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Liver stiffness is not associated with short- and long-term plasma HIV RNA replication in immunocompetent patients with HIV infection and with HIV/HCV coinfection

Saverio Giuseppe Parisi[a], Monica Basso[a], Carlo Mengoli[a], Renzo Scaggiante[b], Samantha Andreis[a], Marzia Maria Franzetti[b], Anna Maria Cattelan[b], Daniela Zago[a], Mario Cruciani[c], Massimo Andreoni[d], Sara Piovesan[a], Giorgio Palù[a], Alfredo Alberti[a]

University of Padova; Padova Hospital, Center of Diffuse Disease, Verona; Tor Vergata University of Rome, Italy

Abstract

Background Human immunodeficiency virus (HIV) may be directly responsible for liver damage but there are contrasting data regarding the influence of detectable plasma viremia. We analyzed the influence of plasma HIV RNA (pHIV) detectability and of other clinical and viro-immunological variables on liver stiffness (LS) measurement in adult immunocompetent HIV-monoinfected patients and in patients coinfected with hepatitis C virus (HCV).

Methods Logistic regression analysis was performed using the value of LS>7.1 kPa as the dependent variable. A linear regression model was applied using LS measurement after $\log_{10}$ transformation (lkpa) as the dependent variable and we analyzed the predicted values versus the observed lkpa values; pHIV was classified as detectable or undetectable in the 12- and 36-month study periods before LS measurement.

Results We studied 251 patients (178 with HIV monoinfection), most of whom were on antiviral treatment; 36-month study time was available for 154 subjects. The mean CD4+ cell count was 634 cells/mm^3 in HIV-monoinfected patients and 606 cells/mm^3 in coinfected patients. No difference in LS was found between patients with detectable or undetectable pHIV in either the 12- or the 36-month study period before transient elastography. The mean LS was higher in HIV/HCV coinfected patients (P<0.0001) than in the HIV-monoinfected subjects; lkpa was positively correlated with HCV coinfection (P<0.0001) and aspartate aminotransferase levels (P<0.0001). Detectable pHIV failed to reach significance. Eight HIV-monoinfected patients had a predicted LS measurement lower than the observed one, while eight patients had the opposite result.

Conclusion LS was not correlated with ongoing HIV replication during the 12- and 36-month study periods in immunocompetent HIV-monoinfected and HIV/HCV-coinfected patients.

Keywords Liver stiffness, HIV RNA, immunocompetent

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[a]Department of Molecular Medicine, University of Padova, Padova (Saverio Giuseppe Parisi, Monica Basso, Carlo Mengoli, Samantha Andreis, Daniela Zago, Sara Piovesan, Giorgio Palù, Alfredo Alberti); [b]Infectious Disease Unit, Padova Hospital, Padova (Renzo Scaggiante, Marzia Maria Franzetti, Anna Maria Cattelan); [c]Center of Diffusive Diseases, ULSS 20, Verona (Mario Cruciani); [d]Clinical Infectious Diseases, Tor Vergata University of Rome, Rome (Massimo Andreoni), Italy

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Introduction

Chronic liver disease is a major cause of morbidity and mortality in human immunodeficiency virus (HIV)-positive patients, and coinfection with hepatitis C virus (HCV) is one of the most clinically important comorbidities [1]. However, many other factors, such as alcohol abuse, drug-related hepatotoxicity and nonalcoholic fatty liver disease, may also be responsible for liver damage [2,3]. This scenario is evolving as a result of the availability of direct-acting antivirals for the treatment of HCV infection and the current minimal exposure to antiretroviral drugs with a potentially hepatotoxic profile,

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such as didanosine, stavudine or zidovudine [4-6]. HIV may be directly responsible for liver damage; Kupffer cells, hepatocytes, and human stellate cells (HSCs) do not express CD4 receptors, and HIV cannot infect these cells, but the virus can stimulate HSCs through a C-C chemokine receptor type 5- or C-X-C chemokine receptor type 4-dependent pathway. HSCs are key cells involved in the progression of fibrosis: transforming growth factor-β, secreted by human peripheral blood mononuclear cells infected by HIV-1, was found to promote HSC modulation in an *in vitro* model [7,8]. Updated guidelines recommend that antiretroviral treatment (ART) should be started in all HIV-infected subjects with detectable plasma HIV viremia, regardless of CD4+ cell count; successful plasma HIV viremia suppression is achieved in most patients, but long-term efficacy may be suboptimal [6,9].

