Disease Progression in Patients With Hepatitis C Virus Infection Treated With Direct-Acting Antiviral Agents

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BACKGROUND & AIMS: **Little is known about how a sustained virologic response (SVR) to treatment of hepatitis C virus infection with direct-acting antivirals (DAAs) affects patient mortality and development of new liver-related events. We aimed to evaluate the incidence of disease progression in patients treated with DAAs.**

METHODS: **We performed a prospective multicenter cohort study of 1760 patients who received DAA treatment at 23 hospitals in Latin America, from May 1, 2016, through November 21, 2019. We excluded patients with a history of liver decompensation, hepatocellular carcinoma (HCC), or solid-organ transplantation. Disease progression after initiation of DAA therapy included any of the following new events: liver decompensation, HCC, liver transplantation, or death. Evaluation of variables associated with the primary outcome was conducted using a time-dependent Cox proportional hazards models.**

RESULTS: **During a median follow-up period of 26.2 months (interquartile range, 15.3–37.5 mo), the overall cumulative incidence of disease progression was 4.1% (95% CI, 3.2%–5.1%), and after SVR assessment was 3.6% (95% CI, 2.7%–4.7%). Baseline variables associated with disease progression were advanced liver fibrosis (hazard ratio [HR], 3.4; 95% CI, 1.2–9.6), clinically significant portal hypertension (HR, 2.1; 95% CI, 1.2–3.8), and level of albumin less than 3.5 mg/dL (HR, 4.1; 95% CI, 2.3–7.6), adjusted for SVR achievement as a time covariable. Attaining an**

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Abbreviations used in this paper: CSPH, clinically significant portal hypertension; DAA, direct-acting antivirals; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IQR, interquartile range; LALREAN, Latin American Liver Research, Educational and Awareness Network; SVR, sustained virologic response.

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SVR reduced the risk of liver decompensation (HR, 0.3; 95% CI, 0.1–0.8; $P = .016$) and de novo HCC (HR, 0.2; 95% CI, 0.1%–0.8%; $P = .02$) in the overall cohort.

CONCLUSIONS: **Treatment of hepatitis C virus infection with DAAs significantly reduces the risk of new liver-related complications and should be offered to all patients, regardless of disease stage. Clinicaltrials.gov: NCT03775798.**

Keywords: Viral Infection; Long-Term; Survival; Cancer.

Therapeutic options for the treatment of chronic hepatitis C virus (HCV) infection have evolved rapidly over the past 5 to 7 years with the development of highly effective all-oral, direct-acting antiviral (DAA) therapies. These drugs can achieve sustained virologic response (SVR) or cure in more than 95% of patients with minimal side effects and with a short treatment duration.[1,2] However, there is a marked regional disparity concerning access to these novel therapies. Although some countries allow an unrestricted use of DAAs (ie, Spain, Australia), other regions experience several structural limitations to DAA access (ie, Latin America).[3] Expanding access to HCV treatment should be a political priority, largely because the achievement of SVR results in substantial reductions in hepatocellular carcinoma (HCC) and liver-related mortality.[2,4,5] However, the risk of hepatic decompensation is not entirely eradicated after cure of HCV infection.[2,6,7] This finding can be attributed to the fact that the safety of DAAs permits their use in patients with portal hypertension and a history of liver decompensation. Eradication efforts therefore should be made in individuals with chronic HCV at earlier stages, before the onset of cirrhosis and hepatic decompensation. Nevertheless, very few studies have evaluated the clinical outcomes of patients treated with DAAs with no history of decompensated liver disease.[4] Thus, new data are needed to help support the use of costlier all-oral antiviral therapies, particularly in developing countries.

Quality prospective data describing the outcomes of patients with HCV after eradication of infection with antiviral treatment are needed. Therefore, our aim was to evaluate the incidence and baseline risk factors of disease progression in patients with HCV and no prior history of liver decompensation, HCC, or solid-organ transplantation after treatment with DAAs. We also intend to propose a risk-stratification model to identify patients who present with a higher risk of disease progression after DAA treatment. We analyzed these end points in a large prospective cohort from the Latin American Liver Research, Educational and Awareness Network (LALREAN).

Patients and Methods

Study Design, Setting, and Participating Centers

This prospective cohort study was performed from May 1, 2016, through November 21, 2019, in 23 different Hospitals in Argentina, Brazil, Chile, Colombia, and Uruguay. This study has been registered in an open public registry (clinicaltrials.gov: NCT03775798). Each Ethical Committee from all participating centers approved the study protocol, which was in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[8] Written informed consent was obtained from each patient before enrollment, following ethical standards (institutional and national), as well as those mandated by the Helsinki Declaration of 1975, as revised in 2008. All authors had access to the study data and reviewed and approved the final version of this manuscript.

Cohort Characteristics and Study Variables Recorded Before Direct-Acting Antiviral Initiation

All eligible patients were enrolled consecutively at each clinical site. Study data were registered prospectively into a web-based electronic system (https://temasis.com.ar/lalrean-org). Central revision and resubmission was requested in cases of erroneous or missing data.

Adult patients, older than 18 years of age, with chronic HCV infection, confirmed with the quantitative real-time polymerase method, and with any degree of liver fibrosis were included. All patients who received at least 1 pill of any DAA were included in the study, as in an intention-to-treat analysis. The primary exclusion criteria were a previous history of the following: (1) decompensated liver disease, as determined by a history of ascites, variceal hemorrhage, hepatic encephalopathy, or other complications secondary to portal hypertension; (2) HCC; and (3) any solid-organ transplantation. Liver stiffness measurements were recorded as a continuous variable in kilopascals as obtained from liver elastography and categorized according to international consensus guidelines.[9] Cut-off values for advanced fibrosis and cirrhosis were 9.5 and 12.5 kPa, respectively, with transient elastography. A specific cut-off value of 23 kPa was defined as risk for development of HCC, as previously reported elsewhere.[10] Clinically significant portal hypertension (CSPH) was defined as the presence of gastroesophageal varices on endoscopy or the presence of a platelet count less than 100,000/mm^3 with splenomegaly (spleen >120 mm on radiographic imaging).[11]

Primary Outcome Definition

The primary end point analyzed was the cumulative incidence of disease progression after DAA initiation, defined as the occurrence of any of the following: (1) liver decompensation events (ascites, variceal hemorrhage, hepatic encephalopathy, or jaundice), (2) de novo HCC, (3) need for liver transplantation, or (4) death. The date of the first event was determined for cumulative failure curves. Death was categorized further as liver-related and non–liver-related. All patients underwent HCC surveillance before and after DAAs and HCC was diagnosed according to international guidelines.[12]

Sample Size Calculations and Statistical Analysis

The sample size was calculated based on an annual incidence of the primary end point of 2.9% to 4% as previously reported,[4] including a minimum number of 60 primary events during the first 24 months of follow-up evaluation. Assuming a type I error of 5% ($P < .05$) and a type II error of 0.20 (80% power), a total sample size of at least 1713 patients needed to be enrolled in the study. We estimated 5% to 10% losses to follow-up evaluation, with a total estimated sample size of 1899 patients to be recruited.

