

# Increased Rates Of Fibrosis Progression Between Sequential Liver Biopsies In HIV/Hepatitis C Virus (HCV)-Coinfected Patients.

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## ABSTRACT

**BACKGROUND:** A few studies have assessed the observed fibrosis progression between serial liver biopsies (LB) in HIV/HCV-coinfected patients. The observed fibrosis progression was faster than in single-biopsy studies. Approximately half of the patients progressed at least one stage and a quarter of them were very fast progressors, ie. liver fibrosis increased two or more stages in these patients. The risk factors for progression were not clear. These findings need confirmation due to their deep clinical implications. Because of this, we evaluated the observed fibrosis progression rates of HIV/HCV-coinfected patients and the risk factors for accelerated progression.

**METHODS:** Patients with HIV/HCV coinfection who underwent two serial LB, separated at least by one year, were included in this retrospective cohort if they did not show other possible causes of liver disease. Patients with cirrhosis (F4) in the first LB were excluded. Fibrosis was staged according to the Scheuer score (F0-F4). Variables with  $p < 0.2$  in the univariate comparisons between progressors and non-progressors were entered in a logistic regression analysis.

**RESULTS:** Ninety-two patients with complete data were included in this analysis. The median (Q1-Q4) time between both LB was 40 (31-65) months. Eighteen (50%) of 36 patients who received anti-HCV treatment after the first LB showed end of treatment response or eradication (ETR/SVR). Patients showed the following changes in stage: Regression  $\geq 1$  stage: 13 (14%), no change: 36 (40%), progression 1 stage: 29 (32%), progression  $\geq 2$  stages: 13 (14%). Among 56 patients without anti-HCV treatment, 7 (13%) regressed  $\geq 1$  stage, 22 (39%) did not change of stage and 27 (48%) progressed  $\geq 1$  stage. In the multivariate analysis, factors associated with progression  $\geq 1$  stage were moderate-severe lobular inflammation (L0-1 vs. L2-4): adjusted OR (AOR) (95% confidence interval, 95%CI) 3.6 (1.3-9.7),  $p = 0.05$ , and ETR/SVR: AOR (95%CI) 0.26 (0.7-0.9),  $p = 0.05$ .

**CONCLUSIONS:** Fibrosis progression is frequently observed in HIV/HCV-coinfected patients over a period of time of three years. Moderate-severe lobular necro-inflammation at baseline LB is associated with an increased risk of progressing  $\geq 1$  fibrosis stage. Achievement of response with anti-HCV treatment can prevent progression.

(Updated data)

## BACKGROUND

Studies on serial liver biopsies are more reliable to evaluate fibrosis progression than single-liver biopsy studies, because changes in fibrosis are observed between two dates with fibrosis documented by biopsy. Importantly, this eliminates the assumption of normal liver at HCV acquisition and the estimation of length of HCV infection. Moreover, factors that could influence fibrosis progression can be more reliably gathered. A few studies have assessed the observed fibrosis progression between serial liver biopsies (LB) in HIV/HCV-coinfected patients. The observed fibrosis progression was faster than in single-biopsy studies. Approximately half of the patients progressed at least one stage and a quarter of them were very fast progressors, ie. liver fibrosis increased two or more stages in these patients. The risk factors for progression were not clear. These findings need confirmation due to their deep clinical implications.

## OBJECTIVE

To evaluate the observed fibrosis progression rates of HIV/HCV-coinfected patients and the risk factors for accelerated progression.

## PATIENTS AND METHODS

**Design:** Retrospective cohort study.

**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.
- Two serial liver biopsies separated at least by one year.
- Regardless of exposure to antiretroviral therapy or anti-HCV treatment between the biopsies.
- Negative serum HBsAg and no liver disease of autoimmune, tumoral, biliary or vascular cause.
- No cirrhosis (F4) in the first biopsy.

**Methods:**

- Biopsy data: Grading and staging were scored according to the Scheuer index. The length of liver biopsies was recorded.
- Statistical analysis:

The main outcome variable was the progression of fibrosis between biopsies. The change in the stage of fibrosis was measured as the proportion of patients that increased, decreased or showed no changes in the stage of fibrosis between biopsies. The parameters that showed a relationship with the outcome variables with  $p < 0.2$  in the univariate analyses were entered in a stepwise logistic regression analysis.

