Impact of HIV infection on the dynamics of liver stiffness in patients with hepatitis C virus chronic infection after sustained virological response

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Summary

Background After sustained virological response (SVR), liver stiffness (LS) usually decreases. However, information related to the impact of HIV co-infection in patients with advanced fibrosis is scarce. The aim was to analyze the impact of HIV co-infection on the LS dynamics after HCV cure.

Methods Prospective study conducted in the GEHEP-011 multicenter cohort (initiated in October 2011–November 2023, ID NCT04460157), including patients with chronic HCV infection, with or without HIV co-infection, fulfilling: 1) SVR with direct-acting antivirals; 2) pre-treatment LS ≥ 9.5 kPa; 3) available measurement of LS at SVR. Pre-treatment, SVR and annual post-treatment LS were assessed. The primary outcome was time to LS normalization achievement (≤7.2 kPa) in two consecutive examinations.

Findings 1138 patients were included, 678 (60%) of whom were living with HIV (PLWH). The median time between the first to the last measure was 35 (17–69) months. In total, 390 [34% (95% confidence interval, 31%–37%)] patients achieved LS normalization, 169 [37% (CI 95%, 34%–43%)] individuals with HCV mono-infection vs. 221 [32% (CI 95%, 29%–36%)] PLWH achieved LS normalization (p = 0.003). The propensity score (PS) for HIV infection was calculated. In a multivariate model for competing risks (death was the competing event) adjusted for HIV, PS and

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diabetes, HIV infection was associated with a lower probability of achieving normalization [sHR = 0.82 (95% CI, 0.67–1.00), p = 0.045]. Matching by closer PS was performed. In the resultant subset, the probability of achieving LS normalization was again lower in PLWH [sHR = 0.76 (0.56–0.97), p < 0.001].

Interpretation After SVR, the probability of reaching LS normalization is significantly lower in PLWH. This could have implications on the development of long-term clinical events.

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Keywords: Liver stiffness; HIV; Hepatitis C; Sustained viral response; Transient elastography

Research in context

Evidence before this study

Prior to this study, it was well-established that HIV infection accelerates the progression of HCV-related liver disease. Achieving sustained virological response (SVR) has been associated with a significant reduction in the risk of mortality and hepatic complications. Liver stiffness (LS), which decreases in the short term after SVR, serves as an excellent prognostic marker for clinical outcomes in individuals with HIV/HCV-coinfection after HCV clearance. However, the impact of HIV on the evolution of LS in individuals with HCV following SVR remains poorly understood, largely due to the limited number of studies focused on HIV-coinfected patients and the inconsistent findings reported. We searched PubMed from database inception to July 1, 2024, for English or Spanish language publications, using the search terms "Liver stiffness" or "transient elastography" and "HIV" and "HCV" or "sustained virological response". Liver stiffness dynamics after sustained virological response is widely described in the short term and in small samples. In these studies, HIV patients are usually under-represented and data are controversial. Understanding changes after SVR in people living with HIV is a pivotal element in the long-term care of these patients.

Added value of this study

The dynamics of liver stiffness following sustained virological response remain underexplored in individuals living with HIV. Our findings reveal that the likelihood of achieving lower liver stiffness values is both significantly reduced and delayed in people living with HIV compared to those with HCV mono-infection. These results were observed even after adjusting for multiple potential confounding factors using competing risks models and propensity score matching, reinforcing their robustness. This evidence suggests that HIV co-infection adversely affects the long-term outcome of liver disease after successful HCV treatment. Our study addresses an important question concerning the long-term evolution of liver stiffness post-HCV cure, leveraging a large cohort with extended follow-up, wherein 25% of participants were monitored for more than 69 months. Rigorous statistical methods were employed to mitigate potential biases associated with differences in HIV infection status.

Implications of all the available evidence

The slower regression of liver stiffness in people living with HIV may result in a sustained elevated risk of long-term complications, including hepatocellular carcinoma, as well as higher liver-related morbidity and mortality, since liver stiffness is a surrogate marker of clinical outcome. These findings highlight the critical need for more proactive measures in PLWH to mitigate the risk of liver complications, including routine liver stiffness monitoring, hepatocellular carcinoma and esophageal varices surveillance, and timely therapeutic interventions when indicated.