Kaplan–Meier survival and cumulative incidence curves were compared using the log-rank test. We estimated the risk of developing disease progression at any time point during follow-up evaluation accounting for baseline pretreatment variables by conducting a multivariable Cox regression analysis (hazard ratios [HRs] and 95% CI estimations). Cumulative hazard curves were assessed (Nelson–Aelen cumulative function). The length of follow-up evaluation was recorded from the date of DAA initiation until death or last visit. For censoring and failure events, each date of the first primary event was registered (decompensated cirrhosis, liver transplantation, HCC, or death), whichever occurred first (failure event and time to event were evaluated). Adjustment of each Cox model was evaluated for proportional hazards (log-minus-log curves, cumulative hazard Cox regression curves, smoothed hazard estimates, and Schoenfeld residuals test). Calibration was assessed by comparison of observed and predicted curves and evaluation of the models' goodness of fit by the Harrell c-statistic index.

In addition, we performed a time-covariate analysis. The exposure period was divided into before SVR (from the date of DAA initiation to the date of sustained virologic response at week 12 after completion of treatment evaluation) and after SVR evaluation (from the date of SVR to last follow-up evaluation). This SVR time-dependent covariate was included in the final Cox model to adjust for the effect of baseline variables with SVR achievement during follow-up evaluation. Among patients in whom SVR status was evaluated according to the time of follow-up evaluation, the absolute risk reduction and the number needed to treat to prevent 1 case of disease progression were calculated.

Finally, 2 sensitivity analysis were conducted: excluding patients who were coinfected with human immunodeficiency virus (HIV) and including patients with a full-course DAA treatment. Data were analyzed with STATA 13.0 (StataCorp, College Station, TX).

Additional information regarding the methods used is provided in the Supplementary Methods section.

What You Need to Know

Background

Little is known about how a sustained virologic response to treatment of hepatitis C virus (HCV) infection with direct-acting antivirals (DAAs) affects patient mortality and development of new liver-related events.

Findings

A prospective study of 1760 patients who received DAA treatment at 23 hospitals in Latin America found that treatment of HCV infection with DAAs significantly reduced the risk of new liver-related complications.

Implications for patient care

DAAs should be offered to all patients with HCV infection, regardless of disease stage.

Results

From a total of 2491 HCV-infected patients prospectively followed up and enrolled in LALREAN's registry, 1760 were eligible for study (Supplementary Figure 1). Baseline characteristics of the study population are shown in Table 1. Overall, SVR was assessed in 1414 patients with an SVR rate of 96.6% (95% CI, 95.5–97.5). The most frequently used antiviral regimen was sofosbuvir + daclatasvir in 1158 (65.8%) patients, followed by paritaprevir/r/ombitasvir/dasabuvir in 216 (12.3%) and sofosbuvir/ledipasvir in 128 (7.7%) patients. Ribavirin was used in 599 (34.0%) patients and SVR rates were not significantly different among genotypes. Late relapse or HCV re-infection has not been reported during follow-up evaluation.

Cumulative Incidence of Disease Progression

During a median follow-up period of 26.2 months (interquartile range [IQR], 15.3–37.5 mo), 72 patients presented with evidence of disease progression, with a cumulative incidence of 4.1% (95% CI, 3.2%–5.1%). The median time to disease progression from DAA initiation was 12.9 months (IQR, 8.9–24.5 mo). Only 3 patients

Table 1. Baseline Patient Characteristics (n = 1760), Excluding Patients With Previous Liver Decompensation Events and Those Who Underwent Solid-Organ Transplantation

Variable	Values
Age, *y*, means ± SD	59 ± 12
Male sex, n (%)	930 (52.8)
Body mass index, means ± SD	26.5 ± 4.2
HCV genotype, n (%)	
1a	480 (27.4)
1b	695 (39.8)
1 (without subgenotype)	89 (5.1)
2	164 (9.4)
3	276 (15.7)
4	32 (1.8)
Unknown	14 (0.8)
Comorbidities, n (%)	
Hypertension	470 (26.7)
Diabetes mellitus	225 (12.8)
Ischemic heart disease	58 (3.3)
COPD	23 (1.3)
Renal replacement therapy	37 (2.1)
HIV co-infection, n (%)	239 (13.6)
Liver fibrosis grade, n (%)	
F0–F1	472 (26.3)
F2	160 (9.1)
F3	259 (14.7)
F4	869 (49.4)
Previous IFN-based regimens, n (%)	506 (28.7)
Previous IFN + telaprevir or boceprevir, n (%)	104 (5.9)

COPD, chronic obstructive pulmonary disease; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon.

presented with disease progression during the first 3 months after DAA initiation (4.2%), and 51 events occurred after SVR evaluation (70.8%). The cumulative incidence of disease progression after SVR evaluation was 3.6% (95% CI, 2.7%–4.7%), during a median time from SVR evaluation of 18.1 months (IQR, 10.6–29.5 mo).

Overall, 14 patients died (8 were liver-related deaths and 6 were non–liver-related deaths), 58 patients presented with a new liver decompensation event, 14 patients underwent liver transplantation, and 32 patients developed de novo HCC. Interestingly, 8 patients with mild to moderate fibrosis (F0–F2) had disease progression, including 4 patients who developed HCC. The cumulative incidence of disease progression at 12 and 24 months was 1.9% (95% CI, 1.3%–2.7%) and 3.1% (95% CI, 2.3%–4.0%), respectively (Supplementary Figure 2). The corresponding cumulative incidence of individual events was as follows: (1) liver decompensation, 3.3% (95% CI, 2.5%–4.2%); (2) HCC, 1.8% (95% CI, 1.2%–2.5%); and (3) death, 0.8% (95% CI, 0.4%–1.3%).

