# Effect of HIV on Liver Fibrosis Among HCV-Infected African Americans

**D. Silver,[1] G. Karnik,[2] A. Osinusi,[2] R. Silk,[2] L. Stabinski,[3] L. Doonquah,[4] S. Henn,[5] G. Teferi,[6] H. Masur,[1] S. Kottilil,[3] and D. Fishbein[2,7]**

[1]Critical Care Medicine Department, National Institutes of Health Clinical Center, [2]Clinical Research Directorate/Clinical Monitoring Research Program, SAIC-Frederick Inc, Frederick National Laboratory for Cancer Research, and [3]Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; [4]Family and Medical Counseling Service, [5]Whitman-Walker Health, [6]Unity Healthcare, Inc, and [7]MedStar Washington Hospital Center, Washington, District of Columbia

**Degree of liver fibrosis largely determines treatment urgency for hepatitis C virus (HCV). This retrospective study examined fibrosis stages and predictive factors in African Americans with HCV monoinfection and human immunodeficiency virus (HIV)/HCV coinfection. Nearly 50% of patients had early-stage fibrosis in the study, despite the long duration of infection in many patients. HIV was associated with the early fibrosis group. These results indicate that a large proportion of patients with HCV infection, including those with HIV, could possibly await more-effective and better-tolerated treatment.**

***Keywords.*** liver fibrosis; HIV; HCV; African Americans.

Approximately 130 million people, or 2.2% of the world's population [1] and 1.8% of the US population [2], are infected with hepatitis C virus (HCV). Chronic HCV is the leading cause for liver transplantation [2] and the most common cause of liver-associated death in the United States [3].

An estimated 25% of individuals infected with human immunodeficiency virus (HIV) have HCV [2]. Life-threatening infections due to AIDS have declined with the advent of antiretroviral therapy (ART), yet the incidence of morbidity and mortality from liver disease has increased [4], and end-stage liver disease has become the leading cause of non-AIDS-related death in HIV patients [4].

HIV/HCV-coinfected patients not receiving ART have more rapid liver fibrosis compared to HCV-monoinfected individuals [5]. Advanced fibrosis translates into poor response to HCV therapy [6] and increased rates of cirrhosis, liver failure, and hepatocellular carcinoma [2, 7]. In contrast to prior studies of HIV [8], recent reports suggest that rates of advanced fibrosis and liver disease progression in persons with controlled HIV are similar to the rates of those with HCV alone [9, 10].

HCV is more common among African Americans than among other racial groups [3, 7]. African Americans have poor response rates to pegylated interferon and ribavirin compared to whites (28% vs 52%, respectively) [11, 12], independent of HCV genotype 1 [11], which is associated with lower sustained virologic response (SVR) rates [6]. Recent studies have found earlier fibrosis stages, lower rates of cirrhosis progression [3, 11], and higher hepatocellular carcinoma rates in African American HCV-monoinfected persons compared to whites [3].

Coinfected African Americans are underrepresented in clinical studies [3] and their liver fibrosis has not been well characterized. Existing studies demonstrate low SVR rates [7] and significantly higher median HCV RNA levels in coinfected African Americans [13], but have not primarily evaluated fibrosis staging. As current standard-of-care regimens have low efficacy and poor tolerability [6], liver disease characterization is clinically utilized in treatment decisions.

The objectives of this study were to (1) measure the prevalence of early liver fibrosis in HCV monoinfected and HIV/HCV-coinfected African American patients, and (2) determine factors associated with earlier fibrosis stages.

## METHODS

The District of Columbia Partnership for HIV/AIDS Progress was formed in 2008 as a partnership between the National Institutes of Health and the District of Columbia Department of Health to address the HIV epidemic in Washington, D.C. Integrated hepatitis clinics providing clinical care and research were established in existing D.C. clinics.

