Liver stiffness at the time of sustained virological response predicts the clinical outcome in HIV/HCV-coinfected patients with advanced fibrosis treated with direct-acting antivirals

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Summary: Liver stiffness at the time of sustained virological response after direct-acting antivirals predicts the emergence of liver events and survival in HIV/HCV-coinfected patients with advanced fibrosis. This parameter may identify candidates to be withdrawn from surveillance programs from hepatic complications.

Abstract

Background: Some HCV-infected patients with sustained virological response (SVR) develops hepatic complications. Liver stiffness (LS) predicts clinical outcome in HIV-infected patients with active HCV coinfection, but information after SVR is lacking. We aimed to analyze the predictive ability of LS at SVR for liver complications in HIV/HCV-coinfected patients with advanced fibrosis treated with direct-acting antivirals (DAA).

Methods: 640 HIV/HCV-coinfected patients fulfilling the following criteria were included: i) Achieved SVR with DAA-including regimen; ii) LS ≥9.5 kPa before therapy and; iii) LS measurement available at SVR. The primary end-point was the occurrence of a liver complication –hepatic decompensation or hepatocellular carcinoma (HCC) - or requiring liver transplant after SVR.

Results: During a median (Q1-Q3) follow-up of 31.6 (22.7-36.6) months, 19 (3%) patients reached the primary end-point. In the multivariate analysis, variables (subhazard ratio [SHR] [95% CI]) associated with developing clinical outcomes were: prior hepatic decompensations (3.42 [1.28-9.12]), pre-treatment CPT class B or C (62.5 [3.08-1246.42]) and MELD scores (1.37 [1.03-1.82]), CPT class B or C at SVR (10.71 [1.32-87.01]), CD4 cell counts <200/μL at SVR time-point (4.42 [1.49-13.15]), FIB-4 index at SVR (1.39 [1.13-1.70]) and LS at SVR (1.05 [1.02-1.08] for 1 kPa increase). None out of 374 patients with LS <14kPa at SVR time-point developed a liver complication or required hepatic transplant.

Conclusions: LS at the time of SVR after DAA therapy predicts the clinical outcome of HIV/HCV-coinfected patients with advanced fibrosis. These results suggest that LS measurement may be helpful to select candidates to be withdrawn from surveillance programs.

Keywords: HIV/HCV-coinfection, sustained virological response, direct-acting antivirals, cirrhosis, hepatocellular carcinoma.

Introduction

Achieving sustained virological response (SVR) with antiviral therapy is associated with a marked reduction of the incidence of liver complications and with an increase of survival in HCV-infected patients harboring advanced fibrosis or cirrhosis [1–3]. However, a few subjects continue to develop hepatic decompensations and hepatocellular carcinoma (HCC), despite attaining SVR [4–7]. These complications usually emerge in subjects showing cirrhosis or advanced fibrosis before starting HCV therapy. This is the reason why long-term surveillance for complications is unanimously recommended in HCV-infected patients showing cirrhosis [8] and, according to some experts, also in patients with METAVIR F3 fibrosis [9,10], even after SVR. However, the majority of HCV-infected patients, irrespective of HIV coinfection, who show advanced fibrosis, with or without cirrhosis, and attain SVR, do not develop complications [6,7]. Because of this, searching for factors that could identify those patients who will not suffer from liver complications after SVR is of the highest interest. In fact, the cost-effectiveness of surveillance programs may be maximized if subjects with very low risk of complications are withdrawn from these programs.

Liver stiffness (LS), measured by vibration-controlled transient elastography (VCTE), is a strong predictor of liver disease outcome in patients with active HCV infection, both in HCV-monoinfected and HIV/HCV-coinfected subjects [11,12]. LS correlates with hepatic venous pressure gradient (HPVG) [13], which accurately predicts the development of cirrhosis decompensations [14] and HCC [15]. In addition, in HCV-infected patients who have achieved SVR, LS also correlates with HPVG [16]. Consequently, it can be hypothesized that LS might also predict the risk of liver complications after SVR. If so, VCTE could also be used as an easy and convenient tool to identify patients with lower likelihood of liver complications subsequent to

SVR, who could be potential candidates to be withdrawn from surveillance programs. However, data on the prognostic value of LS measured by VCTE for clinical events after SVR are scarce. In studies including a low proportion of patients with SVR, mostly achieved with pegylated interferon (Peg-IFN)-based regimens [11,17], LS was found to be a predictor of clinical outcome. Nevertheless, studies specifically designed to appraise the prognosis value of LS measured by VCTE in patients with SVR, particularly in those treated with direct-acting antiviral agents (DAA), are lacking.