Introduction

Hepatitis C virus (HCV) active infection triggers a cascade of liver damage, progressing to liver fibrosis and cirrhosis. Clinically significant portal hypertension, a frequent consequence of advanced fibrosis, is a major contributor to the development of life-threatening liver complications. Thus, early detection and accurate monitoring of fibrosis are crucial for effective patient management and improved clinical outcomes. In this context, liver stiffness (LS), as measured by vibration-controlled transient elastography (VCTE), has emerged as a useful non-invasive test in the evaluation of the liver disease extent. As a matter of fact, LS closely correlates with the histological stage of fibrosis and provides essential information on the prognosis of individuals with active and cured HCV infection,[1–4] both in individuals with HCV mono-infection and in people living with HIV (PLWH).[5–9] For this reason, LS is currently used for continuous risk stratification of patients, enabling personalized surveillance of liver events.[10–12]

Nowadays, HCV chronic infection is a curable disease with direct-acting antivirals (DAAs). However,

concerns persist regarding long-term outcomes after sustained virological response (SVR). Particularly, the contribution of risk factors, such as HIV co-infection, to the potential for residual liver disease is not well characterized. It is widely recognized that, during HCV active infection, HIV co-infection accelerates liver fibrosis progression, potentially due to alterations in cell-mediated immunity, and the increased production of proinflammatory and profibrotic mediators.[13,14] Despite the HCV cure significantly reduces LS and improves long-term prognosis, regardless of HIV co-infection,[15,16] the impact of HIV infection on the dynamics of LS after SVR remains unclear, and information on this issue is very limited. Recent studies did not observe significant differences in LS reduction after SVR between patients with and without HIV co-infection.[17–19] However, these findings should be interpreted cautiously due to the small sample sizes[18] and the limited follow-up period.[17,19] In a longer term, factors such as premature aging[20] or persistent immune activation and inflammation[21,22] associated with HIV may influence the evolution of LS in subjects with HIV/HCV co-infection.

This study aims to analyze the impact of HIV co-infection on the LS dynamics in patients with HCV chronic infection and advanced fibrosis who achieved SVR with DAAs based therapy, after a prolonged follow-up.

Methods

Study design and patients

This was a prospective study conducted in the multicenter cohort GEHEP-011 (clinicaltrials.gov; ID: NCT04460157), initiated in October 2011, in which 17 Infectious Diseases Units throughout Spain participated. Patients with chronic HCV mono-infection or HIV/HCV co-infection were recruited in this cohort if they fulfilled the following inclusion criteria: 1) to have achieved SVR with DAAs-based regimens; 2) to show LS values $\geq$ 9.5 kPa before treatment; and 3) to have an available LS determination, performed with VCTE, at the SVR time-point. Individuals with positive hepatitis B surface antigen at any moment were excluded.

Follow-up

The baseline time-point was the date of initiation of DAAs-based treatment. Clinical and analytical follow-up examinations were conducted at each site every 6 months under a common protocol, as reported in detail elsewhere.[23] Individuals were followed until the date of death, liver transplantation, HCV reinfection, loss to follow-up or the censoring date (November 30th, 2023), whatever occurred first. Each medical evaluation included a clinical examination and routine laboratory tests. Patients with cirrhosis were followed according to a protocol reported in detail in previous works.[24]

VCTE examinations

LS was assessed by VCTE (FibroScan®, Echosens, Paris, France), according to a standardized procedure,[7] using the M probe. Examinations were performed by a trained operator. To be considered valid it had to include at least 10 measures, with a success rate greater than 60%, and the median of the interquartile range should be less than 30%. LS was assessed within the 30 days before starting DAAs therapy and on the day of SVR. From that moment on, LS was measured once a year, when a VCTE device was available, at each center. In centers where VCTE were not continuously available, portable devices were shared among several physicians.

Outcomes and definitions

The primary endpoint was the achievement of LS normalization. LS normalization was defined as showing two consecutive LS values $\leq$ 7.2 kPa after SVR, because this figure presumably correlates with lack of significant fibrosis.[6,25] The date of LS normalization was established as the first date when this figure was reached. We considered LS progression as an increase of 20% over the baseline value.[26] LS levels were categorized to stratify patients based on the severity of fibrosis. The following categories were considered: $\leq$7.2 kPa; 7.3–9.4 kPa; 9.5–13.9 kPa; 14–20.9 kPa; and $\geq$21 kPa. The cut-off point chosen to define cirrhotic patients before SVR was $\geq$14 kPa because this value correlates better with cirrhosis in HCV/HIV co-infected cohorts.[1,11,24] Finally, LS $\geq$ 21 kPa was selected because its correlation with the presence of clinically significant portal hypertension[27] and its ability to predict esophageal variceal bleeding.[1,24,28]

Data analysis

Descriptive statistics were used to summarize the data, and appropriate statistical tests were applied based on the nature of the variables. Continuous variables are presented as median (quartile 1-quartile 3) and categorical variables as counts (percentage). Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using chi-square tests or Fisher's exact tests. The time-to-event was computed as the months elapsed from the baseline time-point to the emergence of the endpoint. Survival estimates were calculated using life tables and were expressed as the cumulative proportions of patients who reached the specific endpoint. Survival curves were constructed using the Kaplan–Meier method, and comparisons were performed by the log-rank test, according to different categories. A 95% confidence interval (95% CI) is provided for all estimates.

