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Original article

Antiretroviral therapy and sustained virological response to HCV therapy are associated with slower liver fibrosis progression in HIV–HCV-coinfected patients: study from the ANRS CO 13 HEPAVIH cohort

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Background: The aim of this study was to describe changes in repeated liver stiffness (LS) measurements and to assess the determinants of increase in LS in HIV–HCV-coinfected patients.
Methods: HIV–HCV-coinfected adults enrolled in the ANRS CO 13 HEPAVIH cohort, for whom two results of LS, evaluated over ≥24 months, were available. Patients with unreliable LS results were not included. LS was measured at baseline and every year thereafter. Determinants of LS increase were assessed using linear (primary outcome: last LS minus first LS value) and logistic (secondary outcome: ≥30% increase in the initial LS value) regression analyses.
Results: A total of 313 patients (mean age 45 years, 67.4% male) were included. Overall, 93.9% were receiving antiretroviral treatment (ART). The mean baseline CD4$^+$ T-cell count was 471 cells/mm^3 and 72.2% of patients had undetectable plasma HIV RNA. The mean interval between the first and last LS measurements was 33.5 months. No significant difference was found between baseline and follow-up mean LS values (*P*=0.39). However, a decrease of ≥30% in LS was observed in 48 (15.3%) patients and an increase of ≥30% in 64 (20.5%) patients. In multivariate linear and logistic analyses, excessive alcohol intake (β coefficient 6.8; *P*=0.0006) and high HCV viral load (OR 1.7, 95% CI 1.1, 2.5; *P*=0.01) were independently associated with an increase in LS, whereas time on ART>114.5 months (OR 0.5, 95% CI 0.3, 0.9; *P*=0.03) and achievement of sustained virological response (OR 0.1, 95% CI 0.01, 0.9; *P*=0.04) were independently associated with no increase in LS.
Conclusions: Our findings show that long-term ART and achieving sustained virological response in HIV–HCV-coinfected patients are both significantly associated with lack of increase in LS over a 33-month period.

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Introduction

HCV infection is common in patients infected with HIV, and leads to progressive liver fibrosis and cirrhosis. The progression of liver fibrosis in HIV–HCV-coinfected patients has been evaluated in very few studies so far and based only on liver biopsy (LB), which is currently the gold standard for such evaluation but is more and more rarely performed [1–3]. Because of the limitations and potential complications of LB, many patients and their physicians are indeed reluctant to undergo repeated liver biopsies to monitor liver disease progression [4,5]. Consequently, published studies on liver fibrosis progression, based on serial LBs present selection biases, patients refusing LB being *de facto* excluded.

Numerous non-invasive methods including biochemical markers and imaging techniques are now being used as alternatives to LB. Among these, transient elastography (Fibroscan™; Echosens, Paris, France), which measures liver stiffness (LS), has been validated and has demonstrated a good correlation with LB for assessing liver fibrosis in various liver diseases [6–8]. Contrary to LB, LS measurement is well accepted by patients and can be easily repeated.

The purpose of the present study was to describe changes in repeated LS measurements and to assess the determinants of an increase in LS in HIV–HCV-coinfected patients.

Methods

Patients

This study involved HIV–HCV-coinfected adults enrolled in the ANRS CO 13 HEPAVIH cohort, for whom two LS measurements over ≥24 months were available.

Exclusion criteria were non-valid criteria for LS interpretation (success rate <60%, IQRs>30% or alanine aminotransferase [ALT] value at the time of LS measurement > fivefold the normal value) or elevated LS result at the baseline evaluation (>57.6 kPa) in order to avoid a ceiling effect.

Briefly, the ANRS CO 13 HEPAVIH cohort is a French nation-wide prospective hospital-based cohort of HIV–HCV-coinfected adults initiated in 2005 and involving 17 hospital wards in France [9]. The following data were collected at enrolment and/or during follow-up visits: age, sex, risk categories for HIV and HCV infection, body mass index, time since HIV diagnosis, use of HAART (cumulative duration in months on each drug), time since HCV infection (estimated by the date of the first blood transfusion, the date of initial intravenous narcotic use, or the estimated date of contamination in subjects infected through sexual contact and who did not develop acute hepatitis C), biochemical findings, liver enzyme activities, $CD4^+$ T-lymphocyte count (absolute number and percentage), and plasma HIV RNA and HCV RNA loads. Insulin resistance was measured using the homeostasis model assessment of insulin resistance (HOMA) [10]. A self-administered questionnaire was used to collect sociodemographic characteristics and past and current substance and alcohol use. Hepatic steatosis was diagnosed by ultrasound examination. Ultrasound signs of hepatic steatosis included a bright hepatic parenchyma, enhanced liver–kidney contrast, vascular blurring and deep hepatic attenuation.