The aim of the present study was to analyze the predictive ability of LS measured by VCTE at the time of SVR for the emergence of liver complications in HIV/HCV-coinfected patients with advanced liver fibrosis treated with DAA-based therapy.

Methods

Patients and follow-up

Individuals from the HEPAVIR cohort (clinicaltrials.gov ID: NCT02057003), where HIV/HCV-infected patients treated with DAA in 17 units of Infectious Diseases throughout Spain are enrolled, were included in this prospective study, if they fulfilled: i) SVR after receiving therapy including at least one DAA, either with or without Peg-IFN; ii) LS before starting DAA therapy ≥9.5 kPa, and; iii) A LS measurement available at SVR time-point. Individuals seropositive for HBsAg were excluded.

After SVR, which was considered as the baseline time-point, all patients included in the study were followed with visits at least every six months until death, liver transplant, HCV reinfection or the censoring date (November 30th, 2018). A clinical examination was completed and routine laboratory examinations were carried out at every visit. Patients with cirrhosis were managed according to a specific protocol reported elsewhere [11]. Namely, liver ultrasound examinations and plasma alpha-fetoprotein determinations were conducted every six months for HCC surveillance and serial upper gastrointestinal endoscopy were performed in patients with LS ≥21 kPa for gastroesophageal varices detection.

VCTE examinations

LS was measured by VCTE (FibroScan®, Echosens, Paris, France), according to a standardized procedure [18], within the 30 days before starting DAA therapy and at the day of SVR. An experienced operator performed examinations at each participating institution. M probe was used in all patients. Determinations were considered evaluable if they included at least 10 measurements, with a success rate ≥60% and an interquartile range less than 30% of the median. Although a LS value ≥ 12 kPa is considered as cirrhosis in HCV-monoinfected patients [19,20], we selected 14 kPa as cutoff for

defining pre-treatment cirrhosis, because this figure is derived from previous studies specifically conducted in HIV/HCV coinfected subjects [11,21].

End-point Definitions

The primary end-point of this study was the emergence of a first hepatic complication or undergoing a liver transplant after having achieved SVR, whichever happened first. HCC and liver decompensations were considered as hepatic complications. Liver decompensations included portal hypertensive gastrointestinal bleeding, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorrenal syndrome and acute on chronic liver failure. The diagnosis of decompensations was carried out as reported elsewhere [11,22]. HCC diagnosis was performed following the criteria of the American Association for the Study of Liver Diseases (AASLD) [8]. The indication of liver transplant was established on the basis of the criteria currently in force in Spain [23].

Death of any cause was the secondary end-point. In subjects who dropped out the follow-up, the vital status was established by contacting the patient or a next of kin.

Statistical Analysis

Continuous variables were expressed as median (quartile 1–quartile 3) and categorical variables as numbers (percentage). 95% confidence interval (95% CI) is provided for incidence and mortality rates, as well as for survival estimates. The time-to-event was calculated as the months elapsed from SVR time-point to the occurrence of end-points.

Survival estimates at specific time-points were calculated using life tables and are expressed as the cumulative proportions of patients who reached or who did not the specific end-point. Estimated survival functions were calculated using the Kaplan-Meier method, and survival curves were compared by the log-rank test. For this analysis, continuous variables were categorized according to the median value, using clinically significant cutoffs and analysis of under receiver operator characteristic (ROC) curves. The relationship between the time to the endpoint and the following variables was analyzed in the bivariate study: i) variables at starting DAA therapy: age, sex, HCV genotype, way of HCV infection, alcohol intake, LS, Child-Pugh-Turcotte (CPT) class, MELD score and drug regimen resulting in SVR; ii) variables at SVR time-point: LS, prior decompensation of cirrhosis, CPT class, MELD score, fasting plasma glucose, alpha-fetoprotein, albumin, bilirubin, platelet counts, AST to platelet ratio index (APRI), Fibrosis-4 index (FIB-4), CD4 cell counts and plasma HIV-RNA load; and, iii) changes in LS from treatment starting to SVR time-point. Areas under ROC (AUROC) curves were compared by the Hanley and McNeil test.

Variables associated with the main end-point in the bivariate analysis with a p value <0.05, along with age, and sex were entered in a Fine-Gray multivariate regression model to adjust for competing risk of death. For death of any cause, variables associated with the endpoint in the bivariate analysis were included in a Cox regression model.

Statistical analyses were conducted using the SPSS statistical software package release 4.0 (IBM, Chicago, IL, USA) and the Stata 12.0 Statistics/Data Analysis (StataCorp College Station, TX, USA) package.

Ethical Aspects

This study was conducted according to the Helsinki declaration and was approved by the Ethics Committee of the Hospital Universitario de Valme. All patients gave written informed consent before being recruited in the cohorts.