Liver fibrosis in HIV-positive patients is a multifactorial process; parameters modifiable over time (e.g., HBV-DNA and HCV-RNA detectability or undetectability) or parameters not modifiable over time (e.g., sex) may influence liver fibrosis [3,10,11]. The measurement of liver stiffness (LS) by transient elastography (TE) represents a rapid and noninvasive method for predicting liver fibrosis, and the result, which is expressed in kilopascals (kPa), is available immediately; this imaging modality is highly accurate in the detection of moderate fibrosis and cirrhosis in patients with HIV/HCV coinfection [12]. Abnormal LS values were found in a percentage of HIV-monoinfected patients, ranging from 41.9% (LS values >5.3 kPa were considered abnormal) to 11.2% (LS values ≥7.2 kPa were considered abnormal) [13-15].

TE was shown to be more reliable than the aspartate aminotransferase (AST)-to-platelet ratio index and the Fibrosis-4 score (FIB-4) in the staging of liver fibrosis in HIV/HCV coinfected patients; both indices include platelet count, which may be lower in viremic HIV-positive patients because of HIV-related thrombocytopenia [16,17]. The first aim of this study was to describe the demographic and viro-immunological parameters that influence TE results in a cohort of immunocompetent HIV-monoinfected patients and HIV/HCV-coinfected patients; the second aim of this study was to evaluate the reliability of a model (linear predictor) that included clinical variables in predicting LS value.

Patients and methods

We retrospectively enrolled patients into this study based on the following eligibility criteria: 1) age over 18 years; 2) diagnosis of chronic HIV infection; 3) hepatitis B serum antigen (HBsAg)-negative; 4) HCV treatment-naïve or previously treated relapsers or non-responders; 5) regular viro-immunological follow up of the HIV disease during at least the 12 months before TE; 6) no acute HCV infection; 7) no alcohol abuse; 8) no didanosine, stavudine or zidovudine therapy; and 9) valid TE performed between December 1, 2013, and September 30, 2015. Patients were excluded from the study if they showed a sustained virological response (SVR), experienced a spontaneous clearance of HCV, or had other known causes of liver disease or previous liver transplantation. Alcohol abuse was defined as the daily consumption of alcohol in doses of more than 20 g/day for women and more than 30 g/day for men. This study was conducted in accordance with local legislation and received approval from the local Ethics Committee of Padova University Hospital (61946/15). Anonymous data were collected retrospectively.

Patients were either untreated for HIV infection or received ART according to the current international guidelines. Decisions on HIV therapy were made at the discretion of the treating physician; there were no restrictions on CD4+ cell count.

Patients were classified based on plasma HIV viremia (detectable or undetectable when TE was performed and in the 12 months and the 36 months before TE) and on the presence of HCV infection (patients were either HCV-positive or HCV-negative). We defined T0 as the study time corresponding to the execution of TE, T1 as the study time corresponding to the 12-month period (short term) before TE and T2 as the study time corresponding to the 36-month period (long term) before TE. Plasma HIV viremia data during T2 were available for a subgroup of subjects.

Study of HIV and HCV infection

Plasma HIV-1 RNA levels were measured using blood samples at all visits; regular monitoring was defined as a visit frequency of at least every four months. We considered plasma HIV viremia to be undetectable when the viral load was below the limit of 50 copies/mL [6]. Only a single viral blip (an increase in the HIV RNA plasma viral load above 50 copies/mL but below 500 copies/mL, followed by an undetectable HIV RNA) was tolerated [18]; HIV viremia was classified as detectable if any other result was obtained.

Both naïve and HCV treatment-experienced patients were included. Previously failed antiviral treatment included therapy with interferon (standard or pegylated) as monotherapy or with ribavirin, according to the current international guidelines at the start of HCV treatment. Any virological response that was different from SVR was classified as having no response to antiviral treatment.

HCV RNA genotypes were determined using the VERSANT® HCV genotype 2.0 assay (INNOLiPA, Innogenetics, Belgium). HIV and HCV plasma viral loads (copies/mL and IU/mL, respectively) were evaluated using the Abbott Real-Time assay (Abbott Molecular Inc., Des Plaines, IL).