Missing LS values were handled using multiple imputation methods, up to the last available measurement, and the imputed data were then used for further analysis. For that purpose, LS missing data were imputed using a novel hybrid method that considers

both global and local trends to impute them. On the one hand, for each LS follow-up measure at time *t*, a ridge regression model[29] was built considering as input the LS measures before time *t* and the one immediately after *t*, while the LS measure at time *t* was considered as output. Those subjects that had missing values in any of those columns were not considered for such a model. Thus, these models aimed to capture the global trend of the LS measures across time, and could have been used to impute LS data at any column. Note that, at imputation time, a given subject may have had a missing value at time *t*, but also at the next follow-up measure; thus, the aforementioned model could have not been used. For such cases, ridge regression models considering as input only the LS measures before time *t* were also created. On the other hand, for each missing value in subject *p* at time *t*, a KNN-imputation method[30] was followed, in such a way that the given missing value is obtained as the weighted mean between the values of the k neighbors. The weight was proportional to the similarity, so most similar neighbors affect the imputation more than those that were more different. In this way, data were reconstructed with information from the closet matching patients, assuming that if they were similar in the rest of the characteristics, they would have also been in those with missing values. In order to obtain the neighbors, other characteristics such as the sex assigned at birth, HIV infection, age, and HCV genotype 3 were considered. Finally, to impute each missing value, the average between the prediction of the two aforementioned models (i.e., ridge regression and KNN imputations) was calculated, thus considering both the global and local neighborhood trends to predict such values. Missing values were imputed only up to the last actual follow-up measure of each patient, and not further.

Different imputed datasets were obtained to perform multiple imputation. In particular, 5 imputed datasets were considered, each of them using a different value of neighborhood k = {1, 3, 5, 7, 9}, as well as a random 80% of subjects to train the global ridge regression models. Such a variation aimed to reduce the possible uncertainty given by the original data and its missing values. Finally, each dataset was analyzed individually, and the results were combined using Rubin's rules to account for both within- and between-imputation variability.[31]

A generalized estimating equations (GEE) model was used to analyze repeated LS measurements over time, accounting for both within-subject (time) and between-subject (HIV co-infection status) effects. An autoregressive correlation structure (AR1) was assumed to model the temporal dependency of LS measurements. The analysis was conducted separately on the five imputed datasets to handle missing data using multiple imputation. Results from the five GEE models were subsequently combined using Rubin's rules to provide pooled estimates of coefficients, standard errors, and significance levels.

To address potential confounding biases due to baseline differences between people with and without HIV co-infection, a propensity score (PS) was calculated to balance baseline covariates between the two groups. To estimate the likelihood (propensity) of bearing HIV infection, a logistic regression model was built. Variables that differed among the two subpopulations at baseline time-point with a p-value < 0.20 were included in this model. For the primary analysis, two different approaches were conducted. First, a Fine–Gray regression model for competing risks was performed using the PS as a covariate as well as variables associated with the main endpoint in the bivariate analysis with a p-value < 0.05. Death from any cause was considered the competing event. This analysis was initially conducted on the imputed dataset, and subsequently, as a confirmatory strategy, on the crude dataset without imputation of the missing LS values. Second, a Fine–Gray regression analysis after HIV/HCV co-infected and HCV mono-infected matching of the sample by PS was performed. PS 1:1 matching without replacement was carried out using the 'psmatch2' package.[32] A caliper of 0.10 was employed to limit the maximum allowed distance in the PS between matched units.

Statistical analyses were conducted using Stata 16.0 Statistics/Data Analysis (StataCorp College Station, TX, USA) package and R software (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria) within the RStudio integrated development environment (version 2024.04.2 Build 764; RStudio, PBC, Boston, MA, USA). ChatGPT (version GPT-4; OpenAI, San Francisco, CA, USA), was utilized for assistance with statistical coding.

Ethical statement

This study was designed according to the Helsinki Declaration and approved by the local ethics committee (CEIC Hospital Universitario Ntra. Sra. de Valme, reference number 2069-N-19). All participants provided informed written consent before being enrolled in the cohort.

Role of the funding source

The funders did not play any role in the design, conclusions, or interpretation of the study.

Results

Characteristics of the study population

The flowchart of this study is shown in Fig. 1. One thousand one hundred thirty-eight patients were recruited, of whom 678 (60%) were PLWH. All PLWH were receiving antiretroviral therapy and 617 (91%) had a plasma viral load lower than 50 copies/ml. Among PLWH, median (Q1-Q3) $CD4^+$ cell counts were 573 (351–786) cells/mm^3. Other relevant baseline characteristics of the study population are displayed in Table 1.