Results

Characteristics of the Study Population

Six hundred forty patients were included. At SVR time-point, all participants were receiving antiretroviral therapy. The median (Q1-Q3) CD4 cell count was 580 (367-809) cells/ml. Other relevant features of the study population, prior to DAA therapy and at SVR time-point, are displayed in table 1 and table 2, respectively. DAA combinations which patients had received are listed in table 3.

The median (Q1-Q3) follow-up time was 31.6 (22.7-36.6) months after SVR. Twenty-two (3.4%) patients were lost to the follow-up. Three (0.5%) patients suffered from an HCV reinfection during the follow-up and were censored at that time. Median (Q1-Q3) LS at SVR was 11.8 (8.4-19.5) kPa. The corresponding figures for LS decline from pretreatment to SVR time-points were 4.6 (1.5-9.30) kPa. One hundred and forty-four (36.6%) out of the patients who showed LS ≥14 kPa when starting DAA therapy had values below that figure at the time of SVR. Conversely, 17 (6.9%) subjects with less than 14 kPa at treatment onset had LS equal to or higher than this cutoff at the SVR time-point.

Hepatic Complications

Eighteen (2.8%) patients developed a hepatic complication and two (0.3%) underwent a liver transplant, one of them without prior defined complications. Consequently, 19 (3.0%) patients reached the composite primary end-point of the study. In these patients, the end-point was attained after a median (Q1-Q3) follow-up of 10.2 (5.6-16.8) months.

The incidence rate (95% CI) of developing hepatic complications or undergoing liver transplant was 1.2 (0.7-1.9) events per 100 person-years. The probability (95% CI) of

suffering from a hepatic complication or having a liver transplant at one and two years were, respectively, 2.0% (1.2%-3.4%) and 2.7% (1.7%-4.4%). Ascites and HCC were the most commonly observed hepatic complications (table 4). The incidence rate (95% CI) of HCC was 0.3 (0.1-0.7) cases per 100 person-years and that of any hepatic decompensation 0.8 (0.4-1.4) events per 100 person-years. In the specific subset of patients with LS ≥14 kPa at the time of SVR, the incidence rates of HCC and that of liver complications other than HCC were, respectively, 0.76 (0.25-1.75) y 1.97 (1.05-3.34) events per 100 person-years.

In the bivariate analysis, parameters associated with a greater risk of developing the primary end-point were (table 5): i) Pre-DAA therapy: LS, MELD and CPT scores, and prior liver decompensations, and, ii) At SVR time-point: MELD and CPT scores, LS (figure 1), lower platelet counts and lower CD4 cell count (table 5). In the multivariate analysis (tables 5 and supplementary 1), pre-treatment MELD and CPT scores, prior hepatic decompensations, as well as higher CPT score, LS and CD4 cell count below 200 cells/ml at the time of SVR were independently associated with a greater risk of reaching the study primary end- point (table 5). Pretreatment LS was excluded from the models, because this parameter and LS at SVR turned out to be colinear.

Specifically, regarding LS at the time of SVR, none out of the 374 patients showing LS <14 kPa at the SVR time-point reached the primary end-point (figure 1). Accordingly, the sensitivity and negative predictive value of this cut-off were 100% and the specificity 62%. The AUROC (95% IC) was (0.87 [95% IC: 0.81-0.92) versus (0.82 [95% IC: 0.73-0.89]) (p=0.11) for pretreatment LS. The probability (95% CI) of reaching the primary end-point of the study at 1 and 2 years, according to the value of LS at SVR, were, respectively: i) LS <14 kPa, 0 and 0; ii) LS 14-21 kPa, 2.5% (0.8%-7.7%) and 2.5% (0.8%-7.7%); LS 21.1-40 kPa, 3.9% (1.5%-10.1%) and 7.2%

(3.5%-14.6%); and, iv) LS>40 kPa 13.3% (5.8%-29.1%) and 16.2% (7.6%-32.6%) (p<0.001) (figure 1 and table 5).

Survival

Eighteen (2.8%) patients died during the follow-up. The all-cause mortality rate (95% CI) was 1.2 (0.7-1.8) cases per 100 person-years. The causes of death are shown in table 4.

Higher pretreatment MELD score, prior liver decompensations, as well as greater MELD and CPT scores, LS and lower platelet counts at SVR were associated with mortality in the bivariate analysis. Only LS at SVR predicted mortality in the adjusted multivariate study (table 6). The probability (95% CI) of death at 1 and 2 years, according to the value of LS at SVR, at one and two years, were, respectively: i) LS <14 kPa, 0.8% (0.3%-2.6%) and 0.8% (0.3%-2.6%); ii) LS 14-21 kPa, 0.8% (0.1%-5.8%) and 3.6% (1.4%-9.4%); iii) LS 21.1-40 kPa, 1.9% (0.5%-7.5%) and 4.1% (1.6%-10.7%); and, LS>40 kPa, 10.5% (4.1%-25.7%) and 16.0% (7.5%-32.3%) (p<0.001).