Correspondence to: Saverio G. Parisi, Department of Molecular Medicine, University of Padova, Via Gabelli 63, 35121 Padova, Italy, Tel.: +39 0498 272344, Fax: +39 0498 272355,
e-mail: saverio.parisi@unipd.it

The work was conducted at the Department of Molecular Medicine, University of Padova, Padova, Italy

Saverio Giuseppe Parisi and Monica Basso contributed equally to this work

Study of liver fibrosis

LS was measured by TE (FibroScan®; Echosens, Paris, France). Significant liver fibrosis was defined as an LS of at least 7.1 kPa [19,20]. At least 10 successful measurements were performed on each patient; the result was considered valid when the interquartile range was lower than 30% of the median and a minimum success rate of 60% was obtained. Patients had been fasting for at least 8 h when TE was performed. An expert examiner carried out the LS assessments [21].

Statistical analysis

Conventional descriptive statistics were applied to describe the characteristics of the HIV-monoinfected subjects and the HIV/HCV coinfected patients. Continuous data were expressed as mean and standard deviation and were compared using Student's *t*-test, while categorical data were compared using Fisher's exact test. In addition, the variables were submitted to a pairwise correlation analysis using Pearson's linear model to outline the underlying link pattern in the study population, and a logistic regression analysis was performed using the value of LS>7.1 kPa as the dependent variable. Then, a linear regression model was set up with lkpa (LS value after $\log_{10}$ transformation) as the dependent variable. The mathematical model is a linear predictor; the final result was the predicted value of TE (expressed as lkpa) in a single patient and it was obtained by using the algebraic sum of each clinical variable multiplied by its own coefficient and of the intercept value. A locally weighted regression was applied for the empirical validation of the model. A regression analysis of predicted lkpa values versus observed lkpa values was also performed and the characteristics of the left outliers (patients with predicted values that were higher than or comparable to the observed values) and of the right outliers (patients with predicted values that were lower than the observed values) were analyzed using the chi-square test with no continuity correction and Student's *t*-test. Analyses were conducted using Stata software version 14.0 (College Station, Texas), and a P-value <0.05 guided the statistical interpretation.

Results

A total of 413 patients underwent a TE; a complete description of the selection process is summarized in Fig. 1. Overall, 251 of the 277 (90.6%) patients were suitable for the main analysis (T1 study time); 26 patients were not included in the study because of a discordant plasma HIV viremia result at T1 and at T0 (21 patients had successful virological suppression at T0 and detectable viremia 12 months before TE).

The group of 251 patients included 178 HIV-monoinfected patients (124 with undetectable HIV RNA and 54 with detectable HIV RNA) and 73 HIV/HCV coinfected subjects (54 with undetectable HIV RNA and 19 with detectable HIV RNA). The demographic and viro-immunological characteristics of all the patients included in the study are presented in Table 1. Patients with HIV/HCV coinfection had a significantly higher LS value (P<0.0001), a greater incidence of significant fibrosis (P<0.0001), higher AST and alanine aminotransferase values (P<0.0001), and a lower number of CD4+ cell counts at nadir (P=0.003).

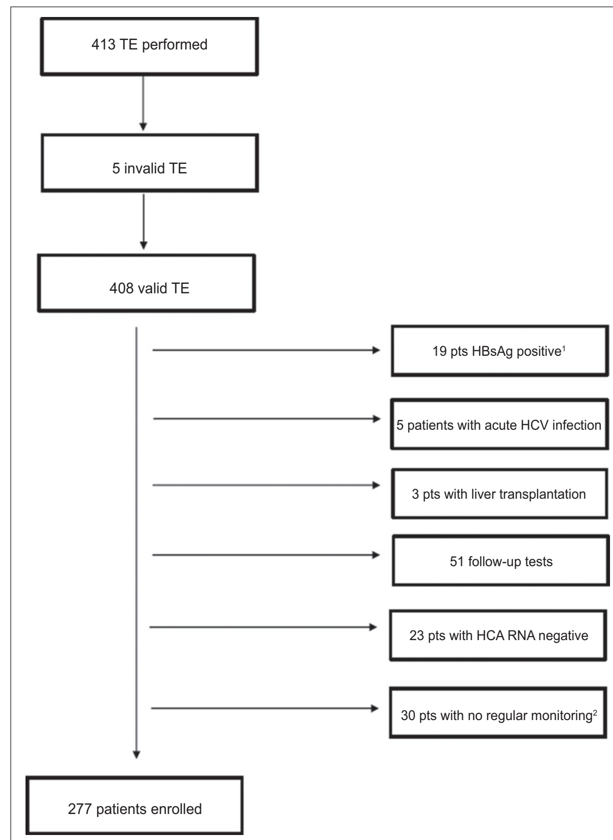

Figure 1 Flow chart describing the selection of the study patients
[1]*Alcohol abuse in 5 patients*
[2]*Therapy with didanosine, stavudine or zidovudine in 3 patients*
TE, transient elastography

