

Fast Liver Damage Progression in HIV/HCV-coinfected Patients in Spite of Effective HAART.

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ABSTRACT

BACKGROUND: Elevated frequencies of fibrosis progression have been observed in studies on serial liver biopsies (LB) in HIV/HCV coinfection. However, sequential LB studies might not be representative of the coinfecting population. Patients that undergo a second LB are selected. Clinicians refer them for LB because of suspicion of progression. Thus, rates of fibrosis progression may have been overestimated by these studies. Liver stiffness (LS) measurement can be repeated easily in unselected patients. LS is useful to discriminate F0-F1 and F2, and can identify cirrhosis. Because of these, our aim was to analyze the frequency of changes in LS and the factors associated with them in HIV/HCV-coinfected patients without anti-HCV therapy.

METHODS: Patients with HIV/HCV coinfection, without anti-HCV treatment, were prospectively included in this cohort study. LS was measured at baseline and, at least, every 12 months. Classification of fibrosis followed LS cut-offs: ≤ 6 KPa (F0-F1), 6.1-8.9 KPa (intermediate stage), ≥ 9 KPa (F2) and ≥ 14.2 KPa (F4). The main outcome variable was change in this classification.

RESULTS: 449 patients had follow-up LS values. 435 (97%) patients were under HAART at baseline. Median (Q1-Q3) baseline CD4 counts were 444 (287-654) and 324 (74%) subjects showed undetectable HIV load. Among 179 individuals with LS at 18-24 months, 28 (16%) regressed, 97 (54%) showed no change, and 54 (30%) progressed ≥ 1 category of LS. In the multivariate analysis, CD4 counts increase ≥ 50 /mL [adjusted OR 0.33 (95% confidence interval, 95%CI, 0.15-0.72), $p=0.006$], and undetectable HIV load during the follow-up [AOR 0.42 (95%CI 0.18-0.97), $p=0.04$] were associated with change ≥ 1 category of LS at 18-24 months of follow-up.

CONCLUSIONS: Achievement of HIV suppression and increase of CD4 cell counts with HAART is associated with a lower risk of worsening of liver damage. However, in spite of effective HAART, liver fibrosis progresses in a significant proportion of HIV/HCV-coinfected patients over a short period of time.

(Updated data)

BACKGROUND

Studies on serial liver biopsies in HIV/HCV coinfection have observed elevated frequencies of fibrosis progression over relatively short periods of time. However, sequential liver biopsy studies might not be representative of the whole coinfecting population. Indeed, patients that undergo a second liver biopsy are highly selected, as clinicians usually refer them for follow up biopsy because of suspicion of fibrosis progression. Because of these, the progression of fibrosis in HIV/HCV-coinfected patients could be slower than previous estimated from sequential liver biopsy studies.

Liver stiffness measurement (LSM) is non-invasive and can be repeated easily in unselected patients. LSM is accurate to discriminate mild and significant fibrosis, and can identify with certainty cirrhosis.

OBJECTIVE

To analyze the frequency changes in liver stiffness and the factors associated with them in HIV/HCV-coinfected patients without anti-HCV therapy.

PATIENTS AND METHODS

Design: Prospective multicenter cohort study (2006-2009).

Patients: All HIV-infected patients evaluated in the participating hospitals that met the following inclusion criteria were eligible:

- HCV infection demonstrated by EIA and PCR.
- No active anti-HCV treatment during the follow-up.

Follow-up:

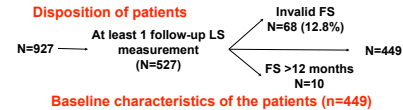
- LSM was measured at baseline and, at least, every 12 months.
- Patients were censored if anti-HCV treatment was started during the follow-up.

Methods:

1. LSM was measured by transient elastometry.
 - Measurements were considered valid if the success rate was $\geq 60\%$ and the IQR was $< 30\%$.
2. Classification of LSM according to validated cut-offs:
 - ≤ 6 kPa: Mild or absent liver fibrosis.
 - 6.1-8.9 kPa: Indeterminate result.
 - ≥ 9 kPa: Significant liver fibrosis.
 - > 14.6 kPa: cirrhosis
3. Statistical analysis:

1. Main outcome variable: Change in the classification of LSM to a higher category. Secondary outcome variable: Increase in the baseline LSM $\geq 20\%$.
2. Independent variables: Sex, age, risk group, alcohol, CDC stage, CD4, HIV load, HCV load, HCV genotype, ALT, ART exposure.