Discussion

The results of this study show that LS, measured by VCTE at the time of SVR, predicts the risk of subsequent hepatic complications and mortality in HIV/HCV-infected patients with advanced fibrosis who receive treatment with DAA. Thus, LS measurements may identify subjects with low risk of complications, who could be considered as potential candidates to be withdrawn from surveillance programs.

Currently, there is not agreement on what patients who had attained SVR should be included in surveillance programs for complications, particularly for HCC. Thus, the AASLD guidelines for HCC recommend that all patients with cirrhosis and SVR should continue surveillance [8]. Conversely, the European Association for the Study of the Liver states that in patients with cirrhosis and in those with F3 surveillance for HCC must be continued despite achieving SVR [10]. The latter opinion is shared by other authors [9]. In the present study, only one patient with LS <14 kPa prior to treatment developed a hepatic complication (table 5), namely ascites, with no case of HCC in this subset. Our findings suggest that LS could have a higher predictive value for clinical outcome at SVR than previously to DAA treatment. Thus, no patient with LS <14 kPa at SVR developed HCC, hepatic decompensations or required transplant. This data suggest that the incidence of HCC in this subpopulation must be much lower than 1.5 cases per 100 person-years, the threshold required to HCC screening is cost-effective [8,24]. That indicates that this level of LS, alone or combined with other predictive markers, could be considered as a candidate to identify patients in whom HCC surveillance is not cost-effective. If surveillance programs for HCC were carried out only in patients with LS at SVR ≥14 kPa, biannual ultrasonography could be discontinued in a significant proportion of patients. Thus, if such programs were carried out in all patients with pretreatment cirrhosis, 393 patients participating in this study would have required it. However, if only patients with LS ≥14 kPa at SVR were kept in

surveillance for HCC, 127 (32%) could have been spared of such a program.

Although the predictive value of LS measured by VCTE at SVR for subsequent clinical outcome had not been definitely proven so far, some previously published results are consistent with this finding. Thus, Mandorfer et al [16] reported that LS strongly correlates with HPVG in patients achieving SVR without significant portal hypertension. Namely, LS <12.5 kPa showed a 100% negative predictive value for HPVG >10 mmHg. This data supports that LS could identify patients with low risk of decompensation, but without the inconveniences of HPVG measurements: invasiveness and limited availability. Likewise, in a Japanese study with a limited number of patients [25], LS measured by shear wave elastography predicted the risk of HCC after SVR. In addition, LS measured by VCTE predicted clinical outcome in populations including a low proportion of HIV/HCV-coinfected patients with SVR [11,17]. However, there are also some relatively conflicting results on this issue. Specifically, Lens et al [26] found that the correlation of LS measured by VCTE with HPVG was only moderately good in patients with SVR, so that almost half of the patients with LS <13.6 kPa had significant portal hypertension. Moreover, reversal of fibrosis in patients with cirrhosis with SVR could be overestimated by LS measurement [27]. In addition, patients with SVR with documented histological regression of cirrhosis continue to be at risk for HCC [28]. However, LS is a combined expression of fibrosis, inflammation, HPVG, etc [29], which might confer this procedure a higher prognostic value for clinical outcomes than that of each these factors separately.

The associations of prior liver decompensations, pre-treatment CPT and MELD scores, CPT score at SVR, and FIB-4 with poor clinical outcome found were expected, as they reflect advanced liver disease and markers of impaired hepatic function correlate with a higher risk of hepatic complications in patients treated with DAA [30–33]. The association between low CD4 cell count and the emergence of liver complications may

be attributable to splenic sequestration ensuing portal hypertension [22,34].

This study could have some limitations. Firstly, our analysis is restricted to HIV/HCV-coinfected patients. However, HIV coinfection does not impact clinical outcome after SVR [6,7]. Because of this, it is conceivable that these results could be extrapolated to the overall HCV-infected population. Anyway, specific data in HCV-monoinfected subjects are needed. Secondly, the median follow-up time after SVR was 31 months. Hepatic complications, particularly HCC, may occur later in the follow-up of the patients, until several decades thereafter [35,36]. Thus, with a longer follow-up, the incidence of cases of HCC in patients with LS<14 KPa could not be zero. However, this would not diminish the practical value of LS to select candidates for HCC surveillance programs. In fact, we should consider two points on this issue: i) As happened herein, most cases of liver complications, including HCC, tended to gather in the first 12-15 months after SVR in other studies [31,37]. Thus, the incidence of cases of HCC in patients with LS <14 kPa with longer follow-up must be beneath 1.5 cases/100 person-years, the figure which make HCC screening cost-effective [8,24]. A recent report from another Spanish cohort showed the incidence of HCC after SVR in HCV-infected patients –a minority with HIV coinfection- with pretreatment LS below 14.5 kPa is very low [38], which is consistent with the former statement. ii) Although confirmation of the very low risk of hepatic complications in HIV/HCV-coinfected patients with LS <14 kPa at SVR is needed in studies with longer follow-up, fortunately, the incidence of these events after SVR is so low that we should wait for a long time to have firmer data. And the overload and costs that continued surveillance programs of all patients with advanced fibrosis and/or cirrhosis who achieve SVR are very high, so that shorter-term decisions are required. Because of this, despite the above-stated limitations, in our opinion, the results of this study should prompt the application of LS at the time of SVR to select candidates for subsequent surveillance programs.