Risk Factors for Disease Progression

The cumulative incidence of disease progression was higher in individuals with advanced fibrosis (F3–F4) (5.7%; 95% CI, 4.4%–7.2%), in comparison with patients with mild to moderate fibrosis (F0–F2) (1.3%; 95% CI, 0.5%–2.5%; $P = .0006$) (Figure 1*A*). In univariate Cox regression analysis, pretreatment variables associated with disease progression were male sex, CSPH, albumin level less than 3.5 mg/dL, platelet count less than 100,000 mm^3, and liver fibrosis grades 3 and 4 (Table 2). Variables associated independently with the composite end-point were F3 to F4 fibrosis (HR, 3.4; 95% CI, 1.2;9.6), CSPH (HR, 2.1; 95% CI, 1.2–3.8), and albumin level less than 3.5 mg/dL (HR, 4.1; 95% CI, 2.3–7.6), adjusted for SVR achievement (HR, 0.3; 95% CI, 0.1–0.8) (Table 2). This effect remained after adjusting for SVR time-dependent covariate analysis (Table 3).

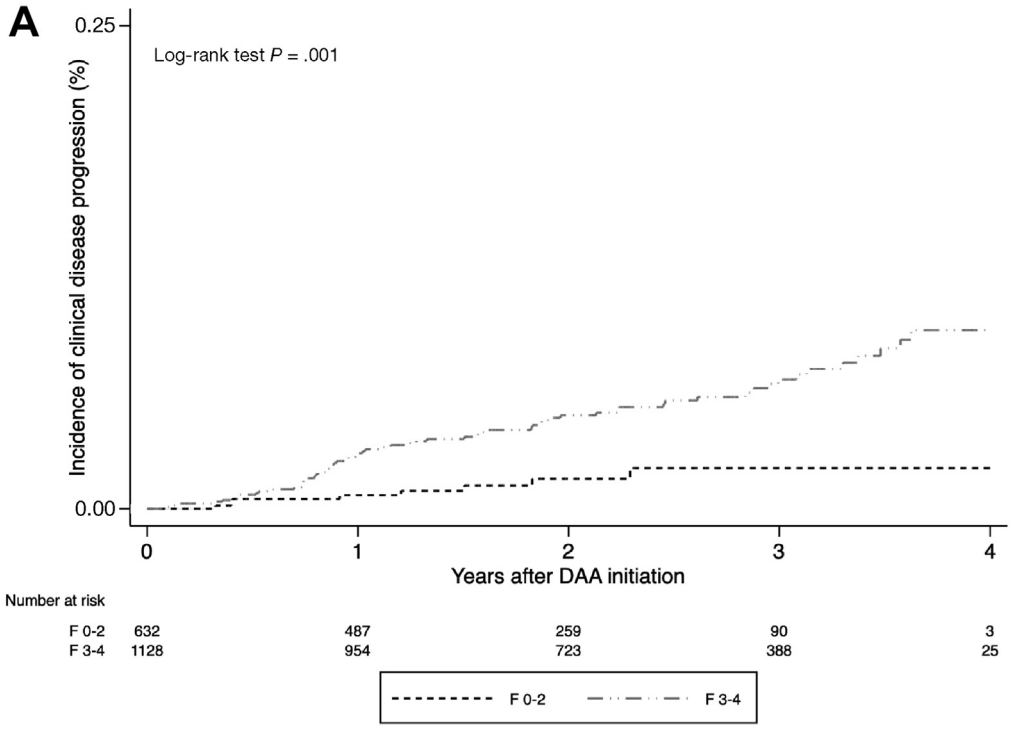
From this final multivariable Cox model, we performed a risk-stratification analysis according to the number of independently associated baseline variables. Subjects with 0 (n = 523), 1 (n = 778), 2 (n = 379), and 3 (n = 80) pretreatment variables presented with a cumulative incidence of disease progression of 0.4% (95% CI, 0.04%–1.3%), 3.3% (95% CI, 2.2%–4.8%), 6.6% (95% CI, 4.3%–9.6%), and 23.7% (95% CI, 14.9%–34.6%), respectively (Figure 2).

Impact of Sustained Virologic Response on Disease Progression

Patients achieving SVR had a lower cumulative incidence of disease progression (non-SVR, 8.3% [95% CI, 2.3%–20.0%] vs SVR, 3.9% [95% CI, 2.9%–5.0%]) (Figure 1*B*), with a HR of 0.2 (95% CI, 0.1–0.8) (Table 3). Thus, achieving SVR was associated with an 80% relative reduction for disease progression with an absolute risk difference of -0.044 (95% CI, -0.02 to -0.009) when compared with DAA failure. This represented a number needed to treat of 23 patients to prevent 1 case of disease progression. In a stratified analysis, the impact of achieving SVR had a trend toward a lower incidence of disease progression in patients with advanced liver fibrosis (HR, 0.4; 95% CI, 0.1–1.3), and in those with mild to moderate fibrosis (HR, 0.1; 95% CI, 0.01–1.13) (Table 4). Specifically, SVR was associated with a lower incidence of liver decompensation in patients with advanced fibrosis, whereas the incidence of HCC was lower in those with mild to moderate fibrosis (Table 4). Finally, in the overall cohort, SVR significantly reduced the risk of liver decompensation (HR, 0.3; 95% CI, 0.1–0.8; $P = .016$) and de novo HCC (HR, 0.2; 95% CI, 0.1–0.8; $P = .02$) from the date of SVR assessment to the last follow-up evaluation.