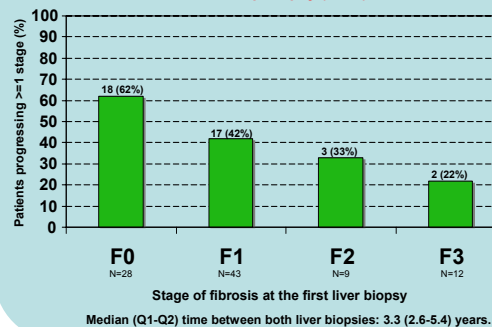
## RESULTS

### Characteristics of the patients (n=92)

Characteristic	
Age at infection by HCV <sup>1</sup> , median (Q1-Q3)	20 (18-26)
Age at liver biopsy, median (Q1-Q3)	37 (33-40)
Male sex, n (%)	72 (80)
Injecting drug users, n (%)	76 (84)
Alcohol intake >50 g/day <sup>2</sup> , n (%)	24 (27)
CDC clinical category C, n (%)	28 (31)
CD4+ cell counts at liver biopsy, median (Q1-Q3)	460 (319-598)
Nadir CD4+ cell counts, median (Q1-Q3)	212 (84-331)
Undetectable HIV viremia at 1 <sup>st</sup> liver biopsy, n (%)	50 (67)
ART during the follow-up, n (%)	66 (73)
Length of HCV infection <sup>1</sup> , median (Q1-Q3)	15 (12-19)
Genotype 1 or 4, n (%) <sup>3</sup>	71 (79)
HCV RNA at liver biopsy, median log (Q1-Q3)	5.93 (5.59-7.4)
ALT levels at liver biopsy, median (Q1-Q3)	66 (45-98)
SVR or ETR during the follow-up <sup>4</sup> , n (%)	18 (50)
Liver fibrosis stage, n (%)	
F0	28 (30)
F1	43 (47)
F2	9 (10)
F3	12 (13)

1. Available in 81 patients. 2. Available in 84 patients. 3. Available in 84 patients. 4. For 36 patients with anti-HCV therapy.

### Progression of at least 1 stage of fibrosis between the first and follow-up biopsy (n=92).



### Changes in fibrosis stage between biopsies.

- Regression  $\geq 1$  stage: 13 (14%) patients.
- No change: 36 (40%) patients.
- Progression 1 stage: 29 (32%) patients.
- Progression  $\geq 2$  stages: 13 (14%) patients.

### Factors associated with observed fibrosis progression ( $\geq 1$ fibrosis stage increase in the follow-up biopsy).

Characteristic	Progression $\geq 1$ fibrosis stage, n (%)	p univariate	Adjusted OR (95% CI)	p multivariate
Sex				
Male	36 (50)	0.4		-
Female	7 (39)			
Age at first liver biopsy				
<37 years	26 (58)	0.1		0.9
$\geq 37$ years	17 (38)			
Alcohol during follow-up <sup>1</sup>				
<50 g/day	27 (45)	0.5		-
$\geq 50$ g/day	13 (54)			
CD4+ cell counts at first liver biopsy				
<300	8 (44)	1		-
$\geq 300$	31 (46)			
HIV viremia at first liver biopsy				
Detectable	11 (44)	0.6		-
Undetectable	19 (38)			
ART exposure				
Without ART	16 (67)	0.04		0.5
With ART	26 (40)			
HCV genotype				
Non 1 or 4	3 (23)	0.1		0.07
1 or 4	34 (48)			
HCV RNA at first liver biopsy				
<6 log	22 (44)	1		-
$\geq 6$ log	14 (42)			
Necroinflammatory activity at first liver biopsy				
L0-L1	18 (38)	0.05	3.6 (1.3-9.7)	0.05
L2-L4	24 (60)			
ALT levels at first liver biopsy				
<100	28 (42)	0.1		0.6
$\geq 100$	13 (62)			
SVR or ETR as response to anti-HCV treatment				
No	39 (53)	0.03		0.05
Yes	4 (24)		0.26 (0.7-0.9)	

### Changes in the stage of fibrosis between the first and follow-up biopsy. Patients without anti-HCV therapy (n=56).

First biopsy	Follow-up biopsy				
	F0	F1	F2	F3	F4
F0, n (%)	8 (40)	6 (30)	3 (15)	3 (15)	0 (0)
F1, n (%)	5 (16)	14 (45)	12 (39)	0 (0)	0 (0)
F2, n (%) 3	1 (20)	1 (20)	0 (0)	3 (30)	0 (0)

### Changes in the stage of fibrosis between the first and follow-up biopsy. Patients with anti-HCV therapy (n=36).

First biopsy	Follow-up biopsy				
	F0	F1	F2	F3	F4
F0, n (%)	3 (38)	2 (25)	2 (35)	0 (0)	1 (10)
F1, n (%)	3 (25)	4 (33)	4 (33)	1 (8)	0 (0)
F2, n (%)	1 (25)	0 (0)	1 (25)	0 (0)	2 (50)
F3, n (%)	0 (0)	1 (11)	1 (11)	8 (67)	2 (22)

Shadowed cells represent groups of patients without changes in fibrosis stage between biopsies

## CONCLUSIONS

Fibrosis progression is frequently observed in HIV/HCV-coinfected patients under HAART over a period of time of three years. Moderate-to-severe lobular necro-inflammatory activity at baseline biopsy is associated with an increased risk of progressing  $\geq 1$  fibrosis stage. Response to anti-HCV treatment can prevent progression.