In summary, LS at SVR can be applied in clinical practice to identify HIV/HCV-coinfected patients unlikely to develop subsequent hepatic complications. Thus, patients without concomitant causes of liver disease showing LS <14 kPa at SVR could be considered as candidates for HCC surveillance stopping, particularly in resource-limited settings. If this step was taken, about one third of HIV/HCV-infected patients with prior cirrhosis would not undergo surveillance for HCC after SVR.

NOTES

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Conflict of interest

ACG has received lecture fees from Gilead. JAP reports having received consulting fees from Bristol-Myers Squibb, Abbvie, Gilead, Merck Sharp & Dome, and Janssen Cilag. He has received research support from Bristol-Myers Squibb, Abbvie and Gilead and has received lecture fees from Abbvie, Bristol-Myers Squibb, Janssen Cilag, and Gilead. Juan Macías has been an investigator in clinical trials supported by Bristol-Myers Squibb, Gilead and Merck Sharp & Dome. He has received lectures fees from Gilead, Bristol-Myers Squibb, and Merck Sharp & Dome, and consulting fees from Bristol Myers-Squibb, Gilead, and Merck Sharp & Dome. RP has received lectura fees and consulting fees from ViiV Healthcare, Gilead Sciences, Merk Sharp and Dohme, Janssen-Cilag. FV has received lecture fees and grants from Gilead, MSD, and Janssen-Cilag. DM has received lectures fees from ViiV Healthcare, MSD, Gilead and

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Table 1. Characteristics of the study population at starting DAA therapy (n=640)

Parameter	Value
Age, years*	52 (49-55)
Male sex, no (%)	559 (87.3)
HCV infection way, no (%)	
- PWID	533 (83.3)
- Blood transfusion	6 (0.9)
- Sexual	72 (11.3)
- Unknown	29 (4.5)
Liver Stiffness (kPa)*	17 (11.8-27)
Pre-treatment cirrhosis, no (%)	393 (61.4)
CPT[§] class before treatment, no (%)	
- A	584 (94.3)
- B	35 (5.7)
- C	0
Pre-treatment MELD score*[‡]	6 (6-8)
Decompensation before SVR, no (%)	42 (6.6)
HCV genotype, no (%)	
- 1a	283 (44.2)
- 1b	113 (17.7)
- 2	5 (0.8)
- 3	107 (16.7)
- 4	122 (19.1)
- Other	10 (1.5)
SVR with interferon-free treatment, no (%)	604 (94.4)

Data are number (%) of participants. Continuous variables (indicated with*) are reported as median (quartile 1-quartile 3). [§]Available in 619 patients. [‡]Available in 589 patients.

Abbreviations: HCV: hepatitis C virus; PWID: People who injected drugs; CPT: Child-Pugh-Turcotte; MELD: Model for End-Stage Liver Disease; SVR: Sustained virological response; HIV: human immunodeficiency virus.

Table 2. Characteristics of the study population at the SVR (baseline time-point) (n=640)

Parameter	Value
Liver stiffness (kPa), no (%)	
- <14	374 (58.5)
- 14-21	121 (18.9)
- 21.1-40	107 (16.7)
>40	38 (5.9)
Fasting plasma glucose (mg/dl)*	94 (85-105)
Diabetes Mellitus, no (%)	58 (9.5)
CPT[¶] class, no (%)	
- A	588 (97.2)
- B	18 (2.8)
MELD[#] score*	6 (6-6)
Platelets x 10^9/μL*	143 (102-195)
APRI	0.5 (0.3-0.8)
FIB-4 score[♦]	1.9 (1.3-2.9)
Decline in liver stiffness from DAA onset (kPa)*	4.6 (1.5-9.3)
Alcohol consumption >50 g/day, no (%)	23 (3.6)
Plasma HIV-RNA < 50 copies/ml, no (%)	554 (86.6)
CD4 cell counts >200/μL	576 (90)

Data are number (%) of participants. Continuous variables (indicated with*) are reported as median (quartile 1-quartile 3). [¶]Available in 605 patients. [#]Available in 604 patients. [♦]Available in 552 patients.