Sensitivity Analysis

After excluding patients with HIV coinfection, baseline variables associated with disease progression were CSPH (HR, 2.2; 95% CI, 1.1–4.3) and albumin level less than 3.5 mg/dL (HR, 5.4; 95% CI, 2.9–10.0) (Supplementary Table 1). Advanced liver fibrosis had a



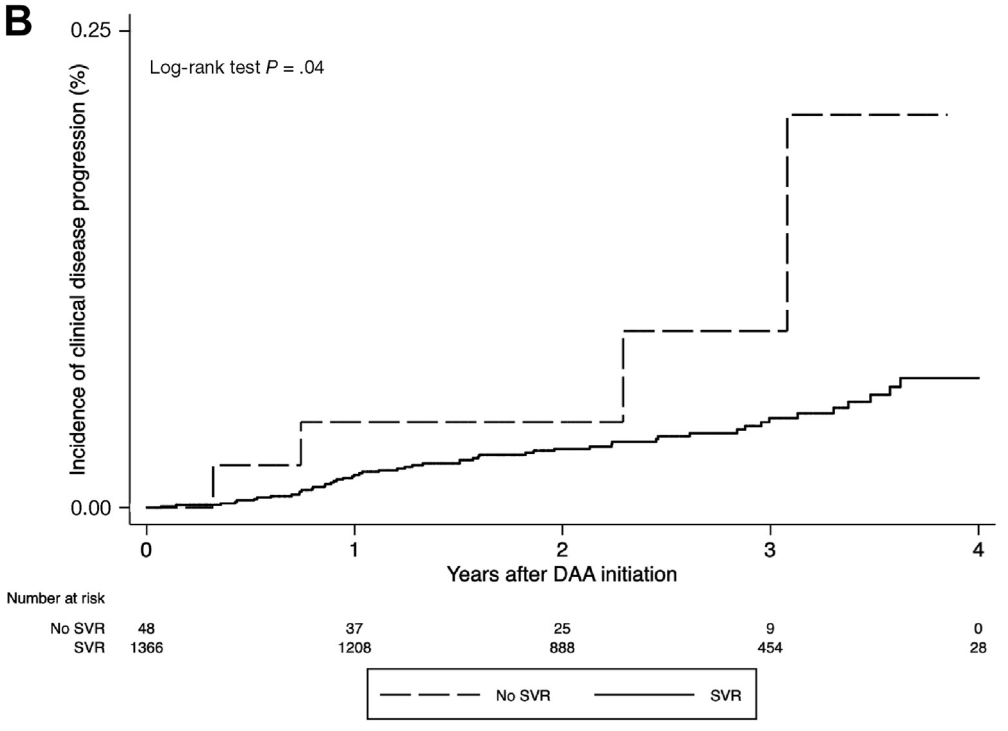


Figure 1. (*A*) Cumulative incidence of disease progression according to liver fibrosis stage (F0–F2 vs F3–F4). F3 to F4, 5.7% (95% CI, 4.4–7.2) vs F0 to F2, 1.3% (95% CI, 0.5–2.5) ($P = .0006$). (*B*) Cumulative incidence of disease progression according to sustained virologic response (SVR). Non-SVR, 8.3% (95% CI, 2.3–20.0) vs SVR, 3.9% (95% CI, 2.9–5.0) ($P = .04$). DAA, direct-acting antiviral.

clinical trend to be associated with the primary outcome (F3–F4 fibrosis: HR, 2.0; 95% CI, 0.8–4.8). A full course of DAA treatment analysis did not significantly change the effect of baseline variables associated with disease progression (Supplementary Table 2).

Discussion

Results of this large prospective cohort study from the LALREAN registry show a cumulative incidence of overall mortality, decompensated liver disease, and de novo HCC of 4.1% in those patients who received all-oral antiviral therapies for HCV. As expected, the cumulative incidence of decompensation events was higher in patients who did not achieve SVR and in those with advanced liver fibrosis stage. We also identified 3 independent baseline variables associated with disease progression (CSPH, liver fibrosis grades 3–4, and hypoalbuminemia), which allowed us to stratify patients into 3 different risk groups. Moreover, these effects still

Table 2. Cox Regression Analysis for Baseline Predictors of Clinical Disease Progression Adjusted for SVR Achievement (n = 1760)

Variable	Event, % (95% CI)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age, *y*		0.99 (0.97–1.09)	.28		
Sex		1.5 (0.9–2.4)	.09	1.2 (0.7–2.2)	.49
Male, n = 930	4.9 (3.6–6.5)				
Female, n = 830	3.1 (2.0–4.5)				
BMI		0.9 (0.5–1.9)	.90		
>30, n = 214	4.7 (2.3–8.4)				
≤30, n = 1000	4.7 (3.5–6.2)				
Diabetes mellitus		1.2 (0.6–2.2)	.63		
Yes, n = 225	4.9 (2.5–8.6)				
No, n = 1535	4.0 (3.0–5.1)				
HIV co-infection		1.5 (0.8–2.8)	.18		
Yes, n = 227	5.0 (2.6–8.6)				
No, n = 1461	3.9 (2.9–5.0)				
Previous IFN regimens		0.9 (0.6–1.5)	.69		
Yes, n = 606	4.5 (2.9–6.4)				
No, n = 1154	3.9 (2.8–5.2)				
LSM, *kPa*		0.9 (0.3–2.6)	.88		
≤23, n = 927	3.6 (2.5–5.0)				
>23, n = 111	3.6 (1.0–10.0)				
CSPH[a]		3.0 (1.9–4.9)	<.0001	2.1 (1.2–3.8)	.02
Yes, n = 485	8.2 (5.9–11.1)				
No, n = 1275	2.5 (1.7–3.5)				
Albumin, *g/dL*		6.8 (4.1–11.2)	<.0001	4.1 (2.3–7.6)	<.001
<3.5, n = 163	17.8 (12.2–24.5)				
≥3.5, n = 1132	2.7 (1.9–3.9)				
Platelets, <100,000/mm^3		5.1 (3.1–8.4)	<.0001		
Yes, n = 275	12.4 (8.7–16.8)				
No, n = 1142	2.4 (1.6–3.5)				
F3–F4		3.4 (1.6–7.1)	.001	3.4 (1.2–9.6)	.02
Yes, n = 1128	5.7 (4.4–7.2)				
No, n = 632	1.3 (0.5–2.5)				
SVR		0.4 (0.2–0.8)	.02	0.3 (0.1–0.8)	.02
Yes, n = 1366	3.9 (2.9–5.0)				
No, n = 48	8.3 (2.3–20.0)				

NOTE. Proportional hazard assumptionvand Schoenfeld test was kept in the model (*P* = .26) and the Harrell's c-statistic was 0.79 (CI, 0.77-0.81) for baseline predictors. A time-covariate analysis was further done in order to adjust the effect of these baseline predictors with development or not of SVR as a time-covariable.