The 36-month study period was available for 154 subjects (61.3%), including 41 subjects (26.6%) with HIV/HCV coinfection and 113 subjects (73.4%) with HIV monoinfection. Most patients were Caucasian (96.8%) and on ART (89.6%). The HCV genotype was available for 72 of the 73 patients with a 12-month study duration; 41 of these subjects (56.9%) had genotype 1 infection. The mean HCV RNA level was comparable in coinfected patients with detectable pHIV and with undetectable pHIV (1,021,736 IU/mL, 95% confidence interval [CI] 393,401-2,653,638 IU/mL and 1,216,888 IU/mL, 95%CI 797,099-1,857,756 IU/mL, respectively; P=0.69). Only a few HIV/HCV patients (14 of 73, 19.2%) had been previously treated with an interferon-based regimen. The mean LS was higher in HIV/HCV-coinfected patients (P<0.0001); most HIV-monoinfected patients (91%) had an LS value ≤7.1 kPa. No significant differences in LS values were found between patients classified as having detectable or undetectable plasma HIV viremia, while HIV/HCV patients had higher LS values than monoinfected subjects, regardless of plasma HIV viremia

Table 1 Characteristics of the 178 HIV-monoinfected subjects and of the 73 HIV HCV coinfected patients

Variables	HCV negative (178 patients)	HCV positive (73 patients)	P-value
Age (years)[1]	47 (11)	48 (7)	0.631
Male sex, n (%)	159 (89.3)	57 (78.1)	**0.019**
BMI[1]	24.3 (3.6)	23.4 (3.3)	0.063
Patients with BMI≥30, n (%)	14 (7.8)	4 (5.5)	0.59
LS (kPa)[1]	4.6 (1.4)	8.4 (1.6)	**<0.0001**
Patients with LS>7.1 kPa, n (%)	16 (9)	40 (54.8)	**<0.0001**
CD4+ cell count at nadir (cells/mm^3)[1]	361 (261)	263 (151)	**0.003**
CD4+ cell count at T0 (cells/mm^3)[1]	634 (296)	606 (333)	0.51
AST (U/L)[1]	29 (16)	60 (33)	**<0.0001**
ALT (U/L)[1]	32 (34)	69 (39)	**<0.0001**
Patients on ART, n (%)	156 (87.6)	69 (94.5)	0.116
Patients with plasma HIV RNA undetectable, n (%)[2]	123 (78.9)	53 (76.8)	0.73
PI as third drug, n (%)[2]	99 (63.5)	49 (71)	0.27
HIV RNA at T0[2] (copies/mL)[3]	8979 (2311-23731)	962 (101-30553)	0.191

Significant P-values are in bold

[1] mean and SD

[2] percentage with respect to patients on ART

[3] median and 95%CI in patients with detectable plasma HIV RNA

ALT, alanine aminotransferase; ART, antiretroviral treatment; AST, aspartate aminotransferase; BMI, body mass index; LS, liver stiffness; PI, protease inhibitor

(Fig. 2). There was a significant correlation between lkpa and age (P=0.025), HCV coinfection (P<0.0001) and AST (P<0.0001). The quadratic variable "bmi2" was added to the linear regression model in order to investigate the hypothesis of a non-linear correlation between lkpa and body mass index (BMI) and this hypothesis was confirmed (P=0.026); the other variables failed to reach significant P-values, including the successful suppression of HIV viremia at T1 and T2. This last finding was confirmed using logistic regression; this statistical approach revealed a positive correlation between an LS value >7.1 kPa and BMI (P=0.006), BMI as a quadratic variable (P=0.003), HCV coinfection (P<0.0001 and AST (P=0.001). The final linear regression model data are reported in Table 2; the mean predicted values were 4.69 kPa (95%CI 4.44-4.95 kPa) in patients with HIV monoinfection and 8.39 kPa (95%CI 7.70-9.15 kPa) in subjects with HIV/HCV coinfection. Fig. 3 depicts the effects of HCV infection and BMI on the original LS data and on the model-based predictions.