Abbreviations: HCV: hepatitis C virus; PWID: People who injected drugs; CPT: Child-Pugh-Turcotte; MELD: Model for End-Stage Liver Disease; SVR: Sustained virological response; APRI: Aspartate aminotransferase to Platelet Ratio Index; FIB-4 score: Fibrosis-4 score. DAA: Direct-acting antivirals.

Table 3. Direct-acting antiviral regimens with which patients achieved sustained virological response (n=640)

DAA regimen	Treatment duration	Value, no (%)
IFN-based	12 weeks	14 (2.2)
	24 weeks	4 (0.6)
	48 weeks	18 (2.8)
LDV/ SOF +/- RBV	8 weeks	23 (3.6)
	12 weeks	204 (31.9)
	24 weeks	42 (6.6)
SOF /DCV +/-RBV	12 weeks	68 (10.6)
	24 weeks	35 (5.5)
SOF/SMP +/-RBV	12 weeks	57 (8.9)
	24 weeks	5 (0.8)
3D/2D +/- RBV	12 weeks	68 (10.6)
	24 weeks	19 (3.0)
SOF/VEL	12 weeks	59 (9.2)
GLE/PIB	8 weeks	1 (0.1)
	12 weeks	9 (1.4)
EBR/GZR	12 weeks	7 (1.1)
	>12 weeks	2 (0.3)
SOF +/- RBV	24 weeks	5 (0.8)

Data are number (%) of participants.

Abbreviations: DAA: direct-acting antiviral; IFN: interferon; LDV: ledipasvir; SOF: sofosbuvir; RBV: ribavirin; DCV: daclatasvir; SMV: simeprevir; 2D/3D: ombitasvir +/- paritaprevir +/- dasabuvir; VEL: velpatasvir; GLE: glecaprevir; PIB: pibrentasvir; GZR: grazoprevir; EBR: elbasvir.

Table 4. Clinical events during the follow-up

Event	n (%)
First hepatic complication after SVR	18 (2.8)
- Ascites	8 (1.3)
- Hepatocellular carcinoma	5 (0.8)
- Hepatic encephalopathy	2 (0.3)
- Portal hypertensive gastrointestinal bleeding	3 (0.5)
Liver transplant	2 (0.3)
Death	18 (2.8)
- Due to liver failure	6 (0.9)
- AIDS related	1 (0.2)
- Other cause	11 (1.7)
- Cancer other than hepatocellular carcinoma	4 (0.6)
- Cardiovascular disease	2 (0.3)
- Sepsis	2 (0.3)
- Other	3 (0.5)

Data are number (%) of participants.
Abbreviations: SVR: Sustained virological response; AIDS: acquired immunodeficiency syndrome.

Table 5. Predictors of the emergence of liver complications or requiring transplant

Parameter	Categories	No. (%) with events	p Bivariate	p Multivariate	Sub-hazard ratio (95% CI)
Age, years	≤52	8 (2.5)			
	>52	11 (3.4)	0.358	0.251	1.06 (0.96-1.18)¶
Sex	Female	2 (2.5)			
	Male	17 (3.0)	0.702	0.369	2.33 (0.37-14.83)
HCV infection way	PWID	18 (3.4)			-
	Other	1 (0.9)	0.167	-	
Diabetes mellitus	Yes	1 (1.7%)			
	Not	18 (3.3%)	0.537	-	-
Pre-treatment liver stiffness (kPa)	<14	1 (0.4)			
	≥ 14	18 (4.6)	0.003	NA	NA
Pre-treatment MELD score*	6-10	8 (1.5)			
	>10	8 (26.7)	<0.001	0.031	1.37 (1.03-1.82)¶
Pre-treatment CPT† score	A	15 (2.6)			
	B	3 (8.6)	0.035	0.007	62.5 (3.08-1246.42)
HCV genotype	3	5 (4.7)	0.200	-	-
	Other	14 (2.6)			
Treatment leading to SVR	Interferon-based	2 (5.6)	0.953	-	-
	All oral	17 (2.8)			
Decompensation before SVR	No	10 (1.7)			
	Yes	9 (21.4)	<0.001	0.014	3.42 (1.28-9.12)
MELD score at SVR‡	6-10	9 (1.6)			
	>10	8 (21.1)	<0.001	0.335	0.85 (0.62-1.18)¶
CPT score at SVR‖	A	12 (2.0)			
	B	6 (33.3)	<0.001	0.027	10.71 (1.32-87.08)
FIB-4♦	≤3.25	5 (1.1%)	<0.001	0.002	1.39 (1.13-1.70)¶
	>3.25	14 (12.2%)			
Liver stiffness at SVR (kPa)	<14	0			
	14.1-21	2 (1.5)			
	21.1-40	5 (3.3)	<0.001	0.002	1.05 (1.02-1.08)¶
	>40	11 (13.3)			
Liver stiffness decline (kPa) from DAA onset to SVR (kPa)	≤4.6	10 (3.1)	0.768		-
	>4.6	9 (2.8)			