BMI, body mass index; CSPH, clinically significant portal hypertension; IFN, interferon; HIV, human immunodeficiency virus; HR, hazard ratio; LSM, liver stiffness measurement; SVR, sustained virologic response.

[a]Clinically significant portal hypertension was defined as presence of at least 1 of the following: gastroesophageal varices and splenomegaly or platelet count less than 100,000/mm^3.

remained after adjusting for SVR as a time-dependent covariate.

Overall, our results are similar to those reported by the Electronically Retrieved Cohort of HCV Infected Veterans retrospective cohort study and more recently by a large French prospective cohort.[4,5] Both studies described a significant decrease in all-cause mortality in subjects receiving DAA regimens. Some patients still developed liver-related complications despite achieving SVR, however, the annual incidence rate of these events was much lower than those documented in other studies describing the natural history of HCV.[13] Several baseline factors such as cirrhosis, anemia, and markers of liver failure were described to be correlated positively with mortality.[4,5] In our study, we were able to identify CSPH, hypoalbuminemia, and advanced fibrosis to be associated strongly with mortality, liver failure, and HCC, even after SVR achievement. Furthermore, we recognized 3 risk groups according to the number of risk factors presented at baseline. The presence of 2 or more variables was associated strongly with a higher risk of developing liver-related events or death after DAA therapy. Thus, treating physicians should evaluate baseline variables at the time of initiation of DAA therapy to ensure patient retention for clinical monitoring and HCC surveillance after achievement of SVR.

We believe our findings also are relevant from a public health perspective. In this article, we report a low incidence of liver-related complications and death after DAA therapy in patients with no previous history of hepatic decompensation. In contrast, other cohorts published with patients with more advanced liver disease showed that they are still at high risk of developing liver-related complications after viral eradication.[2,14] Thus, our study supports the initiation of antiviral therapies at

Table 3. Crude and Adjusted Effect of Baseline Variables Considering SVR as a Time-Dependent Covariate

Variable	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Sex Males, n = 930 Females, n = 830	1.5 (0.9–2.4)	.09	1.3 (0.8–2.2)	.32
CSPH[a] Yes, n = 485 No, n = 1275	3.0 (1.9–4.9)	<.0001	2.2 (1.2–3.9)	.01
Albumin, *g/dL* <3.5, n = 163 ≥3.5, n = 1132	6.8 (4.1–11.2)	<.0001	4.7 (2.7–8.1)	<.001
F3–F4 Yes, n = 1128 No, n = 632	3.4 (1.6–7.1)	.001	2.3 (1.2–6.6)	.02
SVR Yes, n = 1366 No, n = 48	0.2 (0.1–0.8)	.021	0.6 (0.2–1.6)	.32

CSPH, clinically significant portal hypertension; HR, hazard ratio; SVR, sustained virologic response.
[a]Clinically significant portal hypertension was defined as presence of at least 1 of the following: gastroesophageal varices and splenomegaly or platelet count less than 100,000/mm^3.

earlier stages of liver disease to avoid progression to cirrhosis and impact survival rates positively. A retrospective study from the Veterans Affairs Administration reported that SVR was associated with an 80% reduction in risk of death in patients without a history of hepatic decompensation compared with a 67% reduction in risk of death for patients with a history of decompensation.[2] Furthermore, patients with advanced liver disease had lower SVR rates, with the consequent development of resistant-associated substitutions.[14] This outcome not only impacts patient survival negatively, but it considerably increases the cost of HCV care. In Latin America, viral resistance testing is limited and the most potent pangenotypic DAA regimens are not available in many countries. To decrease the costs associated with both cirrhotic-related complications as well as HCC surveillance, it thus might be worthwhile not to neglect individuals with lower stages of hepatic fibrosis, especially those prone to progress to cirrhosis.

Another important message of our study is that even patients with liver fibrosis grades of 0 to 2 who have achieved SVR are still at risk of developing liver-related complications, albeit at a low risk. Similar results were reported by a large nationwide cohort study from Scotland.[15] In this study, Innes et al[15] observed that among SVR patients without cirrhosis at baseline, mortality rates were almost 1.6-fold higher. This finding is alarming because this group of patients tend to be discharged from specialty care without further follow-up evaluation. Thus, do we still need to follow up patients with mild to moderate fibrosis after viral eradication? Because the population infected with HCV is aging and the proportion

