank sum test for continuous variables

† Not applicable

Table 3

Factors associated with SVR among treated patients

Variable	Non-SVR (*N* = 507)	SVR (*N* = 185)	OR (95 % CI)	*P* value
Age at study entry				
Mean ± STD	49.66 ± 5.94	49.56 ± 7.16	1.00 (0.97–1.03)	0.9270
Race/ethnicity				
Black/African American	144 (86.7 %)	22 (13.3 %)	0.34 (0.12–0.99)	0.0495
Other races	363 (69.0 %)	163 (31.0 %)	Ref	
Gender				
Male	498 (73.7 %)	178 (26.3 %)	0.46 (0.05–4.19)	0.2709
Female	9 (56.3 %)	7 (43.8 %)	Ref	
Completed some college or higher				
Yes	243 (70.0 %)	104 (30.0 %)	1.56 (0.69–3.50)	0.1432
No	216 (78.5 %)	59 (21.5 %)	Ref	
HCV genotype				
1 or 4	390 (80.6 %)	94 (19.4 %)	0.30 (0.18–0.51)	0.0032
Mixed GT	8 (66.7 %)	4 (33.3 %)	0.63 (0.11–3.63)	0.5060
2 or 3	101 (55.8 %)	80 (44.2 %)	Ref	
Baseline ALT				
Mean ± STD	103.5 ± 110.33	112.61 ± 86.54	1.00 (1.00–1.00)	0.3556
HIV+				
Yes	65 (89.0 %)	8 (11.0 %)	0.31 (0.06–1.65)	0.0952
No	442 (71.4 %)	177 (28.6 %)	Ref	
Diabetes mellitus				
Yes	147 (79.0 %)	39 (21.0 %)	0.65 (0.27–1.59)	0.1757
No	360 (71.1 %)	146 (28.9 %)	Ref	
Heavy alcohol use within 12 months prior to HCV-001 enrollment				
Yes	39 (76.5 %)	12 (23.5 %)	0.83 (0.19–3.63)	0.6453
No	468 (73.0 %)	173 (27.0 %)	Ref	
Psychiatric condition contraindicating treatment during HCV-001				
Yes	44 (78.6 %)	12 (21.4 %)	0.73 (0.17–3.14)	0.4528
No	463 (72.8 %)	173 (27.2 %)	Ref	
Substance abuse contraindicating treatment during HCV-001				
Yes	49 (83.1 %)	10 (16.9 %)	0.53 (0.11–2.48)	0.2183
No	458 (72.4 %)	175 (27.6 %)	Ref	
Pretreatment cirrhosis				
Yes	90 (82.6 %)	19 (17.4 %)	0.53 (0.17–1.70)	0.1455
No	417 (71.5 %)	166 (28.5 %)	Ref	
Treatment length (week)				
Mean ± STD	30.17 ± 23.59	36.10 ± 17.03	1.01 (1.00–1.02)	0.0062
Interferon type				
Standard IFN-α	218 (65.9 %)	113 (34.1 %)	2.28 (1.60–3.25)	<0.0001

Variable	Non-SVR (*N* = 507)	SVR (*N* = 185)	OR (95 % CI)	*P* value
Pegylated IFN-α	277 (81.5 %)	63 (18.5 %)	Ref	

* OR is SVR versus non-SVR

Table 4

Factors associated with cirrhosis stratified by caseload volume

Variable	Univariate model HR (95 % CI)	*P* value	Multivariate model HR (95 % CI)	*P* value
HCV treatment outcome				
Untreated[a]	Ref		Ref	
Nonresponder	2.14 (1.67–2.76)	<0.0001	2.11 (1.61–2.76)	<0.0001
Relapser	1.08 (0.48–2.42)	0.8586	0.94 (0.38–2.28)	0.8867
SVR	0.77 (0.48–1.24)	0.2840	0.61 (0.35–1.04)	0.0717
ETD/unknown outcome	1.07 (0.55–2.08)	0.8443	0.60 (0.27–1.33)	0.2076
Age at study entry	0.99 (0.98–1.00)	0.1058	1.00 (0.98–1.01)	0.6812
Male gender	1.48 (0.76–2.86)	0.3360		
Race/ethnicity				
Black	0.64 (0.52–0.79)	<0.0001	0.62 (0.50–0.78)	<0.0001
Latino	1.19 (0.94–1.51)	0.1465	1.03 (0.80–1.34)	0.8036
Other	0.96 (0.61–1.50)	0.8506	1.13 (0.70–1.80)	0.6220
White	Ref			
Completed some college or higher	1.09 (0.91–1.29)	0.3646		
HCV genotype	1.03 (0.86–1.24)	0.7445		
1 or 4				
Mixed genotype	0.76 (0.47–1.21)	0.2410		
2 or 3	Ref			
HIV+	1.01 (0.79–1.28)	0.9678		
Diabetes ever	1.39 (1.16–1.65)	0.0002	1.41 (1.17–1.71)	0.0004
Baseline ALT per 10 unit increment	1.03 (1.02–1.04)	<0.0001	1.03 (1.02–1.04)	<0.0001
Heavy alcohol use ([80 g/day) within 12 months Prior to HCV-001 enrollment	1.01 (0.77–1.32)	0.9530		
Psychiatric condition contraindicating treatment during HCV-001	0.99 (0.77–1.27)	0.9160		
Substance abuse contraindicating treatment during HCV-001	0.97 (0.77–1.23)	0.8058		