Platelets at SVR x $10^3/\mu L$	≤100 >100	13 (8.8) 6 (1.3)	<0.001	0.478	1.00 (0.99-1.00)[#]
CD4 counts at SVR cells/μL	≤200 >200	6 (11.1) 12 (2.4)	<0.001	0.002	0.22 (0.076-0.67)
Plasma HIV-RNA at SVR	<50 ≥50	18 (3.2) 1 (3.8)	0.713	-	-

Table shows patient's characteristics associated with a greater risk of developing liver events. For the bivariate analysis, continuous variables were categorized according to the median value or using clinical significant cutoffs. Estimated survival functions were calculated using the Kaplan-Meier method, and survival curves were compared by log-rank test. Variables associated with the main end-point in the bivariate analysis with a p value <0.05, along with age and sex, were entered in a multivariate analysis and a Fine-Gray regression model was conducted to adjust for competing risk of death. The parameter pre-treatment liver stiffness was not entered in the model because of colinearity with liver stiffness at SVR. A regression model including pre-treatment, instead at SVR, LS is shown in supplementary table 1.

*Available in 589 patients. [†]Available in 619 patients. [‡]Available in 604 patients. [‖]Available in 605 patients. [♦]Available in 552 patients [¶]For one unit increase and [#]for 1000 units increase (included as continuous variables in the multivariate model).

Abbreviations: HCV: hepatitis C virus; PWID: People who injected drugs; CPT: Child-Pugh-Turcotte; MELD: Model for End-Stage Liver Disease; SVR: Sustained virological response; NA: Not applicable; FIB-4 score: Fibrosis-4 score; DAA: Direct-acting antivirals; HIV: human immunodeficiency virus.

Table 6. Predictors of all-cause mortality

Parameter	Categories	No. (%) with events	p Bivariate	p Multivariate	Hazard ratio (95% CI)
Age, years	≤52	7 (2.2)			
	>52	11 (3.4)	0.293	0.549	1.03 (0.94-1.12)[¶]
Sex	Female	0			
	Male	18 (3.2)	0.100	0.980	$7.5x10^5$ (0->10^6)
HCV infection way	PWID	18 (3.4)			-
	Other	0	0.059	-	
Diabetes mellitus	Yes	1 (1.7%)			
	Not	17 (2.9%)	0.677	-	-
Pre-treatment liver stiffness (kPa)	<14	3 (1.2)			
	≥ 14	15 (3.8)	0.069	-	-
Pre-treatment MELD score*	6-10	14 (2.6)			
	>10	4 (8.3)	<0.001	0.961	1.01 (0.82-1.24)[¶]
Pre-treatment CPT[†] score	A	16 (2.7)			-
	B or C	2 (5.7)	0.336	-	
HCV genotype	3	4 (3.7)			-
	Other	14 (2.6)	0.452	-	
Nadir CD4 count	≤100	6 (3.5)			-
	>100	9 (2.6)	0.563	-	
Treatment leading to SVR[§]	Interferon-based	1 (2.8)			-
	All oral	17 (2.8)	0.898	-	
Decompensation before SVR	No	14 (2.3)			
	Yes	4 (9.5)	0.010	0.562	1.48 (0.39-5.61)
MELD score at SVR[‡]	6-10	13 (2.3)			
	>10	4 (10.8)	0.004	0.731	1.05 (0.80-1.39)[¶]
CPT score at SVR[‖]	A	15 (2.6)			
	B	3 (17.6)	<0.001	0.565	1.62 (0.31-8.38)
Liver stiffness at SVR (kPa)	<14	3 (0.8)			
	14.1-21	5 (4.1)		0.001	1.04 (1.02-1.07)[¶]
	21.1-40	4 (3.7)	<0.001		
	>40	6 (15.8)			
Liver stiffness decline (kPa) from DAA onset to SVR (kPa)	≤4.6	11 (3.6)	0.315		-
	>4.6	7 (2.2)			

FIB-4♦	≤3.25 >3.25	11 (2.5) 7 (6.1)	0.068	-	-
Platelets at SVR x 10^3/μL	≤100 >100	9 (6.1) 9 (1.9)	0.009	0.342	1.00 (1.00-1.00)[#]
CD4 counts at SVR cells/μL	≤200 >200	2 (3.7) 14 (2.8)	0.614	-	-
HIV viral load at SVR	<50 ≥50	15 (2.7) 1 (3.8)	0.532	-	-

Table shows the parameters associated with a greater risk of death for any cause. Continuous variables were categorized according to the median value or using clinical significant cut-offs. Estimated survival functions were calculated using the Kaplan-Meier method, and survival curves were compared by the log-rank test. Variables associated with the endpoint in the bivariate analysis, along with sex and age, were included in a Cox regression model.