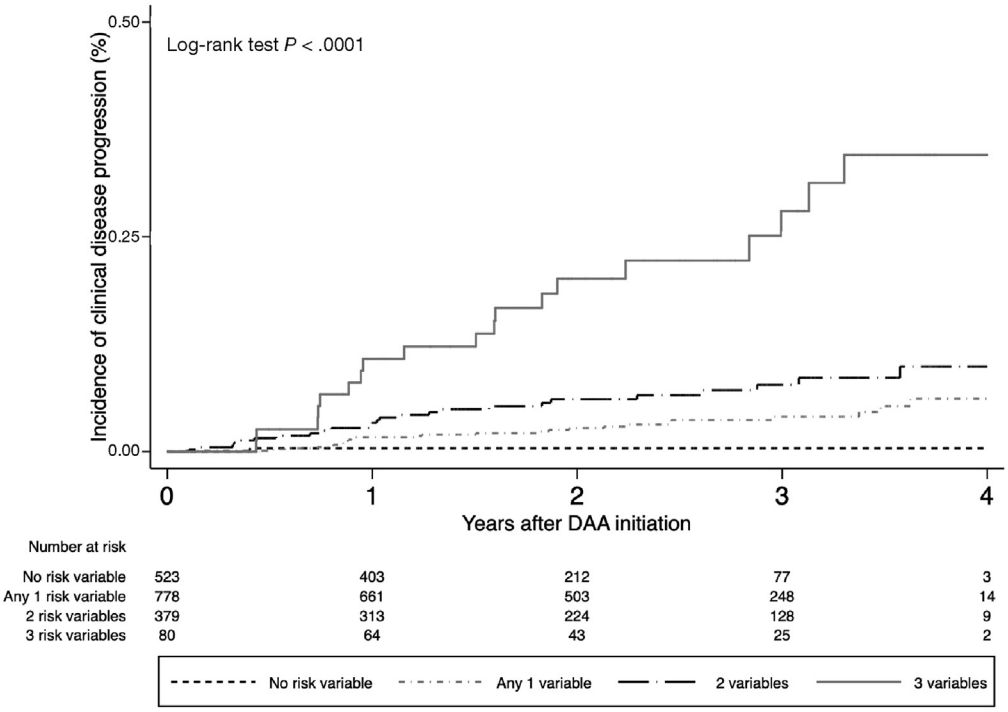


Figure 2. The cumulative incidence of disease progression according to the number of variables present associated with the main event. Variables associated independently with disease progression were albumin level less than 3.5 mg/dL, clinically significant portal hypertension (CSPH), and liver fibrosis grades 3 to 4. The cumulative incidence of disease progression increased significantly according to the number of variables present. Absence of any variable was the reference stratum; 1 variable: hazard ratio (HR), 6.7 (95% CI, 1.6–28.4; $P = .009$); 2 variables: HR, 13.4 (95% CI, 3.1–56.5; $P < .0001$); and 3 variables: HR, 49.8 (95% CI, 11.6–213.9; $P < .0001$). DAA, direct-acting antiviral.

Table 4. Association Between Sustained Virologic Response and Overall Clinical Disease Progression According to Fibrosis Stage From the Date of SVR Assessment to Last Follow-Up Evaluation

Variable	Combined end-point (95% CI)	Death (95% CI)	Liver decompensation (95% CI)	HCC (95% CI)
SVR12[a]				
Yes, n = 1366	3.9 (2.9–5.0)		3.0 (2.2–4.0)	1.8 (1.1–2.6)
No, n = 48	8.3 (2.3–20.0)	0.9 (0.4–1.5)	8.3 (2.3–20.0)	6.2 (1.3–17.2)
	HR, 0.2 (0.1–0.8); $P = .021$	0	HR, 0.3 (0.1–0.8); $P = .016$	HR, 0.2 (0.1–0.8); $P = .021$
F3–F4				
With SVR, n = 935	5.3 (3.9–6.9)		4.1 (2.9–5.5)	2.3 (1.5–3.5)
Without SVR, n = 31	9.7 (2.0–25.7)	1.3 (0.6–2.2)	9.7 (2.0–25.7)	6.4 (0.8–21.4)
	HR, 0.4 (0.1–1.3); $P = .14$	0	HR, 0.3 (0.09–0.9); $P = .04$	HR, 0.3 (0.07–1.3); $P = .11$
F0–F2				
With SVR, n = 431	0.7 (0.1–2.0)		0.7 (0.1–2.0)	0.5 (0.05–1 .7)
Without SVR, n = 17	5.9 (0.1–28.7)	0	5.9 (0.1–28.7)	5.9 (0.1–28.7)
	HR, 0.1 (0.01–1.13); $P = .06$	0	HR, 0.1 (0.01–1.13); $P = .06$	HR, 0.08 (0.01–0.8); $P = .036$

HCC, hepatocellular carcinoma; HR, hazard ratio; SVR, sustained virologic response; SVR12, sustained virologic response after 12 weeks of completion of therapy.
[a]Overall population.

of patients with associated comorbidities that can possibly affect liver fibrosis is increasing, our results suggest that we might need to monitor these patients with cured HCV infection in the following years.[16] The omission of some covariables during follow-up evaluation such as alcohol consumption, drug intoxication, or presence of nonalcoholic fatty liver disease also can impact liver fibrosis progression. Finally, pretreatment hepatic fibrosis can be evaluated erroneously and some patients with advanced fibrosis may be classified incorrectly as having mild fibrosis. Certainly, cohorts with longer follow-up periods are necessary to address this question.

We previously reported that achieving SVR with different DAA regimens is associated with a significant reduction in the risk of developing de novo HCC.[7] Still, adequate and continuous HCC surveillance is strongly recommended after achieving viral eradication, especially in patients with cirrhosis. In our study, in which half the patients were not cirrhotic at baseline and those who were cirrhotic never had a liver-related decompensation event, we report a low, but present, incidence of de novo HCC. In line with our results, a large population-based cohort study previously reported that individuals without cirrhosis who cleared their HCV infection had a risk of liver cancer death that was 9 times higher than the general population.[15] In this specific population, metabolic syndrome has been described as a possible risk factor for developing HCC after achieving SVR.[17] This could be explained by the known impact of obesity and diabetes on HCC development.[6] Furthermore, nonalcoholic steatohepatitis has been described recently as the fastest-growing cause of HCC in liver transplant candidates from Latin America and the United States.[18,19] It is highly relevant that physicians are aware of the continuing health risks after successful viral eradication among patients with HCV-induced advanced liver disease. At present, there are no reliable fibrosis markers or elastography scores below which clinicians can confirm the absence of HCC risk with sufficient confidence to warrant discontinuation of surveillance.

The major strengths of our study were the inclusion of a large and geographically diverse population treated for HCV. Our study was conducted using the LALREAN database, in which patient selection, data collection, and outcome measures have been developed carefully by all the participating centers. However, we must acknowledge certain limitations in the interpretation of the results of our study. First, it is possible that after excluding patients with a history of decompensated cirrhosis and solid-organ transplantation that our study underestimated the potential benefits of DAAs. However, we intended to and did show that patients with milder forms of liver diseases are still at risk of developing liver-related complications after successful viral eradication. Second, as a consequence of the latter introduction of DAAs in Latin America, the follow-up period of our study was relatively short. Nevertheless, an inverse relationship between treatment and risk for liver-related outcomes has been reported and a longer duration of follow-up evaluation probably would not modify our findings.[4] Finally, despite controlling for numerous factors, it is possible that nonmeasurable or unmeasured factors might have influenced our results. In that sense, we carefully selected the variables that we understand potentially can be associated with the study outcomes.

In summary, our study shows that achieving SVR with DAA regimens was associated with a significant reduction in the risk of all-cause mortality, hepatic decompensation, and HCC in patients with no previous liver decompensation. However, the risk of developing liver-related events still remains after achieving viral eradication, especially in

those patients with advanced liver fibrosis. A policy shift toward treating all individuals with HCV, irrespective of disease stage, has the potential to decrease not only morbidity and mortality, but transmission as well. The development of public health programs adapted to national settings is needed to achieve this goal.[20] Future studies are required to assess the predictive accuracy of post-treatment markers and their kinetics during follow-up evaluation to further refine our concepts of appropriate management of patients' post-SVR in the years ahead.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.02.044.