Liver stiffness measurement

LS was assessed by elastometry (Fibroscan™) at inclusion in the cohort and every year thereafter. The technical description and examination procedures have been reported elsewhere [11]. At least 10 validated measurements were performed for each patient. Results were expressed in kPa and ranged from 2.5 to 75 kPa. The median value was considered as representative of LS for each patient. Only procedures with a success rate of ≥60% and <30% IQRs were considered reliable.

LS was classified in the METAVIR system according to validated cutoffs: F0–F1<7.1 kPa, F2 7.1–9.5 kPa, F3 9.5–12.5 kPa and F4≥12.5 kPa [6].

Statistical analyses

The study baseline corresponded to the date of the first LS measurement.

The change in LS was analysed as outcome under two different forms. First, we examined the change in LS as a continuous variable, computed as the numeric difference between the last and the first LS measurement (a positive value indicating an increase in LS, a negative value indicating a decrease in LS). For each patient, the significance of change in LS was then evaluated using the Wilcoxon signed-rank test for paired observations. Then, the change in LS was analysed as a categorical variable defined as a ≥30% increase between the first and the last LS evaluations. This 30% cutoff was chosen based on clinical significance and also because it exceeded inter- or intra-observer error reported for LS evaluation [12].

Determinants of LS increase were assessed using linear (for the continuous outcome) and logistic (for the categorical outcome) regression analyses. The following variables were taken into account as explanatory variables: age, sex, body mass index, alcohol consumption, HCV transmission group and duration of HCV infection, HCV plasma viral load, $CD4^+$ T-cell count (absolute count and percentage), HIV plasma viral load, ALT, moderate to severe steatosis, HOMA and duration of antiretroviral treatment (ART; as a continuous, and then a categorical variable [≤median versus >median]).

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Models were systematically adjusted on the interval between the two LS evaluations in order to take into account the follow-up duration of each patient.

Results

Patient characteristics

A total of 384 HIV–HCV-coinfected patients had two LS evaluations within a minimum of a 2-year period. Among these, 66 were not included due to unreliable LS. Also, five patients with a baseline LS result >57.6 kPa were not included as a 30% increase in their baseline LS value (threshold defining an increase in LS) was not observable, due to the ceiling LS value of 75 kPa. A total of 313 patients were thus included in the analyses.

No significant differences were found between included and unincluded patients concerning age, gender, alcohol consumption, HIV and HCV plasma viral load, CD4+ T-cell count and duration of ART (data not shown).

Baseline characteristics of patients included in analyses are detailed in Table 1. Their mean age was 45 years and the majority was male. The principal route of HCV acquisition was intravenous drug use (74.9%) and the estimated mean duration of HCV infection was 21 years. The mean CD4+ T-cell count was 471 cells/mm^3 at baseline and 564 cells/mm^3 at follow-up. HIV RNA was undetectable in 72.2% and 81.0% of patients at baseline and follow-up evaluations, respectively. Only 12.5% of patients had a HIV viral load >1,000 copies/ml. The majority of patients (93.9%) had received ART for a median duration of 114.5 months. A total of 81 patients received HCV treatment between their first and last LS measurements and sustained virological response (SVR) was reported for 28 patients (34.6%).

Liver stiffness measurement changes

The median (range) interval between the baseline and the follow-up LS evaluations was 33.5 months (24–56). The median (range) LS values at baseline and at follow-up were 6.7 kPa (3.0–56.1) and 6.3 kPa (2.5–75.0), respectively. The Wilcoxon signed-rank test did not show any significant difference between the baseline and follow-up LS values (P=0.39). However individual values showed different spectrums of LS changes during follow-up. LS increased by ≥30% in 64 (20.5%) patients, decreased by ≥30% in 48 (15.3%) patients and remained stable in most patients (n=201; Figure 1). The median (range) LS at baseline was 6.3 kPa (3.0–26.3) in the 64 patients for whom there was a ≥30% increase in LS and 6.7 kPa (3.3–56.1) in the 249 others. In the 64 patients with ≥30% increase in LS, the median LS increase at the follow-up evaluation was 3.2 kPa (mean 6.4 kPa, Q1–Q3: 2.3–5.2).