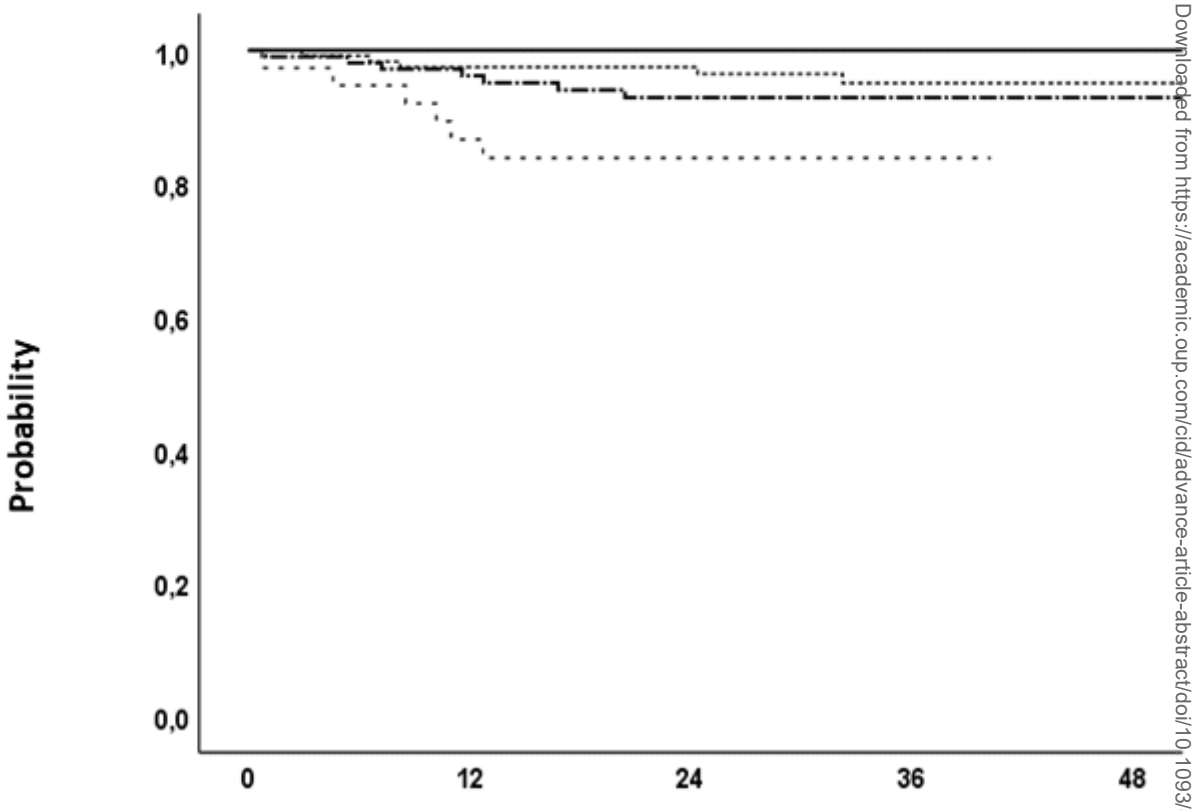
*Available in 589 patients. [†]Child-Pugh-Turcotte; available in 619 patients. [‡]Available in 604 patients. [‖]Available in 605 patients. [¶]For one-unit increase and [#]for 1000 units increase (included as continuous variables in the multivariate model).

Abbreviations: HCV: hepatitis C virus; PWID: People who injected drugs; CPT: Child-Pugh-Turcotte; MELD: Model for End-Stage Liver Disease; SVR: Sustained virological response; FIB-4 score: Fibrosis-4 score; DAA: Direct-acting antivirals; HIV: human immunodeficiency virus.

Figure 1. Probability of developing hepatic complications or requiring liver transplant, according to the value of liver stiffness at the sustained virological response time-point ($p<0.001$).

Abbreviations: LS: Liver stiffness

Figure 1



Patients at risk					
LS<14 kPa	374	336	259	93	18
LS 14-21 kPa	121	112	95	40	2
LS 21.1-40 kPa	107	94	75	37	4
LS >40 kPa	38	32	27	15	0