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CRediT Authorship Contributions

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Conflicts of interest

These authors disclose the following: Manuel Mendizabal has received fees as a speaker for Gador; Alejandro Soza has received research grants from Gilead, donations for research from Gador, speaker fees from MSD, Roche, and BMS, has participated in Advisory Board Meetings for MSD, AbbVie, Gilead, Vertex, Roche, and Janssen, and has stock ownership in Gilead; Hugo Cheinquer has served as a consultant and received research grants from AbbVie, Gilead, and Bayer; and Marcelo Silva has received speaker fees from AbbVie and MSD. The remaining authors disclose no conflicts.

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Supplementary Methods

Cohort Characteristics and Study Variables Recorded Before Direct-Acting Antiviral Initiation

Genotyping/subgenotyping was conducted before treatment initiation. Before DAA initiation, all subjects were under routine clinical evaluation including HCC surveillance to exclude liver decompensation events and HCC diagnosis, according to international guidelines.[12]

Baseline exposure variables were recorded for all enrolled subjects and included detailed demographic data and relevant past medical history. Evaluation of liver fibrosis stage was assessed by liver biopsy or noninvasive methods (transient elastography or serum biomarkers). Cirrhosis also could be determined by the site investigator or treating physician based on a combination of clinical signs of portal hypertension, biochemical parameters, and/or radiologic findings consistent with cirrhosis. The severity of liver disease was evaluated according to Child–Turcotte–Pugh score.

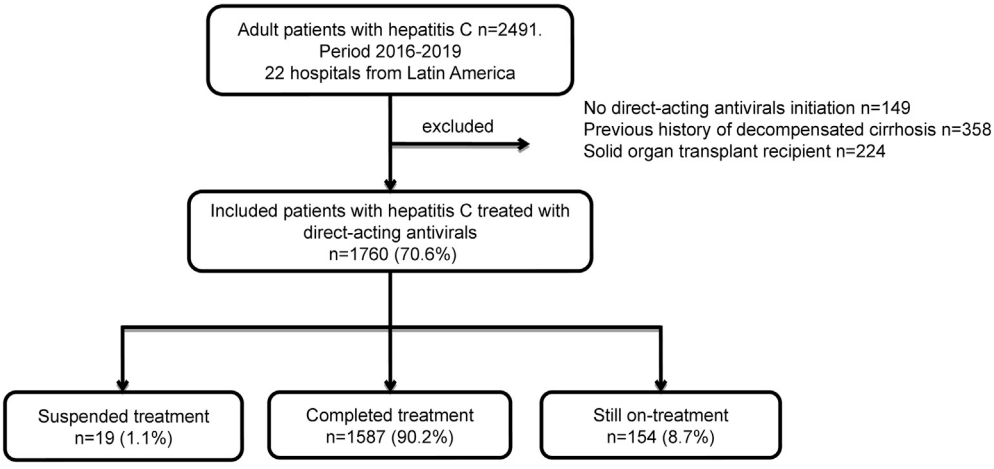
Intervention and Main Exposure Variables

The specific DAA regimen used was based on physicians' criteria according to the available regimens in each country following local and international guidelines. Laboratory values collected before and after DAA therapy included HCV viral load (IU/mL) and other laboratory values registered. We assessed response to DAA therapy by assessing SVR, defined as an undetectable HCV RNA level (HCV viral load, $<$15 UI/mL) 12 weeks after completion of therapy. Treatment failure was defined as the presence of detectable HCV RNA level after discontinuation of the antiviral regimen. Laboratory operators were blinded to baseline patient characteristics, treatment regimens, and primary outcome events.

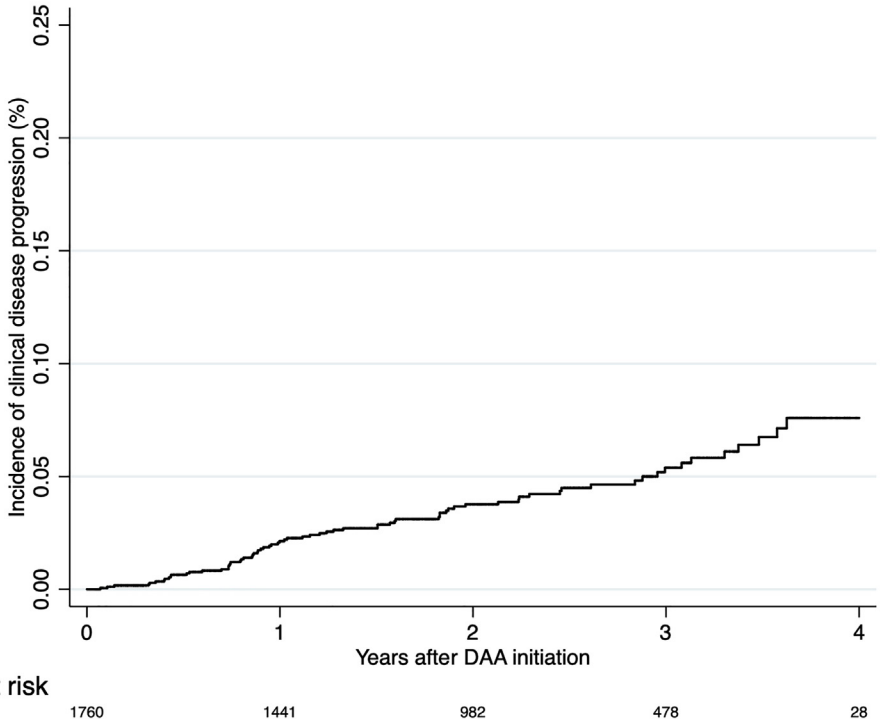
Statistical Analysis

Categoric data were compared using the Fisher exact test (2-tailed) or the chi-squared test as appropriate. Continuous variables are reported with means ($\pm$SD) or median (interquartile range, 25%–75%) and were compared with the Student *t* test or the Mann–Whitney *U* test according to their respective distributions. Dummies for ordinal variables were assessed.