Following the linear regression model, an analysis was performed to describe bivariate normal distributions for predicted and observed LS values in patients with and without HCV coinfection. Two subgroups of outliers were identified in the group with HIV monoinfection (8 patients in each subgroup, 9% of HIV-monoinfected patients) (Fig. 4). The predicted LS values included in the left outlier group were higher than or comparable to the observed LS values; conversely, the predicted LS data in the right outlier group were lower than the observed LS values. Patients included in the right outlier cohort had more frequent undetectable plasma HIV RNA (62.5% versus 12.5%, P=0.03) and lower mean AST (33 U/l versus 89 U/l, 95%CI of the difference 40-81 U/l, P<0.0001. Notably, the mean BMI was greater than 25 in both left outlier (28.6) and right outlier (29.6) groups (95%CI for combined groups 26.7-31.4).

Discussion

We performed a linear model analysis to describe the correlations between clinical and viro-immunological variables and LS measurement (LSM) in a cohort of patients with HIV infection or with HIV/HCV coinfection, focusing on the role of plasma HIV viremia detectability or undetectability during two different study periods (12 and 36 months before LSM). In the overall study population, no correlation was reported for either HIV-monoinfected patients or subjects with HCV coinfection. Consistently with our results, Merchante *et al* [15] reported that HIV viremia (binary variable, <200 copies/mL versus >200 copies/mL) at the time of TE is not a factor that is associated with an abnormal LS value (defined as >7.2 kPa in a cross-sectional study including only HIV-monoinfected subjects). Conversely, Mohr *et al* [22] showed that detectable HIV viremia for a