A retrospective chart review of 154 HCV monoinfected and 180 HIV/HCV-coinfected African American patients was conducted in 5 clinics from August 2010 to March 2011. Demographics; clinical and laboratory parameters; HIV, HCV, and hepatitis B virus (HBV) data; and medications were abstracted

Received 21 September 2012; accepted 22 January 2013; electronically published 1 February 2013.

Correspondence: Dana Silver, DC Partnership for HIV/AIDS Progress, Critical Care Medicine Department, National Institutes of Health, 1101 Highland Dr, Silver Spring, MD 20910 (dana.r.silver@gmail.com).

**Clinical Infectious Diseases 2013;56(9):1280–3**
Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2013.
DOI: 10.1093/cid/cit037

from electronic medical records. Patients were included if they were seen at least once in a participating clinic, were at least 18 years of age, had laboratory-documented chronic HCV, and had a liver biopsy within 10 years prior to 2011. Those with a positive hepatitis B surface antigen or HBV DNA, and those who had spontaneous HCV clearance were excluded. This cross-sectional analysis included all eligible patients seen during the time period. All pathology was reported with Metavir or Knodell fibrosis staging (0–4) score. Liver biopsies were performed for routine disease staging.

### Statistical Analysis

HCV-monoinfected and HIV/HCV-coinfected persons were compared using the $\chi^2$ test for categorical variables and Student *t* test or nonparametric Mann-Whitney statistics for continuous variables. Univariate and multivariate analyses were performed comparing fibrosis stages, stage 0–1 vs 2–4; logistic regression was used for multivariate analysis. Variables tested in the multivariate analysis had a *P* value of <.25 on univariate analysis, with a *P* value of <.05 used for statistical significance. SPSS 17.0 was used for data analysis.

Variables included age, age at time of HCV infection, sex, race/ethnicity, years since HIV diagnosis, nadir CD4, current CD4 cell count, HIV RNA, current and prior ART, HCV genotype and RNA, history of ever receiving HCV treatment, liver biopsy information (including grade, stage, and steatosis), ever and heavy alcohol use, marijuana use ever, and obesity.

Institutional review board approval was obtained from the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

## RESULTS

Table 1 depicts baseline characteristics of study participants. Of the 334 African American patients evaluated, 154 (46.1%) were HCV monoinfected and 180 (53.9%) were HIV/HCV coinfected. The mean age was 54.5 ± 6.5 years. Eighty-seven patients (62.6%) had an estimated duration of HCV infection of >25 years. Patients were predominantly male (71.0%), and the primary HCV risk factor was prior intravenous drug use (66.8%). Eighty-four percent of biopsies were done in the 3

