



# Rate and Predictors of Liver Fibrosis Progression among Hepatitis C Infected Injection Drug Users

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## Abstract

**Background.** The majority of those chronically infected with hepatitis C virus (HCV) are injection drug users (IDUs). Data on liver fibrosis progression (FP) by paired biopsies in this difficult-to-reach population are sparse. Rates of FP and predictors of FP were assessed among a community-based cohort of HIV+ and HIV- IDUs.

**Methods.** Between 1996-1998, baseline liver biopsies were obtained on a random sample of 1667 HCV+ IDUs participating in a community-based natural history study. Subjects were followed every 6 months with liver enzyme testing and questionnaires. A second biopsy was offered to subjects with no contraindication. Paired biopsies were scored from 0-6 according to the modified histologic activity index (MHA1). FP was defined as an increase in fibrosis score of  $\geq 2$  units. Factors associated with FP were evaluated by Chi-square testing and Mantel Haenszel for categorical data. Wilcoxon rank sum compared continuous data non-parametrically.

**Results.** Of 117 IDU with paired liver biopsies (median: 4.2 years apart), 26% were HIV+, 95% were African American, 82% male, and median age was 42 years. 51% were current IDU, and 80% used alcohol. Median estimated duration of HCV infection was 22 years.

Ishak modified fibrosis scores at follow-up liver biopsies were: 52% <2, 42% 2-4 and 6% 5-6. FP was noted in 21%.

Median FP rate (fibrosis units/year) was 0.11 (range -0.68-1.42), and did not significantly differ by HIV status.

Those with FP had higher baseline HCV RNA levels (median 7.15 vs 6.63 log<sub>10</sub> units, p=0.03). Risk of FP was higher with elevated liver transaminases at serial study visits (ALT: trend for always normal, >50% normal and the rest, p = 0.03). A trend was seen with greater FP with increased alcohol use and with increased IDU at study visits. Age, gender, race, HCV+ duration, interferon therapy, HIV status, CD4 count, MHA1 inflammatory score or fatty liver change were not associated with FP.

A stratified analysis of HIV+ IDU showed similar predictors of FP. A trend was seen for an increased risk of FP with HAART use reported at >50% of study visits (23% vs 11%).

**Conclusion.** In this HCV-infected IDU cohort, overall FP rates were relatively low (even among those HIV-infected), and especially among those with low serum liver enzyme levels. Further research is needed to understand the basis for the marked person-to-person differences in the risk of FP that cannot be explained by liver enzymes or HIV status.

## METHODS: Study Subjects

- Between 1996 and 1998, 210 subjects were randomly selected from 1667 HCV-infected IDUs who were members of the ALIVE study cohort (a community based natural history study) in Baltimore, MD after initial stratification by ALT levels and underwent initial laboratory evaluation and liver biopsy. (R. Rai et al., Hepatology, 35 (5), 2002, 1247).

- Between March 2001 and May 2002, the 210 subjects originally biopsied were offered a second liver biopsy to determine rate and predictors of liver fibrosis progression.

- Exclusion criteria included decompensated liver disease, severe medical comorbidity, increased bleeding risk, and advanced immunosuppression (at first biopsy only).

## METHODS: Measurements

- A transcutaneous liver biopsy was performed under ultrasound guidance by an interventional radiologist.
- Liver tissue was fixed in 10% formalin and paraffin-embedded sections were stained with hematoxylin and eosin and Masson's trichrome stains. The degree of inflammation was graded and the amount of fibrosis staged using the Ishak modified hepatitis activity index by a single experienced hepatopathologist, who was blinded to clinical markers other than HCV antibody status.
- HCV antibody status was assessed by second or third generation enzyme immunoassay (EIA) (Ortho Diagnostics, Raritan, NJ). HCV viral load was measured by COBAS AMPLICOR MONITOR assay (Roche Diagnostics Systems, Branchburg, NJ).

## METHODS: Statistical Analysis:

- Fibrosis progression was defined as change in MHA1 Fibrosis Score  $\geq 2$  and the analysis compared those with high FP ( $\geq 2$ ) versus low FP (<2).
- The IDU study cohort database was used to analyze associations between fibrosis progression and demographics, HIV characteristics, drug and medication use and viral hepatitis serology.
- Chi-square testing, Mantel Haenszel and Fisher's exact testing were used to compare categorical data on subjects with high versus low FP.
- Age was categorized into the highest quartile and below. Wilcoxon-rank sum was used to compare continuous data non parametrically. Subjects also were stratified by consecutive ALT results (both normal < 40 IU/L or both elevated  $\geq 40$  IU/L) using the two consecutive ALT measurements that most closely preceded the liver biopsy. The relationship between the ALT strata and the extent of fibrosis progression was measured by the chi-square method.