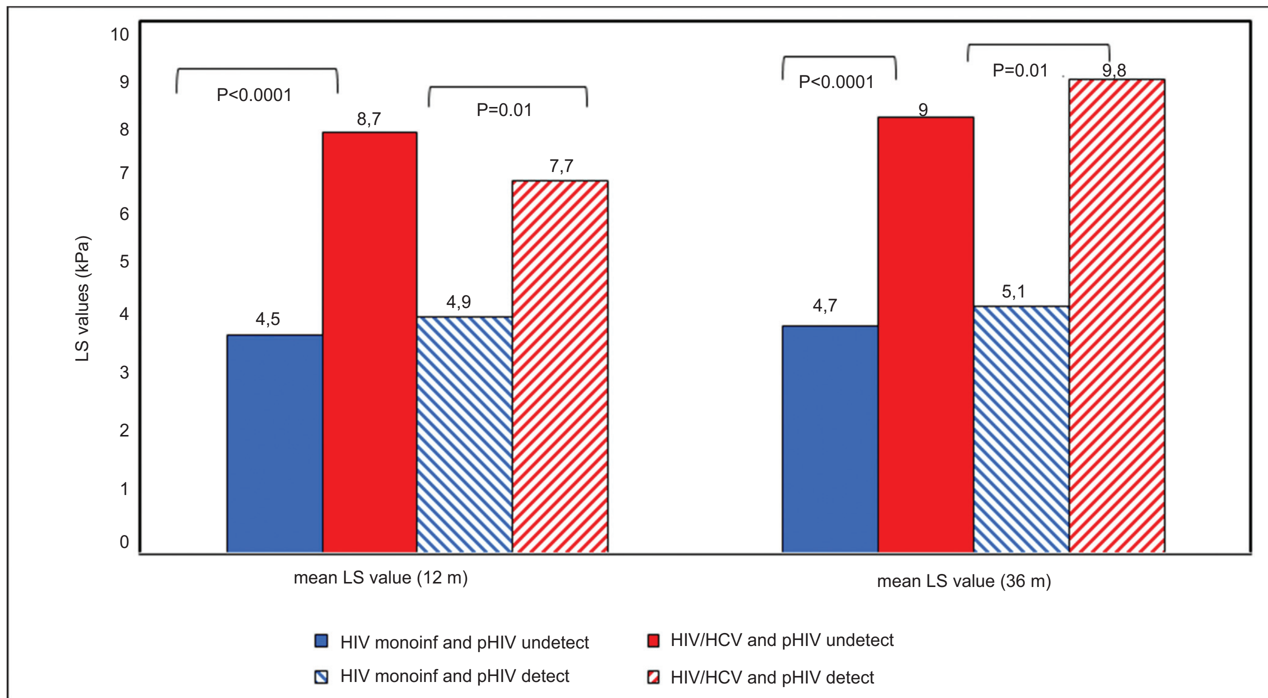

Figure 2 Liver stiffness values in HIV-monoinfected patients and in HIV/HCV patients according to plasma HIV RNA detectability or undetectability in the 12 months or 36 months before transient elastography
LS, liver stiffness; kPa, kilopascal; pHIV, plasma HIV RNA; m, months

Table 2 Linear regression model with lkpa (liver stiffness absolute value after $\log_{10}$ transformation), as dependent variable

lkpa	Coefficient	Standard error	t	P>t	95%CI	
Age (years)	0.0021796	0.0009666	2.25	0.025	0.0002748	0.0040844
Male sex	–0.0366232	0.0325936	–1.12	0.262	–0.1008542	0.0276077
HIV	0.0202064	0.0250061	0.81	0.420	–0.0290721	0.0694849
HCV	0.1490692	0.0265554	5.61	0.000	0.0967376	0.2014008
Nadir CD4	–0.000035	0.0000513	–0.68	0.496	–0.0001362	0.0000662
CD4	–7.53E-06	0.0000401	–0.19	0.851	–0.0000865	0.0000714
BMI	-0.0530044	0.0280289	–1.89	0.060	–0.1082398	0.0022309
BMI2	0.0012249	0.0005458	2.24	0.026	0.0001492	0.0023006
AST	0.0035958	0.0004461	8.06	0.000	0.0027167	0.0044749
Intercept	1.053148	0.3531909	2.98	0.003	0.357129	1.749167

Prob > F=0.0000. R^2=0.4971

ALT, alanine aminotransferase; ART, antiretroviral treatment; AST, aspartate aminotransferase; BMI, body mass index; CD4, CD4+ cell count (cells/mm^3); HIV, plasma HIV RNA undetectable; LS, liver stiffness; Nadir CD4: CD4+ cell count (cells/mm^3) at nadir; Std. Err, standard error

period of more than 2 years was associated with higher LS values in naïve HIV-monoinfected patients; in this study, the subjects were classified as having plasma HIV viremia either greater than 40 copies/mL or undetectable. We were able to evaluate the role of two periods of different length (12 and 36 months) providing the same result. Moreover, the enrolled HIV viremic patients were both naïve and unresponsive to ART; a possible effect of an ART regimen with suboptimal efficacy cannot be excluded. Notably, both in our study and in Mohr's, there were no correlations found in patients with HIV/HCV coinfection.

The plasma HIV viremia burden may play a role in explaining the differences between these results. Matthews *et al* [23] showed an association between HIV viremia and LS value in a population of naïve patients who had a median HIV RNA $\log_{10}$ copies of 4.4 (3.9 $\log_{10}$ copies/mL in our study); only 3.9% of the participants had undetectable viremia (the cutoff was set at ≤400 copies/mL, while it was 50 copies/mL