**Table 1. Baseline Characteristics of HIV/Hepatitis C Virus (HCV)–Coinfected and HCV-Monoinfected Patients**

| Variable | Total | Monoinfected | Coinfected | Odds Ratio (95% CI) | *P* Value |
|---|---|---|---|---|---|
| Total patients | 334 (100) | 154 (46.1) | 180 (53.9) | | |
| Sex, male | 237/334 (71.0) | 108/154 (70.1) | 129/180 (71.7) | 1.08 ( .67–1.73) | *P* = .76 |
| HCV genotype 1 | 291/332 (87.7) | 132/152 (86.8) | 159/180 (88.3) | 1.15 (.60–2.21) | *P* = .68 |
| Stage ≤1 | 154/334 (46.1) | 65/154 (42.2) | 89/180 (49.4) | 1.34 (.87–2.07) | *P* = .19 |
| Stage ≤2 | 239/334 (71.6) | 116/154 (75.3) | 123/180 (68.3) | 0.71 (.44–1.15) | *P* = .16 |
| Age, mean ± SD | 54.5 ± 6.53 | 54.8 ± 5.92 | 54.2 ± 7.01 | | *P* = .39 |
| Ever treated | 100/322 (31.1) | 36/149 (24.2) | 64/173 (37.0) | **1.84 (1.13–3.00)** | ***P* = .01** |
| IVDU primary risk | 223/334 (66.8) | 107/154 (69.5) | 116/180 (64.4) | 0.80 (.50–1.26) | *P* = .33 |
| CD4 count, median (range) | | N/A | 500 (12–2101) | N/A | |
| HIV RNA detectable | | N/A | 34/180 (18.9) | N/A | |
| HIV RNA log[a], mean ± SD | | N/A | 2.98 ± 0.99 | N/A | |
| HIV on ART | | N/A | 153/162 (94.4) | N/A | |
| HCV SVR[b] | 10/334 (3.0) | 4/154 (2.6) | 6/180 (3.3) | | *P* = .78 |
| HCV RNA log[c], mean ± SD | 6.23 ± 0.85 | 6.22 ± 0.79 | 6.24 ± 0.90 | | *P* = .41 |
| Duration of HCV infection, median (y range) | 29.0 (1–46) | 28.0 (1–43) | 29.5 (1–46) | | *P* = .25 |
| Alcohol use, ever | 184/192 (95.8) | 83/84 (98.8) | 101/108 (93.5) | **0.17 (.02–1.44)** | ***P* = .07** |
| Alcohol use, heavy | 114/192 (59.4) | 58/84 (69.0) | 56/108 (51.9) | **0.48 (.27–.88)** | ***P* = .02** |
| Marijuana use, ever | 64/112 (57.1%) | 25/50 (50.0) | 39/62 (62.9) | 1.70 (.79–3.61) | *P* = .17 |
| BMI, kg/m$^2$, mean ± SD | 28.2 ± 5.61 | 29.02 ± 5.74 | 27.54 ± 5.41 | | ***P* = .02** |
| Cirrhosis | 36/334 (10.8) | 12/156 (7.8) | 24/180 (13.3) | 1.82 (.88–3.78) | *P* = .10 |
| Steatosis, any | 131/214 (61.2) | 58/93 (62.4) | 73/121 (60.3) | 0.92 (.53–1.60) | *P* = .76 |
| Biopsy length, cm, mean ± SD | 1.52 ± 0.47 | 1.5 ± 0.44 | 1.54 ± 0.51 | | *P* = .54 |

Data are No. (%) unless otherwise specified. Bold formatting indicates statistically significant data.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IVDU, intravenous drug use; N/A, not applicable; OR, odds ratio; SD, standard deviation; SVR, sustained virologic response.

[a] In those patients with detectable HIV load (defined as >75 copies/mL).

[b] Not including 5 of 334 patients with an early virologic response.

[c] In those patients with detectable HCV (defined as >43 IU/mL).

years preceding data collection. Mean time between date of biopsy and date of data abstraction was 1.25 years.

### Comparison Between HCV Monoinfection and HIV/HCV Coinfection

One hundred thirty-two patients with monoinfection (86.8%) were HCV genotype 1 with median duration of HCV infection estimated at 28 years (range, 1–43 years); 159 patients with coinfection (88.3%) were HCV genotype 1 with median duration of HCV infection of 29.5 years (range, 1–46 years). Characteristics of each population are shown in Table 1. HIV/HCV-coinfected patients were more likely to have ever had HCV treatment, 37.0% compared to 24.2% (odds ratio [OR], 1.84 [95% CI, 1.13–3.00]), were less likely to have a history of heavy alcohol use (OR, 0.48 [95% CI, .27–.88]) and had a lower body mass index ($P = .02$), compared to monoinfected patients.

### Fibrosis Stage

A liver biopsy had been performed in all 334 of the patients included in this cohort. One hundred fifty-four (46.1%) had no or early liver fibrosis (stage ≤1); 239 (71.6%) had stage ≤2 fibrosis. Of the 95 (28.4%) patients with fibrosis stage >2, 36 (10.8%) were cirrhotic. The histologic characteristics did not differ between patients who were HCV monoinfected and those who were HIV/HCV coinfected. Twenty-three patients had paired liver biopsies (Supplementary Data).