**Table 1. Correlates of Fibrosis Progression among 117 HCV-Infected Injection Drug Users with Paired Liver Biopsies**

	FP $\geq 2$ (%) n=24	FP < 2 (%) n=93
Male Gender	83.3	81.7
African American	91.7	96.8
Age > 46 Years*	20.8	19.4
Current Alcohol Use*	58.3	58.2
Current IDU*	66.7	50.6
Detectable HCV RNA*	91.7	85.0
Median HCV RNA Level (log copies/ml)*	7.15	6.63**
ALT $\geq 60$ IU/L*	41.7	23.3
AST $\geq 52$ IU/L*	45.8	30.0
Total MHA1 Inflammatory Score $\geq 5$ *	29.2	32.3
Fatty Change noted on biopsy*	29.2	23.7
HIV Seropositive*	20.8	26.9
CD4 200-499 cells/mm <sup>3</sup> *	20.8	10.9
CD4 > 500 cells/mm <sup>3</sup> *	0.0	14.1
Alcohol at all Follow-up visits	39.1	25.0
IDU at all Follow-up visits	21.7	16.3
Took Interferon Therapy	4.2	2.2
HAART use at >50% visits (HIV positive only)	60.0	37.0

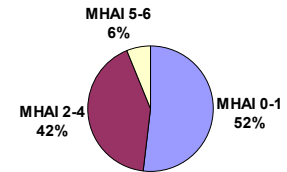
\*Variable measured at baseline biopsy  
\*\*p<0.04

**Table 2. Distribution of MHA1 Fibrosis Score at First and Second Liver Biopsy among 117 HCV Positive Persons\***

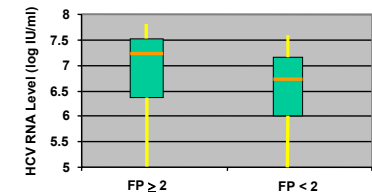
Fibrosis Score Second Biopsy	Fibrosis Score First Biopsy					Total
	0	1	2	3	4	
0	19	8	5	0	0	32 (27.3%)
1	9	11	8	0	1	29 (24.8%)
2	9	9	13	3	0	34 (29.1%)
3	2	2	4	2	0	10 (8.6%)
4	0	3	1	0	1	5 (4.3%)
5	0	0	1	1	0	2 (1.7%)
6	0	2	1	1	1	5 (4.3%)
	<b>39</b>	<b>35</b>	<b>33</b>	<b>7</b>	<b>3</b>	<b>117</b>
	33%	30%	28%	6%	3%	

\*note: those with MHA1 fibrosis score of 5 or 6 at first liver biopsy did not receive repeat biopsy. Two subjects had clinical diagnosis of end stage liver disease rather than repeat biopsy.

**Figure 1. Distribution of MHA1 Liver Fibrosis Scores among IDU at Second Liver Biopsy**



**Figure 2. Distribution of HCV RNA levels among IDU with and without Liver Fibrosis Progression (with Median and Interquartile Range)**



## RESULTS: Liver Fibrosis Progression

- Fibrosis progression was detected in 21% of 117 HCV-infected subjects with paired liver biopsies.
- Median fibrosis progression rate was 0.11 MHA1 fibrosis units/year.
- Analysis stratified by HIV status showed similar rates and predictors of fibrosis progression, although those with fibrosis progression more frequently reported HAART use.

## CONCLUSIONS

- In this community-based cohort of injecting drug users, the overall rate of fibrosis progression was low, and fibrosis progression of > 1 unit was especially uncommon in persons with repeatedly abnormal liver transaminases.
- Most of the observed person-to-person variability in fibrosis progression could not be explained by the factors considered.
- According to published US Public Health Service Guidelines, almost half of the cohort had sufficient liver fibrosis to consider medical treatment of HCV infection. Nonetheless, few cohort members received interferon alpha based treatment.
- Additional research is needed to identify reliable methods of identifying and preventing HCV-related fibrosis progression in this setting.