The median LS at baseline was 9.2 kPa and 6.1 kPa in the HCV-treated and -untreated groups, respectively (P<0.0001).

Determinants of an increase in LS

Univariate and multivariate analyses results are presented in Tables 2, 3 and 4. In univariate analyses, when considering increase in LS as a continuous

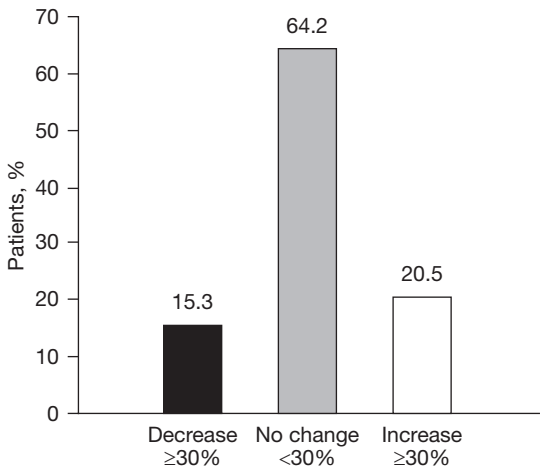
Table 1. Characteristics of the study population at baseline

Characteristic	Value
Age, years	45.0 (41.8–48.0)
Men, *n* (%)	211 (67.4)
Current excessive alcohol consumption, *n* (%)[a]	15 (5.0)
HCV infection through IVDU, *n* (%)	167 (74.9)
Duration of HCV infection, years	23.0 (19.0–26.0)
HCV genotype	–
1, *n* (%)	187 (59.7)
2 or 3, *n* (%)	58 (18.5)
4 or other, *n* (%)	68 (21.7)
HCV RNA, $\log_{10}$ IU/ml	6.2 (5.6–6.6)
AIDS stage, *n* (%)	87 (27.8)
Ongoing antiretroviral treatment, *n* (%)	294 (93.9)
PI, *n* (%)	225 (71.9)
NRTI, *n* (%)	276 (88.2)
NNRTI, *n* (%)	65 (20.8)
Abacavir, *n* (%)	102 (32.6)
Tenofovir, *n* (%)	153 (48.9)
Didanosine, *n* (%)	30 (9.6)
Efavirenz, *n* (%)	33 (10.5)
Nevirapine, *n* (%)	24 (7.7)
Atazanavir/ritonavir, *n* (%)	106 (33.9)
Fosamprenavir/ritonavir, *n* (%)	35 (11.2)
Lopinavir/ritonavir, *n* (%)	51 (16.3)
Duration of antiretroviral treatment, months	114.5 (57.0–143.3)
Duration of PI, months	36.2 (0.0–80.8)
Duration of NRTI, months	106.6 (41.1–138.8)
Duration of NNRTI, months[b]	59.5 (20.7–88.0)
Mean CD4+ T-cell count, cells/mm^3	437.0 (304.0–607.0)
CD4+ T-cell percentage	25.0 (19.6–32.9)
Undetectable plasma HIV RNA (<40 copies/ml), *n* (%)	226 (72.2)
Platelets, G/l	195.0 (148.0–242.0)
AST (×ULN)	1.2 (0.9–1.8)
ALT (×ULN)	1.3 (0.9–1.9)
GGT (×ULN)	1.5 (0.9–3.0)
Body mass index, kg/m^2	21.7 (19.8–23.8)
Steatosis, *n* (%)	45 (19.8)
HOMA	2.3 (1.4–3.4)
HOMA>3.8, *n* (%)	49 (21.0)
Liver stiffness at baseline, kPa	6.7 (5.2–9.4)
Liver stiffness at last follow-up, kPa	6.3 (5.2–9.2)
Time interval between liver stiffness evaluations, months	33.5 (25.9–37.6)
HCV treatment in the interval between liver stiffness measures, *n* (%)	81 (25.9)

Total n=313. Data are median (Q1–Q3) unless indicated otherwise. [a]Defined as >50 g/day for men and >30 g/day for women. [b]Median value for 65 patients receiving non-nucleoside reverse transcriptase inhibitors (NNRTIs). ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; HOMA, homeostasis model assessment of insulin resistance; IVDU, intravenous drugs use; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; ULN, upper limit of normal.

variable (that is, the numeric difference between the last and the first LS measurement), presence of moderate to severe steatosis and excessive alcohol consumption (>50 g/day for men and >30 g/day for women) were associated with an increase in LS, whereas a longer duration of ART was associated with no increase in LS. In multivariate linear analysis, excessive alcohol consumption (β coefficient 6.8; *P*=0.0006) remained the only factor independently associated with an increase in LS (Table 2).