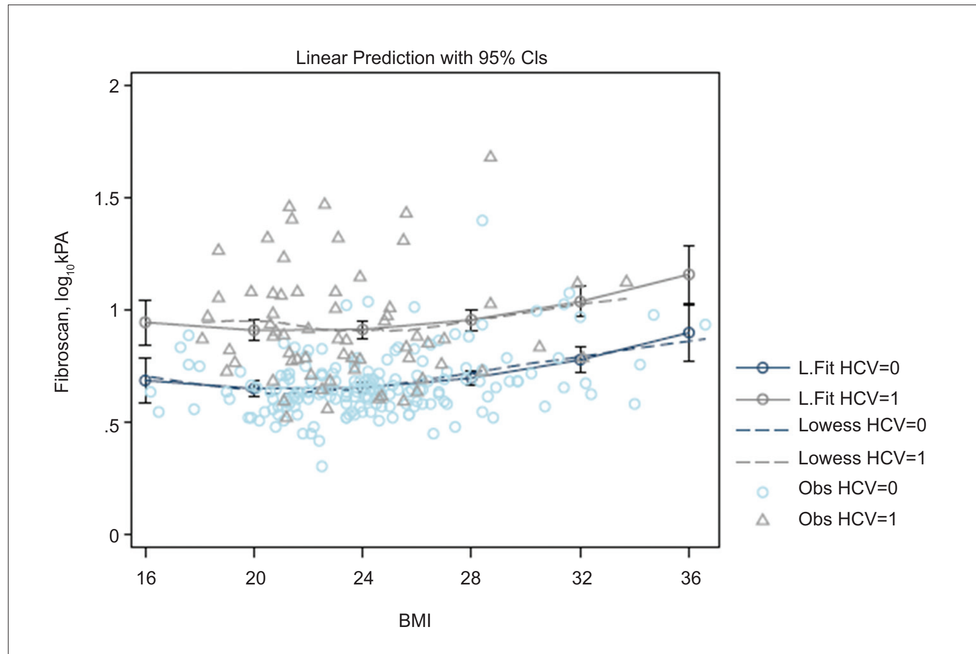

Figure 3 Linear model representation including the three main variables, $\log_{10}$(kPa), BMI, and HCV. The Figure depicts the effects of HCV infection and BMI on the Fibroscan values on the original data and on the model-based predictions
BMI, body mass index; CI, confidence interval; L. Fit, linear fit; Lowess, locally weighted regression; Obs, observations; HCV0, HIV patient HCV-negative; HCV 1, HIV patient HCV-positive

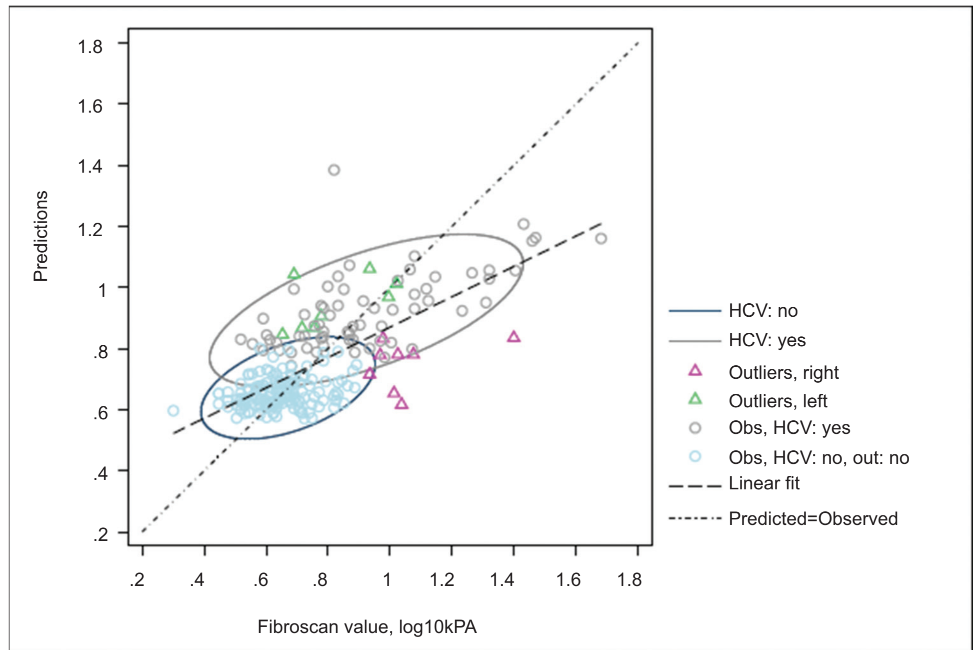

Figure 4 Graph describing the linear fit between predictions and observed Fibroscan values.
The reference line where predictions correspond to observations is also shown. The ellipses indicate bivariate normal distributions for predictions and observed Fibroscan values. Each of them correspond to a probability of 86%; they account for the two subpopulations according to HCV status. Outliers, left: green; outliers, right, magenta;
Obs, observations; HCV 0, HIV patient HCV-negative; HCV 1, HIV patient HCV-positive; Out, outliers

in our study). Moreover, higher LS values were correlated with higher $\log_{10}$ HIV RNA values and a threshold effect that was defined as the upper limit of the first two quartiles (19,999 copies/mL) was described; our median values were under this threshold (8979 copies/mL in HIV-monoinfected patients and 962 copies/mL in HIV/HCV-coinfected subjects).