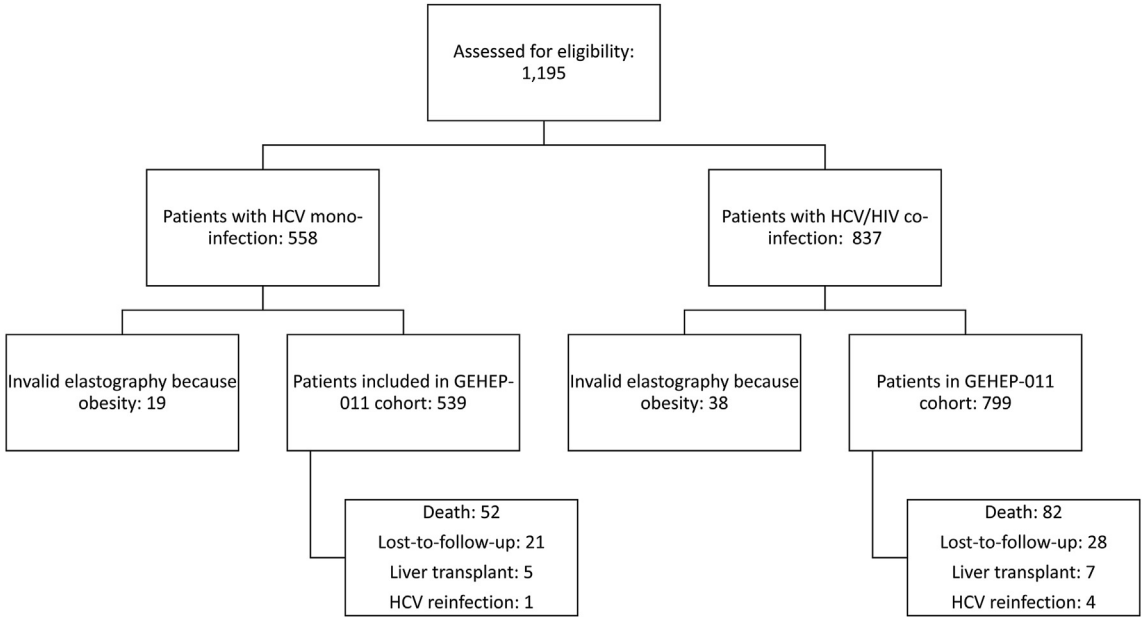

Fig. 1: **Study's flowchart**.

The median (Q1-Q3) time between the first to the last available measure was 35 (17–69) months. One hundred thirty-four (11.8%) patients died, 49 (4.3%) were lost-to-follow-up, 12 (1.1%) underwent a liver transplant, and in 5 (0.4%) individuals HCV reinfection was documented. Seven hundred sixteen patients (63%) have LS measurements in all their follow-up appointments. In 812 (19%) visits, LS had not been measured.

LS dynamics during follow-up

Median LS value at baseline (Q1-Q3) was 17.3 kPa (11.8–27.0) in patients with HIV/HCV co-infection and 15.4 kPa (11.8–26.4) in individuals with HCV mono-infection (p = 0.170). LS (Q1-Q3) median values at the different follow-up time points are shown in Fig. 2. LS showed a total median decrease of 6.4 (2.9–11.0) kPa in individuals with HCV mono-infection and 5.7 (2.9–12.0) kPa in PLWH.

In the GEE model, significant effects were observed for both time and HIV co-infection status on LS. The test of within-subject effects indicated that time was significantly associated with a progressive decrease in LS across measurements (p < 0.001). Between-subject effects revealed that patients with HIV co-infection had significantly higher LS values on average compared to those without HIV (p = 0.030) (Fig. 2).

Taking into account the first and the last LS measurement, 501 (44%) individuals decreased two or more LS categories, 311 (27%) improved only in one category, in 281 (25%) there was no category change, and 45 (4%) worsened one or more category. More specifically, 339 (29.8%) showed a LS value < 7.2 kPa in the last available LS measurement, 188 (28%) patients with HIV/HCV co-infection vs. 151 (33%) individuals with HCV mono-infection (Table 2). There were 65 (5.7%) patients with LS progression, 23 (5%) patients with HCV