Figure 1. Progression of liver stiffness in 313 HIV–HCV-coinfected patients in the ANRS CO 13 HEPAVIH cohort, France



When considering increase in LS as a categorical variable (>30% increase between first and last LS value) in univariate analyses, high HCV viral load was associated with an increase in LS whereas duration of ART>114.5 months and achievement of SVR to HCV treatment were associated with no increase in LS (Table 3). In multivariate logistic analysis, high HCV viral load (OR 1.7, 95% CI 1.1, 2.5; *P*=0.01) remained independently associated with an increase in LS, whereas duration of ART>114.5 months (median value; OR 0.5, 95% CI 0.3, 0.9; *P*=0.03) was associated with no increase in LS (Table 4). Similar results were found when the duration of ART was considered as a continuous variable (OR 0.9 per 12 more months on treatment, 95% CI 0.8, 0.9; *P*=0.04).

These results remained stable when LS was classified according to METAVIR scores, using the validated cutoffs: F0–F1<7.1 kPa, F2 7.1–9.5 kPa, F3 9.5–12.5 kPa and F4≥12.5 kPa. When considering this classification, 56 (21.1%) patients had a change in LS≥1 unit in METAVIR score (change of 1 unit, *n*=39, of 2 units,

Table 2. Factors associated with an increase in liver stiffness considered as a numeric difference between last follow-up and baseline evaluations in HIV–HCV-coinfected patients in the ANRS CO 13 HEPAVIH cohort, France: linear regression analyses

	Univariate analysis		Multivariate analysis	
Variable	Coefficient β (SD)	*P*-value	Coefficient β (SD)	*P*-value
Age[a]	0.1 (0.6)	0.87	–	–
Men	0.4 (0.8)	0.64	–	–
Body mass index[b]	-0.05 (0.1)	0.68	–	–
Steatosis	2.5 (1.0)	0.02	–	–
HOMA>3.8	0.05 (0.9)	0.96	–	–
AIDS stage	0.2 (0.8)	0.81	–	–
Current excessive alcohol consumption[c]	6.2 (1.7)	0.0004	6.8 (1.9)	0.0006
Duration of HCV infection[a]	0.4 (0.5)	0.41	–	–
HCV infection through IVDU	0.7 (1.0)	0.46	–	–
HCV viral load[b]	0.7 (0.5)	0.19	–	–
HCV genotype, 1 versus other	-0.3 (0.7)	0.68	–	–
CD4+ T-cell nadir[a]	-0.003 (0.03)	0.93	–	–
CD4+ T-cell absolute count[a]	0.02 (0.01)	0.30	–	–
CD4+ T-cell percentage[b]	0.02 (0.04)	0.61	–	–
Undetectable plasma HIV RNA	-0.7 (0.8)	0.39	–	–
ALT (×ULN)[b]	-0.1 (0.3)	0.74	–	–
Duration of antiretroviral treatment[a]	-0.13 (0.06)	0.04	–	–
Duration of antiretroviral treatment >114.5 months	-1.2 (0.7)	0.11	–	–
HCV treatment resulting in viral eradication[d]	-3.5 (2.0)	0.08	–	–

[a]Per 10 units increase. [b]Per 1 unit increase. [c]Defined as >50 g/day for men and >30 g/day for women. Variables with a *P*-value <0.20 in univariate analyses were selected for multivariate analyses, except steatosis due to a high number of missing data. [d]Only in the 81 patients treated for HCV. Variables included in multivariate analysis are alcohol, HCV viral load and duration of antiretroviral treatment >114.5 months. ALT, alanine aminotransferase; HOMA, homeostasis model assessment of insulin resistance; IVDU, intravenous drugs use; ULN, upper limit of normal.