The results of the univariate and multivariate analysis to evaluate predictors of early fibrosis (stage ≤1) are described in Table 2. On multivariate analysis, the factors predictive of early fibrosis were HIV infection (adjusted OR, 2.10 [95% CI, 1.15–3.86]) and having ever received prior HCV treatment (adjusted OR, 0.08 [95% CI, .02–.27]).

## DISCUSSION

In this study of African Americans with chronic HCV in Washington, D.C., we demonstrated that almost one-half (46.1%) had very early fibrosis and the majority (71.6%) lacked advanced disease as they had a score of ≤2 on staging of liver biopsy, despite a median infection duration of 29 years. Because African Americans respond poorly to standard HCV therapy, these data are encouraging, and individualized treatment could possibly be deferred until improved emerging treatment strategies are available. Twenty-eight percent of patients had advanced fibrosis, and would therefore require more timely consideration for treatment.

Our analysis found no significant differences between rates of early fibrosis in HCV/HIV-coinfected patients compared with those who were HCV monoinfected. Compared to the literature, we found early fibrosis stages despite the long duration of infection in many patients [8]. This finding of early fibrosis might be related to the racial composition or to the

**Table 2. Predictors of Early Fibrosis in African Americans**

| Predictor | Stage 0–1 Fibrosis | Univariate OR (95% CI) | *P* Value | Multivariate Adjusted OR (95% CI) |
|---|---|---|---|---|
| Sex | | | | |
| Male | 115/154 (74.7) | **1.42 (.87–2.26)** | **P = .17** | |
| Female | 39/154 (25.3) | | | |
| HCV genotype 1 | 135/153 (88.2) | 1.11 (.57–2.14) | P = .77 | |
| HIV infected | 89/154 (57.8) | **1.34 (.87–2.07)** | **P = .19** | **2.10 (1.15–3.86)** |
| Age, mean ± SD | 53.5 ± 7.07 | | **P = .02** | |
| Ever treated | 20/147 (13.6) | **0.19 (.11–.33)** | **P < .001** | **0.08 (.02–.27)** |
| IVDU primary risk | 106/154 (68.8) | | | |
| CD4 count, median (range) | 506.5 (12–1201) | | **P = .09** | |
| HIV RNA[a], median (range) | 410 (90–188 000) | | P = .68 | |
| HCV RNA log[b], mean ± SD | 6.17 ± 0.88 | | P = .59 | |
| Duration of HCV infection, mean ± SD | 26.69 ± 9.57 | | **P = .18** | |
| Alcohol use, ever heavy | 50/84 (59.5) | 1.01 (.57–1.81) | P = .97 | |
| Steatosis | 58/104 (55.8) | **0.64 (.37–1.11)** | **P = .11** | |
| Marijuana use, ever | 30/52 (57.5) | 1.04 (.49–2.21) | P = .92 | |
| BMI, kg/m$^2$, mean ± SD | 27.7 ± 5.10 | | **P = .28** | |
| Biopsy length, cm, mean ± SD | 1.47 ± 0.43 | | **P = .16** | 0.53 (.26–1.08) |

Data are No. (%) unless otherwise specified. Bold formatting indicates statistically significant data.

Abbreviations: BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IVDU, intravenous drug use; OR, odds ratio; SD, standard deviation.

[a] In those patients with detectable HIV loads (defined as >75 copies/mL).

[b] In those patients with detectable HCV load (defined as >43 IU/mL).

primary care setting where this study was performed, both of which contrast with other studies focusing on largely white populations at tertiary referral centers [3, 11].

Data on current HCV regimens using NS3/4A protease inhibitors demonstrate efficacy in coinfection [14]. However, trials continue to show lower SVR rates in monoinfected African Americans compared to whites, and indicate that coinfected African Americans might show similarly lower responses [14].