A role for the HIV RNA level in determining liver disease was reported by Towner *et al* [24] in a cohort study involving 20,775 HIV-positive subjects; the authors demonstrated a higher rate of hepatic dysfunction and hepatic dysfunction-related death in the case of plasma HIV RNA>500 copies/mL, while the risk increased with higher HIV RNA levels. A plasma HIV RNA value <500 copies/mL was shown to protect against liver fibrosis progression (determined with FIB-4 and AST-to-platelet ratio index scores) in a cohort of naïve patients who were starting highly active ART [25]; conversely, a median 12% increase in FIB-4 was associated with a 1 log increase in HIV RNA in the study conducted by Forrester *et al* [26].

The course of liver disease is largely unpredictable on a case-by-case basis, because liver fibrosis is a multifactorial process and the viscoelasticity of the liver may be influenced by inflammatory processes, as demonstrated in post–liver-transplant acute cellular rejection [27]. Our statistical model identified a group of HIV-monoinfected patients with LS values that were discordant with respect to the predicted values; HCV infection had a much stronger hepatic damage capacity than did HIV infection, and this probably justified the absence of coinfected patients among the left and right outliers. The mean BMI was ≥25 in the left outliers (the predicted LS value was higher than or comparable to the observed LS value) and in the right outliers (the observed LS value was higher than the predicted value); increased levels of inflammatory mediators have been described in subjects with HIV who were overweight and this could have perturbed the model [28]. Liver fibrosis is associated with higher BMI values in HIV-monoinfected subjects [29], and we confirmed this correlation using logistic regression in our cohort; however, both left and right outlier subjects were overweight. Almost all right outlier patients (87.5%) had plasma HIV RNA levels that were undetectable in the 12 months before TE, which is in apparent contradiction to the absence of a correlation between the LS value and HIV viremia. Furthermore, HIV RNA is not the only virological parameter that can be used to evaluate HIV infection; cellular HIV DNA constitutes the viral reservoir and is detectable in peripheral mononuclear blood cells in patients with long-term suppressed viremia [30-32]. Recently, HIV DNA was also identified in the hepatic tissue of patients who died while they were on ART and who had undetectable levels of HIV RNA [33].

TE results are currently interpreted as a range in clinical practice, since this provides a more reliable correlation with the degree of fibrosis [34]. We choose to explore the absolute LS value in our HIV-monoinfected patients in order to highlight the differences in a population whose LS values were almost all included in the F0-F1 class of fibrosis (LSM<7.1). No selection bias was evident; our study population had an LSM value comparable to that of previously described cohorts of HIV-positive patients, ranging from 3.9-4.9 kPa [14,15,35]. The main limits of our study are the influence of intra-observer TE reproducibility and the low number of outlier patients. All of the TEs were performed by the same expert operator and only 5 of the 413 patients who were screened (1.2%) were excluded from the study because of an invalid TE, so good reproducibility was expected [36]. One strength of our study was the careful selection of patients; there were no HBsAg-positive subjects included, patients with HCV coinfection were all HCV RNA-positive and almost all of the patients were Caucasian. The independent predictive role of race has scarcely been studied, but Hispanic/Latino ethnicity was independently associated with higher TE scores in HIV patients [23], and HIV coinfection was predictive of early fibrosis in HCV positive African Americans [37].

In conclusion, the present study demonstrated that LS did not correlate with ongoing HIV replication during 12- and 36-month study periods in immunocompetent HIV/HCV-coinfected patients and in HIV-monoinfected subjects.

Summary Box

What is already known:

- HIV may be directly responsible for liver damage
- Data on the influence of ongoing plasma HIV viremia on liver fibrosis progression are discordant, possibly because of differences in study design and patient selection
- Transient elastography is more reliable than the aspartate aminotransferase-to-platelet ratio index and Fibrosis-4 score for staging liver fibrosis in HIV/HCV-coinfected patients

What the new findings are:

- The absolute value of liver stiffness (LS) has no correlation with short- or long-term plasma HIV RNA replication in either immunocompetent HIV-monoinfected subjects or HIV/HCV-coinfected patients
- No significant difference in LS value was found between patients classified by detectable or undetectable plasma HIV viremia, while HIV/HCV patients had higher LS values than did monoinfected subjects, regardless of plasma HIV viremia values
- A minority of HIV-monoinfected patients showed LS values discordant with those predicted by the linear regression model

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