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n=16 and of 3 units, *n*=1). High HCV viral load (OR 1.6, 95% CI 1.1, 2.5; *P*=0.04) and duration of ART (OR 0.4, 95% CI 0.2, 0.9; *P*=0.02) were significantly associated with an increase in LS considered as a change ≥1 unit in the METAVIR score.

In a further adjusted analysis including only the 81 patients treated for HCV, the relationship between SVR and increase in LS was assessed. In this analysis, when considering increase in LS as a continuous variable, SVR (β coefficient -3.9; *P*=0.04) and longer duration of ART (β coefficient -0.4; *P*=0.03) were independently associated with no increase in LS, whereas alcohol consumption (β coefficient 9.1; *P*=0.009) was independently associated with an increase in LS (Table 5). When considering increase in LS as a categorical variable (>30% increase between first and last LS value), only SVR was found to be associated with no increase in LS (OR 0.12, 95% CI 0.01, 0.90; *P*=0.04; Table 6).

Age, sex, duration of HCV infection, moderate to severe steatosis, HOMA value, ALT, aspartate aminotransferase, and antiretroviral drugs (considered individually) were not associated with an increase in LS.

Table 3. Factors associated with an increase in liver stiffness, considered as a >30% increase between baseline and last follow-up evaluations, in HIV–HCV-coinfected patients in the ANRS CO 13 HEPAVIH cohort, France: univariate logistic analyses

Variable	No increase in LS (*n*=249)	Increase in LS (*n*=64)	*P*-value
Age, years	44.7 (6.3)	44.8 (4.5)	0.91
Men[a], *n* (%)	163 (65.5)	48 (75.0)	0.15
Body mass index, kg/m^2	22.2 (3.3)	21.8 (3.3)	0.38
Steatosis, *n* (%)	33 (18.0)	12 (27.3)	0.14
HOMA>3.8, *n* (%)	43 (22.6)	6 (14.0)	0.20
AIDS stage, *n* (%)	70 (28.1)	17 (26.6)	0.79
Current excessive alcohol consumption[a,b], *n* (%)	9 (3.8)	6 (9.7)	0.06
Duration of HCV infection, years	21.3 (7.8)	21.5 (8.2)	0.92
HCV infection through IVDU, *n* (%)	131 (74.0)	36 (78.3)	0.54
HCV viral load, $\log_{10}$[a], IU/ml	6.0 (0.8)	6.3 (0.8)	0.01
HCV genotype	–	–	0.99
1, *n* (%)	148 (59.4)	39 (60.9)	–
2 or 3, *n* (%)	47 (18.9)	11 (17.2)	–
4 or other, *n* (%)	54 (21.7)	14 (21.9)	–
CD4$^+$ T-cell nadir, cells/mm^3	163.6 (124.3)	163.2 (129.2)	0.98
CD4$^+$ T-cell absolute count, cells/mm^3	472.1 (245.1)	468.4 (260.9)	0.91
CD4$^+$ T-cell percentage	26.0 (9.5)	25.2 (9.7)	0.57
Undetectable plasma HIV RNA (<40 copies/ml), *n* (%)	176 (70.7)	50 (78.1)	0.24
ALT (×ULN)	1.7 (1.2)	1.5 (1.0)	0.33
Ongoing antiretroviral treatment, *n* (%)	235 (94.4)	59 (92.2)	0.50
Duration of antiretroviral treatment, months	106.2 (57.9)	91.9 (63.1)	0.08
Duration of antiretroviral treatment >114.5 months[a], *n* (%)	132 (53.0)	25 (39.1)	0.04
Duration of antiretroviral treatment	–	–	0.27
<60 months, *n* (%)	59 (23.7)	21 (32.8)	–
60–120 months, *n* (%)	69 (27.7)	18 (28.1)	–
>120 months, *n* (%)	121 (48.6)	25 (39.1)	–
HCV treatment resulting in viral eradication, *n* (%)	27 (43.5)	1 (7.7)	0.04

Data are mean (SD) unless otherwise indicated. [a]Variables included in multivariate analysis; variables with a *P*-value <0.20 in univariate analyses were selected for multivariate analyses, except steatosis due to a high number of missing data. [b]Defined as >50 g/day for men and >30 g/day for women. ALT, alanine aminotransferase; HOMA, homeostasis model assessment of insulin resistance; IVDU, intravenous drugs use; LS, liver stiffness; ULN, upper limit of normal.