The observed difference in degree of fibrosis between monoinfected and coinfected patients may be secondary to our findings that, within this cohort, coinfected patients were found to be less likely to have a history of heavy alcohol use and more likely to have received HCV treatment than monoinfected patients. The early fibrosis found in our study could be secondary to the protective effect of controlled HIV replication with effective ART use, as 81% of study patients had HIV loads below the level of detection and 94% were on ART.

Some limitations of the study are inherent in the retrospective design and a homogeneous African American population. Disease duration is an assumed estimate based on HCV acquisition within 2 years after starting intravenous drug use. Retrospective analysis of alcohol intake is likely to underestimate use. Liver biopsies are often not performed in patients who are already cirrhotic or who have certain comorbidities, leading to a selection bias in study inclusion criteria. Engaging HIV patients into care soon after their diagnosis has long been a priority, whereas monoinfected patients may not receive care until they become sick. Additionally, HIV patients are routinely HCV tested, but individuals in the general population are not usually HCV tested without a clear risk factor.

### Conclusions

This study expands the current literature by focusing on liver fibrosis prevalence in an African American urban cohort with and without HIV infection, in which there is limited information regarding chronic HCV: Nearly half had early liver fibrosis, and more than half of this group with early fibrosis had HIV/HCV coinfection. Given the long median duration of infection, these African Americans may possibly have a slower disease progression, a future research focus.

Given the poor response rates, results of this study indicate that a large proportion of these patients have early disease and a long duration of infection, and therefore may not have an urgent need to start therapy, allowing treatment with more-effective and better-tolerated future regimens.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

***Acknowledgments.*** This project was supported in whole or in part with federal funds from the National Cancer Institute at the National Institutes of Health (NIH; contract number HHSN261200800001E).

***Disclaimers.*** The content of this publication does not necessarily reflect the views of policies of the US Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

***Financial support.*** This research was supported by the National Institute of Allergy and Infectious Diseases (NIAID). This project has been funded in whole or in part with federal funds from the Intramural Research Program of the NIH (NIAID and the NIH Clinical Center).

***Potential conflicts of interest.*** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

## References

1. Alter M. Epidemiology of hepatitis C virus infection. World J Gastroenterol **2007**; 13:2436–41.
2. Maier IWG. Hepatitis C and HIV co-infection: a review. World J Gastroenterol **2002**; 8:577–9.
3. Pearlman BL. Hepatitis C virus infection in African Americans. Clin Infect Dis **2006**; 42:82–91.
4. Lewden C, Salmon D, Morlat P, et al. Causes of death among human immunodeficiency virus (HIV)–infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. Int J Epidemiol **2005**; 34:121–30.
5. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis **2005**; 5:558–67.
6. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology **2009**; 49: 1335–74.
7. Strader DB. Coinfection with HIV and hepatitis C virus in injection drug users and minority populations. Clin Infect Dis **2005**; 41(suppl 1): S7–13.
8. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatology **1999**; 30:1054–8.
9. Brau N, Salvatore M, Rios-Bedoya CF, et al. Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy. J Hepatol **2006**; 44:47–55.
10. Sterling RK, Wegelin JA, Smith PG, et al. Similar progression of fibrosis between HIV/HCV-infected and HCV-infected patients: analysis of paired liver biopsy samples. Clin Gastroenterol Hepatol **2010**; 8: 1070–6.
11. Sterling RK SR, Luketic VA, Sanyal AJ, et al. A comparison of the spectrum of chronic hepatitis C virus between Caucasians and African Americans. Clin Gastroenterol Hepatol **2004**; 2:469–73.
12. Conjeevaram HS, Fried MW, Jeffers LJ, et al. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. Gastroenterology **2006**; 131:470–7.
13. Matthews-Greer JM, Caldito GC, Adley SD, et al. Comparison of hepatitis C viral loads in patients with or without human immunodeficiency virus. Clin Diagn Lab Immunol **2001**; 8:690–4.
14. Jennings CL, Sherman KE. Hepatitis C and HIV co-infection: new drugs in practice and in the pipeline. Curr HIV/AIDS Rep **2012**; 9:231–7.