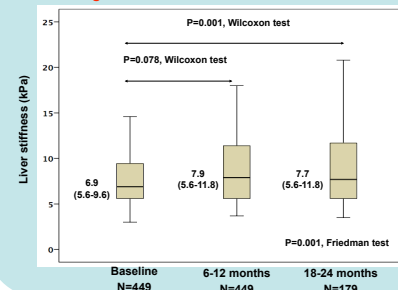
RESULTS



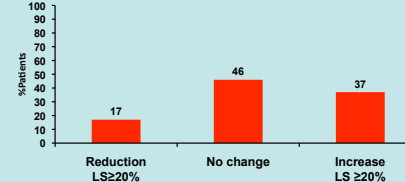
Characteristic	n (%)
Age ¹	44 (42-46)
Male gender, n (%)	360 (80)
Injecting drug users, n (%)	376 (84)
Alcohol intake >50 g/day ² , n (%)	50 (14)
CDC clinical category C, n (%)	150 (30)
CD4+ cell counts ³	444 (287-654)
Undetectable HIV viremia, n (%)	324 (74)
ART, n (%)	435 (97)
Age at HCV infection ^{1,3}	22 (18-26)
Genotype 1 or 4 ⁴ , n (%)	346 (77)
Log HCV RNA ¹	5.99 (5.37-6.58)
ALT levels ¹	63 (40-104)
HBsAg (+) ⁵ , n (%)	24 (5.6)
Liver stiffness measurement ¹	6.9 (5.6-9.6)
Previous anti-HCV therapy	91 (21)

¹ Median (Q1-Q3); ² Available in 360 patients; ³ Available in 195 patients; ⁴ Available in 429 patients; ⁵ Available in 430 patients.

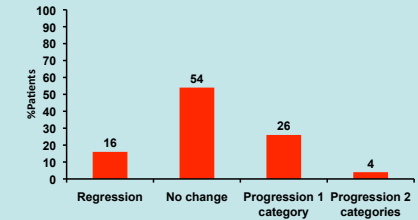
Changes in median liver stiffness measurements.



Liver stiffness measurement changes $\geq 20\%$ after 18-24 months of follow-up (n=179)



Changes in the category of liver stiffness after 18-24 months of follow-up (n=179)



Factors associated with change ≥ 1 liver stiffness measurements at 18-24 months of follow-up (n=179).

Characteristic	Change in ≥ 1 category of LSM, n (%)	p univariate	Adjusted OR (95% CI)	p multivariate
Gender				
Male	46 (34)	0.07	2.47	0.06
Female	8 (19)		(0.95-6.4)	
Age at baseline				
<44 years	42 (31)	0.3		
≥ 44 years	13 (26)			
Alcohol during the follow-up				
<50 g/day	38 (31)	0.6		
≥ 50 g/day	5 (25)			
CD4+ counts increase during the follow-up				
<50	34 (40)	0.002	0.33	0.006
≥ 50	13 (18)		(0.15-0.72)	
HIV viremia during the follow-up				
Detectable	22 (41)	0.07	0.42	0.04
Undetectable	32 (27)		(0.18-0.97)	
HCV RNA				
<6 log ₁₀	24 (27)	0.3		
≥ 6 log ₁₀	28 (34)			
HCV genotype				
1-4	44 (31)	0.3		
2-3	7 (23)			
Baseline ALT				
<63	26 (25)	0.5		
≥ 63	26 (31)			
Antiretroviral drugs				
TDF yes	21 (26)	0.3		
TDF no	33 (34)			
ABV yes	32 (27)	0.2	1.29	0.6
ABV no	22 (36)		(0.52-3.27)	
EFV yes	33 (33)	0.4		
EFV no	21 (27)			
NVP yes	46 (29)	0.2	1.19	0.8
NVP no	8 (44)		(0.36-3.94)	
LPV/r yes	48 (32)	0.2	0.34	0.09
LPV/r no	6 (19)		(0.10-1.18)	

CONCLUSIONS

Achievement of HIV suppression and increase of CD4 cell counts with HAART is associated with a lower risk of worsening of liver damage. However, in spite of effective HAART, liver fibrosis progresses in a significant proportion of HIV/HCV-coinfected patients over a short period of time