Table 4. Factors associated with an increase in liver stiffness, considered as a >30% increase between baseline and last follow-up evaluations, in HIV–HCV-coinfected patients in the ANRS CO 13 HEPAVIH cohort, France: multivariate logistic analysis

	Multivariate analysis	
Variable	OR (95% CI)	*P*-value
HCV viral load[a]	1.7 (1.1, 2.5)	0.01
Duration of antiretroviral treatment >114.5 months	0.5 (0.3, 0.9)	0.03

[a]Per 1 log increase.

Table 5. Factors associated with an increase in liver stiffness considered as a numeric difference between last follow-up and baseline evaluations, in the subgroup of 81 patients treated for HCV in the ANRS CO 13 HEPAVIH cohort, France: linear regression analyses

Variable	Univariate analysis		Multivariate analysis	
	Coefficient β (SD)	*P*-value	Coefficient β (SD)	*P*-value
Age[a]	0. 2 (1.8)	0.90	–	–
Men	-0.8 (2.1)	0.70	–	–
Body mass index[b]	0.3 (0.3)	0.28	–	–
Steatosis	5.2 (2.7)	0.05	–	–
HOMA>3.8	1.9 (2.2)	0.40	–	–
AIDS stage	-1.1 (2.1)	0.60	–	–
Current excessive alcohol consumption[c]	10.9 (3.4)	0.002	9.1 (3.4)	0.009
Duration of HCV infection[a]	0.2 (1.0)	0.87	–	–
HCV infection through IVDU	1.0 (2.8)	0.72	–	–
HCV viral load[b]	0.7 (1.1)	0.51	–	–
HCV genotype, 1 versus other	0.03 (1.9)	0.99	–	–
CD4+ T-cell nadir[a]	0.08 (0.09)	0.33	–	–
CD4+ T-cell absolute count[a]	0.01 (0.04)	0.77	–	–
CD4+ T-cell percentage[b]	0.005 (0.1)	0.96	–	–
Undetectable plasma HIV RNA	-0.1 (2.2)	0.95	–	–
ALT (×ULN)[b]	-0.3 (0.6)	0.60	–	–
Duration of antiretroviral treatment in months[a]	-0.3 (0.1)	0.05	-0.4 (0.2)	0.03
Duration of antiretroviral treatment >125 months	-2.5 (1.8)	0.18	–	–
HCV treatment resulting in viral eradication	-3.5 (2.0)	0.08	-3.9 (1.9)	0.04

Variables included in the multivariate analysis are: alcohol, duration of antiretroviral treatment in months and HCV treatment resulting in viral eradication. [a]Per 10 units increase. [b]Per 1 unit increase. [c]Defined as >50 g/day for men and >30 g/day for women. Variables with a *P*-value <0.20 in univariate analyses were selected for multivariate analyses, except steatosis due to a high number of missing data. ALT, alanine aminotransferase; HOMA, homeostasis model assessment of insulin resistance; IVDU, intravenous drugs use; ULN, upper limit of normal.

Table 6. Factors associated with an increase in liver stiffness, considered as a >30% increase between baseline and last follow-up evaluations, in the subgroup of 81 patients treated for HCV in the ANRS CO 13 HEPAVIH cohort, France: logistic analyses