[a]Untreated includes patients diagnosed with cirrhosis before first IFN/RBV treatment

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Table 5

Factors associated with death stratified by caseload volume (N = 2211)

Variable	Univariate model HR (95 % CI)	*P* value	Multivariate model HR (95 % CI)	*P* value
HCV treatment outcome				
No treatment[a]	Ref		Ref	
Nonresponder	0.57 (0.44–0.76)	0.0001	0.69 (0.51–0.94)	0.0171
Relapser	0.15 (0.04–0.59)	0.0069	0.21 (0.05–0.84)	0.0274
SVR	0.30 (0.19–0.49)	<0.0001	0.37 (0.22–0.64)	0.0004
ETD/unknown treatment response	0.58 (0.35–0.97)	0.0394	0.69 (0.41–1.19)	0.1835
Age at study entry	1.03 (1.02–1.04)	<0.0001	1.03 (1.01–1.04)	<0.0001
Race/ethnicity				
Black	0.85 (0.71–1.03)	0.0956	0.68 (0.54–0.85)	0.0007
Latino	0.77 (0.59–1.01)	0.0566	0.60 (0.43–0.82)	0.0016
Other race	0.85 (0.53–1.35)	0.4908	0.67 (0.39–1.15)	0.1468
White	Ref			
Completed college or higher	0.77 (0.65–0.92)	0.0033	0.85 (0.70–1.03)	0.0885
HCV genotype	0.78 (0.65–0.93)	0.0050		
1 or 4				
Mixed genotype	1.10 (0.76–1.57)	0.6222		
2 or 3	Ref			
HIV+	1.51 (1.22–1.86)	0.0001	1.71 (1.33–2.18)	<0.0001
Baseline ALT per 10 unit increment	1.00 (0.99–1.01)	0.8469		
Diabetes mellitus ever	1.00 (0.83–1.19)	0.9729		
Cirrhosis ever	1.48 (1.25–1.75)	<0.0001	1.27 (1.02–1.57)	0.0294
HCC	2.37 (1.86–3.02)	<0.0001	1.92 (1.41–2.60)	<0.0001
Heavy alcohol use ([80 g/day) within 12 months prior to HCV-001 enrollment	1.35 (1.06–1.71)	0.0153	1.50 (1.14–1.96)	0.0033
Psychiatric condition contraindicating treatment during HCV-001	1.05 (0.83–1.34)	0.6792		
Substance abuse contraindicating treatment during HCV-001	1.14 (0.91–1.42)	0.2488		

[a]Untreated includes patients diagnosed with cirrhosis before first IFN/RBV treatment

Table 6

Age-adjusted risk of cirrhosis, HCC, and death by treatment eligibility in HCV-001 and treatment status at study end

	Developing cirrhosis during follow-up		Developing HCC during follow-up		Death during follow-up	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Eligible in HCV-001 and treated (*N* = 462)	1.15 (0.86–1.55)	0.3494	1.29 (0.62–2.69)	0.4976	1.45 (0.93–2.27)	0.0983
Ineligible in HCV-001 and treated (*N* = 230)	Ref		Ref		Ref	
Eligible in HCV-001 and untreated (*N* = 371)	0.99 (0.77–1.27)	0.9668	1.02 (0.63–1.67)	0.9347	0.73 (0.58–0.91)	0.0061
Ineligible in HCV-001 and untreated (*N* = 1148)	Ref		Ref		Ref	
Eligible in HCV-001 and treated (*N* = 462)	1.52 (1.17–1.98)	0.0019	1.03 (0.59–1.83)	0.9151	0.72 (0.53–0.97)	0.0294
Eligible in HCV-001 and untreated (*N* = 371)	Ref		Ref		Ref	