Characteristics	**Group**		
Previous to treatment	Individuals with HCV mono-infection (N = 460)	Individuals with HCV/HIV co-infection (N = 678)	p-Value
Sex assigned at birth, Male, n (%)	332 (72.2)	584 (86.1)	<0.001
Age (years)[a]	54 (48–60)	51 (48–54)	<0.001
GT3, n (%)	74 (16.1)	114 (16.8)	0.811
Past use of injected drugs, n (%)[b]	166 (36.1)	571 (84.2)	<0.001
Cirrhosis, (LS ≥ 14 kPa), n (%)	266 (57.8)	421 (62.1)	0.149
LS ≥ 21 kPa, n (%)	161 (35.0)	256 (38.2)	0.272
MELD score[a,c]	6 (6–7)	6 (6–8)	0.125
CPT class A, n (%)[d]	442 (91.7)	533 (78.6)	0.021
Liver decompensation, n (%)	14 (3.0)	53 (7.8)	0.001
Diabetes, n (%)[e]	26 (5.7)	37 (5.5)	0.888
Alcohol ≥ 50 g/day, n (%)[f]	41 (8.9)	70 (10.3)	0.242
Alanine aminotransferase > 40 U/L,[g] n (%)	32 (7.0)	60 (9.2)	0.224
Aspartate aminotransferase > 40 U/L,[g] n (%)	39 (8.6)	61 (10.2)	0.372

Data are number (%) of patients. **Abbreviations:** HIV: human immunodeficiency virus; GT3: hepatitis C virus genotype 3; LS: liver stiffness; MELD: Model for End-stage Liver Disease; CPT: Child – Pugh – Turcotte; SVR: sustained virological response. [a]Median (Q1-Q3). [b]Available for 1133 patients. [c]Available for 1069 patients. [d]Available for 997 patients. [e]Available for 886 patients. [f]Available for 909 patients. [g]Available for 1053.

Table 1: **Baseline and at sustained virological response characteristics of the study population (N = 1138).**

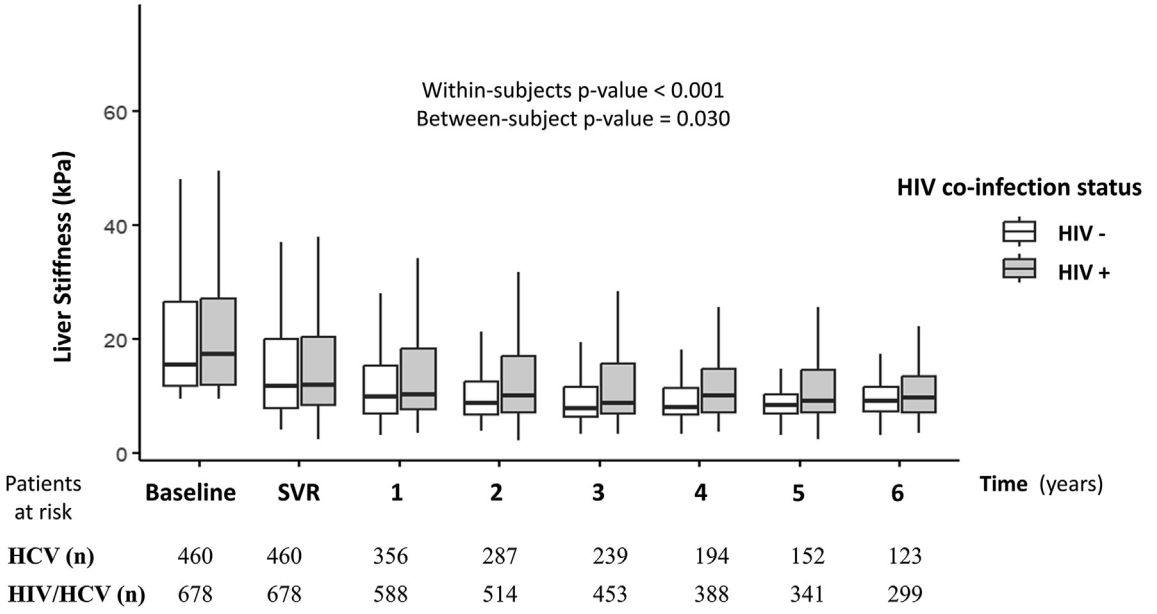

Fig. 2: **Dynamics of liver stiffness according to HIV co-infection status**. Bars represent LS median (Q1-Q3).

mono-infection, and 43 (6.8%) patients with HIV/HCV co-infection (p = 0.871).