Variable	No increase in LS (*n*=68)[a]	Increase in LS (*n*=13)[a]	Univariate analysis, *P*-value	Multivariate analysis	
				Adjusted OR (95% CI)	*P*-value
Age, years	44.4 (5.4)	46.0 (3.6)	0.39	–	–
Men	51 (75.0)	10 (76.9)	0.72	–	–
Body mass index, kg/m^2	22.0 (3.1)	21.8 (3.5)	0.84	–	–
Steatosis	9 (15.8)	3 (25.0)	0.21	–	–
HOMA>3.8	19 (31.1)	3 (30.0)	0.84	–	–
AIDS stage	16 (23.5)	5 (38.5)	0.47	–	–
Current excessive alcohol consumption[b]	5 (7.5)	1 (7.7)	0.63	–	–
Duration of HCV infection, years	20.3 (9.2)	26.1 (5.7)	0.11	–	–
HCV infection through IVDU	36 (72.0)	8 (88.9)	0.17	–	–
HCV viral load per 1 log increase, $\log_{10}$	6.0 (0.9)	6.1 (1.2)	0.49	–	–
HCV genotype 1 versus other	42 (61.8)	11 (84.6)	0.13	–	–
CD4+ T-cell nadir, cells/mm^3	159.6 (117.7)	130.5 (109.2)	0.46	–	–
CD4+ T-cell absolute count, cells/mm^3	452.6 (203.0)	419.7 (285.1)	0.41	–	–
CD4+ T-cell percentage	25.3 (9.4)	27.0 (11.5)	0.84	–	–
Undetectable plasma HIV RNA (<40 copies/ml)	51 (75.0)	12 (92.3)	0.28	–	–
ALT (×ULN)	2.1 (1.7)	1.4 (0.8)	0.18	–	–
Ongoing antiretroviral treatment, %	64 (94.1)	12 (92.3)	0.67	–	–
Duration of antiretroviral treatment, months	111.3 (60.5)	116.1 (61.3)	0.94	–	–
Duration of antiretroviral treatment >125 months	34 (50.0)	7 (53.8)	0.98	–	–
HCV treatment resulting in viral eradication	27 (43.5)	1 (7.7)	0.04	0.12 (0.01, 0.90)	0.04

[a]Continuous variables presented as mean (SD) and categorical variables as *n* (%). [b]Defined as >50 g/day for men and >30 g/day for women. Variables with a *P*-value <0.20 in univariate analyses were selected for multivariate analyses, except duration of HCV infection and HCV transmission group, due to a high number of missing data. ALT, alanine aminotransferase; HOMA, homeostasis model assessment of insulin resistance; IVDU, intravenous drugs use; LS, liver stiffness; ULN, upper limit of normal.

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Discussion

In this study of 313 HIV–HCV-coinfected patients, paired LS evaluation showed no change in LS value over a median time of 33.5 months. The median change in LS between baseline and follow-up evaluations was negative (-0.1 kPa), indicating that more than half of patients had a decrease or stabilization of their LS over this follow-up period. The main finding in this study was the association of longer duration of ART with a decrease or stabilization of LS in HIV–HCV-coinfected patients, suggesting a beneficial effect on liver fibrosis progression, as LS is correlated with liver fibrosis. In agreement with our results, recent studies showed that liver fibrosis progressed more slowly in HIV–HCV-coinfected patients receiving long-term ART and that this progression was similar to that observed in HCV monoinfection [2,13,14]. However these studies failed to establish a link between ART use and lower fibrosis progression, probably because the duration of ART was not fully evaluated. In a recent cross-sectional study performed within our cohort, we showed a negative effect of some antiretroviral nucleoside agents, particularly didanosine-based combinations, on liver fibrosis in HIV–HCV-coinfected patients, probably due to the high mitochondrial hepatotoxicity of this drug [15]. Didanosine is no longer recommended and some new non-hepatotoxic or low-hepatotoxic antiretroviral drugs are used in the management of HIV–HCV-coinfection, which could explain the protective effect of ART in our longitudinal study. Indeed, in our study, the most frequently prescribed nucleoside reverse transcriptase inhibitors were tenofovir (48.9%) and abacavir (32.6%), known to be less toxic for the liver, whereas only 9.6% patients received didanosine.

Our findings were strengthened by other recent data showing an increased risk of fibrosis progression in HIV–HCV-coinfected patients experiencing ART interruption [16,17], suggesting a link between ART intake and fibrosis progression. However, despite this reassuring result, it should be noted that 64 (20.5%) patients in our cohort experienced a significant increase in their LS over time, thus indicating a significant progression of liver fibrosis. This proportion of fibrosis progressors was relatively low, as compared with those reported by repeated LB studies in which the proportion ranged between 36% and 46% [2,3,18]. Population characteristics including ART use, methods and cutoffs used to assess fibrosis progression could explain these discrepancies. In addition, these LB studies were carried out at a time when certain hepatotoxic antiretroviral drugs were still often prescribed. However, consistent with our results, only Macías *et al.* [18] found a positive effect of ART and HCV therapy on liver fibrosis progression.