Sensitivity analysis was performed evaluating the association between baseline exposure variables and the primary outcome after excluding patients with HIV or hepatitis B virus coinfection and the effect of a full course of DAA treatment (excluding those in whom DAAs were discontinued or who were not fully treated).,



Supplementary Figure 1. Flow chart describing the study population.



Supplementary Figure 2. Kaplan–Meier cumulative incidence curve of disease progression in the overall population. The overall cumulative incidence of disease progression was 4.1% (95% CI, 3.2–5.1), at 12 months it was 1.9% (95% CI, 1.3–2.7), and at 24 months it was 3.1% (95% CI, 2.3–4.0). DAA, direct-acting antiviral.

Supplementary Table 1. Cox Regression Analysis for Baseline Predictors of Clinical Disease Progression Excluding HIV Co-infected Patients (n = 1521)

Variable	Event, % (95% CI)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age, *y*		1.0 (0.9–1.01)	.61		
Sex		1.5 (0.9–2.4)	.15		
Male (n = 777)	4.8 (3.4–6.5)				
Female (n = 744)	3.1 (2.0–4.6)				
BMI		1.1 (0.6–2.3)	.72		
>30 (n = 197)	5.1 (2.5–9.1)				
≤30 (n = 883)	4.4 (3.1–6.0)				
Diabetes mellitus		1.2 (0.6–2.4)	.56		
Yes (n = 207)	4.8 (2.3–8.7)				
No (n = 1314)	3.8 (2.8–5.0)				
Previous IFN regimens		0.8 (0.4–1.3)	.32		
Yes (n = 515)	3.9 (2.4;5.9)				
No (n = 1006)	4.0 (2.8;5.4)				
LSM, *kPa*		0.8 (0.2–2.7)	.73		
≤23 (n = 806)	3.5 (2.3–5.0)				
>23 (n = 98)	3.1 (0.6–8.7)				
CSPH[a]		2.9 (1.7–4.8)	<.0001	2.2 (1.1–4.3)	.017
Yes (n = 429)	7.7 (5.3–10.6)				
No (n = 1092)	2.5 (1.6–3.5)				
Albumin, *g/dL*		7.6 (4.3–13.4)	<.0001	5.4 (2.9–10.0)	
<3.5 (n = 144)	17.4 (11.6–24.5)				
≥3.5 (n = 972)	2.4 (1.5–3.5)				
Platelets, <100,000/mm^3		5.1 (2.9–8.8)	<.0001		
Yes (n = 237)	11.8 (8.0–16.6)				
No (n = 978)	2.3 (1.5–3.5)				
F3–F4		2.5 (1.2–5.3)	.017	2.0 (0.8–4.8)	.11
Yes (n = 1009)	5.1 (3.9–6.7)				
No (n = 512)	1.6 (0.7–3.0)				

NOTE. There were 60 primary events in this post hoc sensitivity analysis excluding HIV patients, with a cumulative incidence of 3.9% (95% CI, 3.0–5.0).
BMI, body mass index; CSPH, clinically significant portal hypertension; F3–F4, fibrosis grades 3 and 4; HIV, human immunodeficiency virus; HR, hazard ratio; IFN, interferon; LSM, liver stiffness measurement.
[a]Clinically significant portal hypertension was defined as presence of at least 1 of the following: gastroesophageal varices and splenomegaly or platelet count less than 100,000/mm^3. The proportional hazard assumption through graphic and Schoenfeld test was kept in the model ($P = .75$), and the Harrell's c-statistic was 0.80 (95% CI, 0.77–0.82).

Supplementary Table 2. Cox Regression Analysis for Baseline Predictors of Clinical Disease Progression Including Patients With Full-Course Treatment With DAAs (n = 1587)

Variable	Event, % (95% CI)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Sex		1.5 (0.9–2.4)	.11		
Males (n = 833)	5.4 (4.0–7.2)				
Females (n = 754)	3.4 (2.3–5.0)				
BMI		1.0 (0.5–1.9)	.93		
>30 (n = 192)	5.2 (2.5–9.4)				
≤30 (n = 899)	5.2 (3.9–6.9)				
Diabetes mellitus		1.2 (0.6–2.3)	.52		
Yes (n = 194)	5.7 (2.9–9.9)				
No (n = 1393)	4.3 (3.3–5.5)				
Previous IFN regimens		0.9 (0.5–1.40)	.57		
Yes (n = 585)	4.6 (3.1–6.6)				
No (n = 1002)	4.4 (3.2–5.8)				
LSM, *kPa*		0.9 (0.3–2.7)	.91		
≤23 (n = 846)	3.8 (2.6–5.3)				
>23 (n = 104)	3.8 (1.0–9.5)				
CSPH[a]		3.0 (1.9–4.8)	<.0001	2.2 (1.2–3.9)	.01
Yes (n = 435)	9.0 (6.4–12.0)				
No (n = 1152)	2.8 (1.9–3.9)				
Albumin, *g/dL*		6.7 (4.0–11.1)	<.0001	4.7 (2.7–8.2)	<.0001
<3.5 (n = 144)	19.4 (13.3–27.0)				
≥3.5 (n = 1027)	3.0 (2.0–4.2)				
Platelets, <100,000/mm^3		5.2 (3.1–8.6)	<.0001		
Yes (n = 237)	13.9 (9.8–19.0)				
No (n = 1047)	2.7 (1.8–3.8)				
F3–F4		3.1 (1.5–6.5)	.003	2.7 (1.1–6.3)	.02
Yes (n = 1046)	6.0 (4.6–7.6)				
No (n = 541)	1.5 (0.6–2.9)				

NOTE. There were 71 primary events in this post hoc sensitivity analysis excluding patients without full-course DAA treatment (n = 173), with a cumulative incidence of 4.5% (95% CI, 3.5–4.6).

BMI, body mass index; CSPH, clinically significant portal hypertension; DAA, direct-acting antiviral; F3–F4, fibrosis grades 3 and 4; HIV, human immunodeficiency virus; HR, hazard ratio; IFN, interferon; LSM, liver stiffness measurement.

[a]Clinically significant portal hypertension was defined as presence of at least 1 of the following: gastroesophageal varices and splenomegaly or platelet count less than 100,000/mm^3. The proportional hazard assumption through graphic and Schoenfeld test was kept in the model (*P* = .63), and the Harrell's c-statistic was 0.77 (95% CI, 0.75–0.80).