Impact of HIV co-infection on LS dynamics

To calculate the PS for HIV co-infection, the following variables were taking into account: sex, age, route of HCV transmission, prior liver complication, Child-Pugh score prior-to-treatment, and baseline LS value. The area under the receiver operator characteristic curve (95% CI) for PS was 0.77 (0.74–0.80). Using the dataset with imputed data for missing LS values, 169 [37% (32%–41%)] individuals with HCV mono-infection vs. 220 [32% (29%–36%)] PLWH achieved LS normalization (Table 3). The probability (95% CI) of attaining a LS value < 7.2 kPa at one, three and five years was: 14% (11%–17%), 49% (41%–57%), 80% (74%–87%) among PLWH and 19% (15%–23%), 60% (52%–68%), 83% (76%–99%) in the HCV mono-infection cohort, respectively (Fig. 3). In a multivariable model, adjusted by PS scores, HIV infection and diabetes, HIV co-infection was associated with a lower risk of achieving normalization [sHR = 0.82 (0.67–1.00), p = 0.045] (Table 3). A total of 546 individuals, 273 in each group, could be matched according to PS. In the matched dataset, 83 [30% (25%–36%)] PLWH and 100 [37% (31%–43%)] patients with HCV mono-infection attained the main endpoint. The probability of reaching LS normalization was again lower among PLWH in the matched subpopulation [sHR = 0.76 (0.56–0.97), p < 0.001].

In the crude dataset without imputation, 169 [37% (34%–43%)] individuals with HCV mono-infection vs. 221 [32% (29%–36%)] PLWH achieved LS normalization. Additionally, a similar relationship between HIV co-infection and LS normalization was also observed [sHR = 0.78 (0.61–1.01), p = 0.058]. In this subset, a total of 518 patients could be matched according to PS. Eighty-five [33% (27%–39%)] PLWH and 104 [40% (34%–46%)] individuals with HCV mono-infection attained the main endpoint. The probability of showing a LS value below 7.2 kPa was again lower among PLWH [sHR = 0.74 (0.60–0.92), p = 0.006] in the matched subpopulation.

Pre-treatment category	Final category				
	<7.2 kPa (n = 339)	7.2–9.4 kPa (n = 207)	9.5–13.9 kPa (n = 240)	14-20.9 kPa (n = 156)	≥21 kPa (n = 196)
<14 kPa (n = 451)	221 (49.0%)	127 (28.2%)	80 (17.7%)	**16 (3.5%)**	**7 (1.6%)**
14–20.9 kPa (n = 267)	79 (29.6%)	54 (20.2%)	78 (29.2%)	34 (12.7%)	**22 (8.2%)**
≥21 kPa (n = 420)	39 (9.3%)	26 (6.2%)	82 (19.5%)	106 (25.2%)	167 (39.8%)

Bold font indicates categories in which patients' LS worsened after SVR.

Table 2: **Liver stiffness category in the last available measurement according to the liver stiffness pre-treatment category (N = 1138).**

Discussion

This study shows that a substantial proportion of people with chronic HCV infection and advanced fibrosis, both with and without HIV co-infection, are able to achieve LS normalization during a long-term follow-up after HCV eradication. Interestingly, although HIV co-infection was not associated with LS increase, the study found that the probability of achieving LS normalization is significantly lower and later among PLWH compared to those with HCV mono-infection.

	Categories	LS normalization n/N (%)	p-Bivariate	Adjusted sHR (95% CI)	p-Multivariate
Sex assigned at birth	Male	291/916 (32)	0.403	–	–
	Female	93/222 (42)			
Age (years)	<52	198/553 (36)	0.625	–	–
	≥52	186/585 (32)			
Past use of injected drugs	No	154/401 (386)	<0.001	–	–
	Yes	2730/737 (31)			
HCV genotype	Others	321/950	0.196	–	–
	3	63/188			
HIV co-infection	No	167/460 (36)	0.003	Ref.	0.045
	Yes	217/678 (32)		0.82 (0.67–1.00)	
LS value prior to treatment (kPa)	LS < 14	250/451 (55)	<0.001	–	–
	LS ≥ 14	134/687 (19)			
Alcohol intake (g/day)	<50	301/872 (34)	0.992	–	–
	≥50	11/37 (30)			
Diabetes	No	351/987 (36)	<0.001	Ref.	0.006
	Yes	9/64 (14)		0.40 (0.21–0.76)	
PS[a]	–	–	–	0.95 (0.61–1.48)[b]	0.890

(N = 1138). The propensity score for bearing HIV co-infection was constructed using a logistic regression analysis in which the following variables were entered: age, sex, way of HCV infection, prior hepatic decompensation, pre-treatment CPT score, and baseline LS value. The parameters age, sex, way of HCV infection, and baseline LS value were not entered in the model because they were already accounted for in the PS calculation. Data from five imputed datasets were analyzed individually. Kaplan–Meier survival analysis was performed for time-to-event outcomes, and log-rank tests were used to compare survival curves across groups. Group proportions (n/N) were calculated for each covariate category. Fine-Gray regression models were applied to account for competing events (death was considered the competing event), with the PS introduced as a covariate in the models. Results were combined using Rubin's rules to produce pooled estimates of the sub-distribution hazard ratios (SHR), 95% confidence intervals, and p-values. **Abbreviations:** LS: liver stiffness; HCV: hepatitis C virus; HIV: human immunodeficiency virus; PS: propensity score. [a]Available for 1104 patients. [b]Entered as a continuous variable.