The effect of ART on the liver could be considered as the result of the balance between hepatotoxicity and the consequences of immune reconstitution on the evolution of HIV–HCV-coinfection. Since ART effectively improves HIV-related immune dysfunction and substantially reduces the risk of HIV progression, it is possible that the progression of HCV infection may also be reduced. This beneficial effect of ART on the liver could be the result of an improvement of serum markers of hepatic inflammation and fibrosis following the start of ART, as suggested by some authors [19,20]. Indeed many liver inflammation markers such as cytokeratin-18 (a protein involved in liver cells apoptosis), hepatocyte growth factor and fibrosis markers such as matrix metalloproteinase-2 and tissue inhibitors of matrix metalloproteinase-1 have been found to be decreased in HIV–HCV-coinfected patients treated with ART. In addition, it has been reported in a cross-sectional study that early initiation of ART was associated with less severe liver disease [21].

Furthermore, it has also been demonstrated that HIV itself has a direct effect on liver fibrosis progression [22]. HIV infects hepatic stellate cells, inducing collagen I expression and secretion of the monocyte chemoattractant protein 1, a proinflammatory cytokine. Suppression of HIV via effective ART, could thus lead to an improvement of liver fibrosis. However, plasma HIV RNA was not associated with an increase in LS in our cohort, probably because only few of our patients (12.5%) had a high HIV plasma viral load. It would be interesting to consider the time interval during which HIV RNA was undetectable in the plasma. Unfortunately, these data were not available in our cohort.

Conversely to its beneficial action, ART may also lead to the development of acute toxic hepatitis, steatosis, steatohepatitis, liver fibrosis, and non-cirrhotic portal hypertension, negating any potential benefits of immune reconstitution [23,24]. The mechanisms involved in ART-associated hepatotoxicity include mitochondrial toxicity, steatosis and an increase in inflammation cytokines such as tumour necrosis factor-α, interleukin-6 and interleukin-1β [25,26].

Another finding of our study was the association of high HCV viral load with LS increase. The relationship between the replication level of HCV and liver damage is still controversial, although it has been reported that patients with a higher viraemia might have more intense architectural damage and more severe progression of liver disease than those with lower levels of HCV replication [27–30]. Finally, in line with previous reports, our study showed an inverse association between SVR and increase in LS, probably due to a reduction in liver necroinflammation after HCV treatment [18,31]. Furthermore, HCV replication, which correlates with the extent of mitochodrial DNA depletion in PBMCs in

HIV–HCV-coinfected patients, may be reversed by successful anti-HCV therapy [32].

Several other factors associated with liver fibrosis progression in HIV–HCV patients have been reported in the literature, such as male sex, duration of HCV infection, excessive alcohol consumption, liver histology activity and low $CD4^+$ T-cell nadir [18,33–36]. In keeping with previous reports, we found that excessive alcohol consumption was associated with an increase in LS; thus, counselling for alcohol reduction of all HCV carriers should indeed be strengthened. However, our study failed to find a link between the duration of HCV infection and increase in LS, probably because this duration was only estimated and not precisely documented given that the date of HCV seroconversion was unavailable in our cohort with a high proportion of intravenous drugs users. In addition, no association was found with HOMA value, probably because of the limited follow-up period in our cohort and the very small number of patients with insulin resistance.

Our study has certain limitations. Firstly, a number of covariates such as ILB28 genotypes, recently identified as predictive of liver fibrosis progression in HCV-infected patients, were not included in the analyses [37,38] as ILB28 genotyping has not been performed yet in our patients. Secondly, the cutoff of 30% used to define increase in LS was somewhat artificial and could not mirror sufficiently a clinically relevant evolution of liver fibrosis. Lastly, inter-observer variations in LS measurements could exist and then affect patients' classification [12]. Despite these limitations, our results remain similar to those already published elsewhere concerning the predictive factors of liver fibrosis progression, thus ensuring the robustness of our study.

In conclusion, our findings show that long-term ART and achieving SVR in HIV-positive patients with chronic hepatitis C are both significantly associated with lack of increase in LS over a 33-month period. These results provide support for better access to HCV treatment and early initiation and prolonged ART in HIV–HCV-coinfected patients. Frequent follow-up visits are also required to manage ART side-effects and improve ART compliance and benefits.

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Disclosure statement

The authors declare no competing interests.

Additional file

Additional file 1: A list of the participating members of the ANRS CO 13 HEPAVIH Study Group can be found at http://www.intmedpress.com/uploads/documents/AVT-12-OA-2472_Loko_Add_file1.pdf

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