***Table 3*: Predictors of liver stiffness normalization after sustained virological response.**

These findings were observed even after adjusting for multiple potential confounders through the competing risks model and PS matching, reinforcing the robustness of the results. This suggests that HIV co-infection has a negative impact on the long-term evolution of LS following successful HCV treatment.

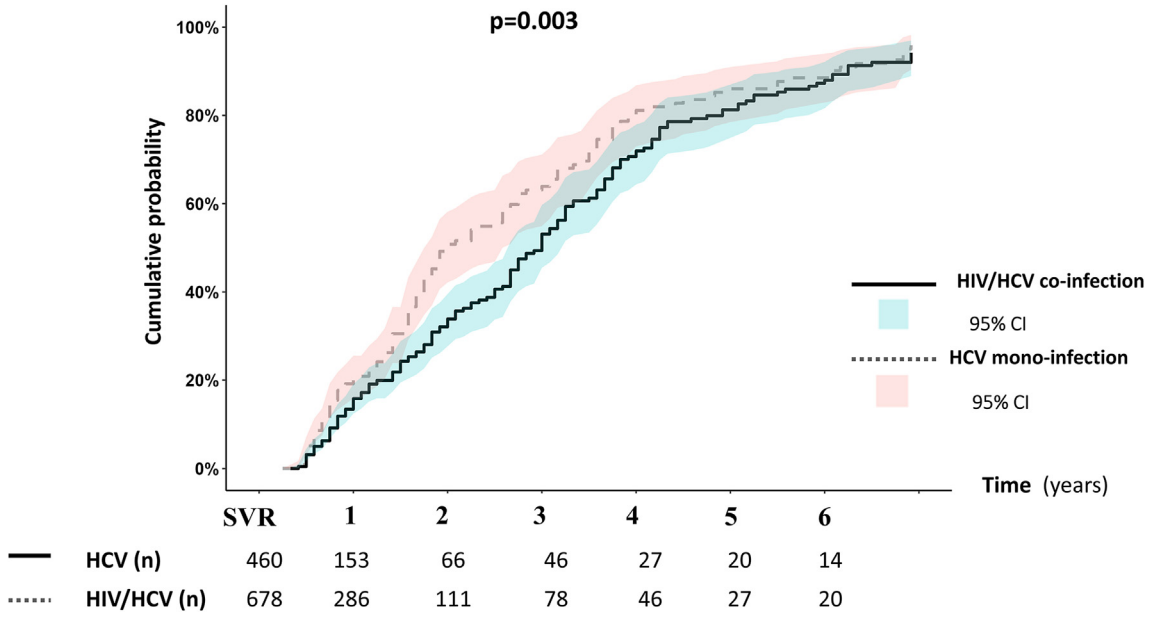

***Fig. 3*: Probability of attaining LS normalization according to HIV co-infection status**. Lines represent cumulative probability of attaining LS normalization in patients with and without HIV.

The factors underlying the impact of HIV on LS changes in HCV-infected patients after SVR are not fully elucidated. Several potential explanations can be considered. HIV infection is known to accelerate liver fibrosis progression, even in the setting of well-controlled viral replication and immune reconstitution with antiretroviral therapy.[13,14] In the same way, it may limit the extent of LS regression that can be achieved after HCV cure in co-infected individuals. Persistent inflammation and immune activation associated with HIV infection may impair the reversal of LS, even after HCV eradication. In fact, persistent inflammation is related with oxidative stress, with reactive oxygen species accumulation, and it may stimulate stellate hepatic cells,[33] leading to increased fibrogenesis. Likewise, the role of immunosenescence in the context of HIV/HCV co-infection may be relevant to explain the impact of HIV on LS evolution after SVR. Senescent cells release several inflammation mediators and factors which promote fibrogenesis, as transforming growth factor alpha (TNF-α), transforming growth factor beta (TGF-B), and interleukins 1 and 6 (IL-1, IL-6). It is well established that HIV accelerates the aging of the immune system, leading to a decline in immune function and an impaired ability to control viral replication and limit liver damage associated with HCV. Thus, it may be hypothesized that immunosenescence also affects fibrosis regression after HCV cure in a similar manner. Very recent data have pointed out the possibility that greater cellular aging, as measured by telomere length, could be responsible for a less effective liver regeneration after SVR.[34] Further research will shed more light on the complex interplay between HIV, HCV, inflammation and immunosenescence in driving liver disease progression and resolution.

The findings of the present work differ from what has been published recently. In former studies, no significant differences were found in LS changes between individuals with and without HIV co-infection at weeks 12 and 24 after the end of HCV treatment.[11] In this sense, Malin et al.[19] showed a decrease in the median LS value from 10.1 to 6.8 kPa, with no difference between mono and co-infected patients in the first year after cure. Similar results were reported by Lledó et al.,[17] with a median reduction of 2.1 kPa in the short term. On the other hand, a study by Balmaceda et al.[18] had a mean follow-up of 4.1 ± 1.7 SD years, but the sample was small and HIV patients were underrepresented, therefore resulting in a low number of patients followed for a long-time. In the present cohort, HIV co-infection was notably prevalent in the study population and the follow-up time was longer than in most of the subjects analyzed in the former studies.

It is important to note that the rapid decline in LS observed shortly after SVR may be primarily driven by the resolution of inflammation rather than the immediate regression of fibrotic tissue. While inflammation subsides relatively quickly after HCV eradication, true fibrosis regression is a more gradual process that can take longer time.[35] Additionally, it should be acknowledged that the current study did not assess long-term clinical outcomes, such as the development of liver-related events or mortality, in relation to LS dynamics. A link between LS dynamic and prognosis has been found in patients with advanced liver disease. Thus, it has been described that a decrease in LS is associated with a reduced incidence of liver-related adverse outcomes.[26,36–38] Consistent improvements in LS post-treatment may allow for discontinuation of complications surveillance, according to Baveno consensus.[10] HIV co-infection has not turned out to be a risk factor for liver-related events and does not shorten the survival of these patients once HCV infection is removed[11,23,39] in the short and mid-term. It seems that, while achieving LS normalization would be very relevant, what is critical in the short-term is to reach a specific level of LS below which the risk of developing clinical events is extremely reduced.[10,11,40] However, deleterious long-term clinical consequences of lower reduction in liver stiffness in HIV infected patients cannot be ruled out at all. As time goes on and aging advances, the effects of HIV infection may be more evident and translate into a different incidence of liver related events.

This study might have some limitations. First, several LS measurements were not captured due to the unavailability of VTCE in specific centers at the time of the clinical visit. To mitigate this, data imputation was performed. Sensitivity analyses conducted in the cohort without imputation of the missing LS values confirmed the findings. Second, adjustment for center effects was not performed in the final model. Although additional analyses were conducted using both fixed-effects Fine–Gray models and random-effects Weibull models, the inclusion of center effects did not significantly alter the hazard ratios of key covariates (HIV infection, diabetes) or improve model fit (Supplementary Material). Furthermore, the high number of centers, some with low patient counts, and the uniformity of protocol used across centers led us to conclude that such an adjustment would not meaningfully change the results. Third, despite performing PS analysis to balance baseline characteristics between groups, we acknowledge than some unmeasured confounder may persist. Specifically, some center-specific sociodemographic characteristics may have not been captured in the present work. In this line, alcohol intake, although similar in both groups at the beginning of follow-up, was not recorded at subsequent visits. Finally, other comorbidities, that were not evaluated in this work, particularly metabolic disorders, may play a role in LS regression. However, it is worth highlighting that this study shows some strengths. The present work addresses a clinically relevant question about the long-term outcomes of LS after HCV cure in a large sample size population, over a prolonged follow-up,

where 25% of patients had more than 69 months of monitoring. Additionally, robust statistical methods (propensity score adjustment and matching) were employed to minimize potential biases due to differences according to HIV infection status. Finally, the election of the primary end-point, namely achieving LS normalization, may have an impact on the long-term liver events such as hepatocellular carcinoma, as the selected threshold to define this event is indicative of lack of significant liver fibrosis.

In conclusion, PLWH with HCV chronic infection and advanced fibrosis, experience a slower LS regression after SVR, compared to individuals without HIV co-infection. Since SVR reduction, significantly improves the prognosis of patients with chronic HCV infection, with or without HIV co-infection, the slower LS regression in PLWH could translate into a persistently elevated risk of long-term complications, hepatocellular carcinoma and liver-related morbidity and mortality. This emphasizes the importance of proactive measures to mitigate these risks, including regular LS assessments, HCC surveillance, and early intervention when appropriate. Further studies with longer follow-ups and comprehensive data collection are needed to establish the relationship between LS kinetics and liver-related clinical events, as well as the impact of HIV infection in the long-term.

Contributors

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Data sharing statement

Anaïs Corma-Gómez (ACG) and Juan Macías had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The data that support the findings of this study are available from the corresponding author (ACG), upon reasonable request.

Declaration of interests

Nothing to report.

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During the preparation of this work the author(s) used ChatGPT (version GPT-4; OpenAI, San Francisco, CA, USA) was utilized for assistance with statistical coding. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103227.

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