Clinical Liver Disease Progression Among Hepatitis C-Infected Drug Users With CD4 Cell Count Less Than 200 Cells/mm³ Is More Pronounced Among Women Than Men

Amy S. Baranoski,1,2,3 Deborah Cotton,2,3 Timothy Heeren,4 David Nunes,5 Rachel W. Kubiak,3 and C. Robert Horsburgh Jr.2,3

1Department of Medicine, Division of Infectious Diseases and HIV Medicine, Drexel University College of Medicine, Philadelphia, Pennsylvania; 2Department of Epidemiology; 3Department of Medicine, Section of Infectious Diseases, and 4Department of Biostatistics, Boston University School of Public Health; 5Department of Medicine, Section of Gastroenterology, Boston University School of Medicine, Massachusetts

Background. Hepatitis C virus (HCV) infection is a leading cause of liver-related morbidity and mortality in the United States, and injection drug users are at particularly high risk.

Methods. This prospective observational cohort study assessed the rate of, and risk factors for, clinical liver disease progression in a cohort of HCV monoinfected and human immunodeficiency virus (HIV)/HCV coinfectected drug users using unadjusted and multivariate Cox proportional hazards regression analyses.

Results. Of 564 subjects including 421 (75%) with HIV/HCV coinfection and 143 with HCV monoinfection, 55 (10%) had clinical liver disease progression during follow-up with a rate of 25.3 events per 1000 person-years. In unadjusted analysis, there was an interaction between sex and HIV status. In sex-stratified multivariate analysis, HIV/HCV-coinfected women with CD4 <200 cells/mm³ had 9.99 times the risk of liver disease progression as HCV-monoinfected women (confidence interval [CI], 1.84–54.31; \(P = .008\)), and white women had a trend towards increased risk of liver disease progression compared with non-white women (hazard ratio, 2.84; CI, .93–8.68; \(P = .07\)). Human immunodeficiency virus/HCV-coinfected men with CD4 <200 cells/mm³ had 2.86 times the risk of liver disease progression as HCV-monoinfected men (CI, 1.23–6.65; \(P = .01\)).

Conclusions. Hepatitis C virus-monoinfected and HIV/HCV-coinfected drug users had high rates of clinical liver disease progression. In those with HIV infection, liver disease progression was associated with advanced immune suppression. This effect was strikingly more pronounced in women than in men.

Keywords. HCV; HIV; drug abuse; drug user.

Hepatitis C virus (HCV) infection is a leading cause of liver-related morbidity and mortality in the United States, with 3 to 5 million people estimated to be chronically infected [1–3]. The prevalence varies widely, with 15%–30% of human immunodeficiency virus (HIV)-infected individuals infected [4] and up to 90% of persons with a history of injection drug use (IDU) infected [2, 4]. With routine HCV screening of blood and organ donations essentially eliminating transmission from those sources, IDU is responsible for a growing proportion of HCV infections; 60% of individuals testing positive for acute HCV in the United States in 2011 reported IDU in the prior 6 months [5].

Received 25 September 2015; accepted 24 December 2015.

Correspondence: A. S. Baranoski, 1427 Vine Street, Mail Stop 959, Philadelphia, PA 19102 (amy.baranoski@drexelmed.edu).

Open Forum Infectious Diseases

© The Author 2015. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com. DOI: 10.1093/ofid/ofv214

Clinical Liver Disease Progression in Drug Users • OFID • 1
viral load, and duration of drug use or HCV infection, the association between male sex and increased risk of fibrosis and liver disease progression has been positive in some studies [18, 21, 22] and negative in others [12, 14, 23].

The relationship between race or ethnicity and liver disease progression is also unclear. People of black race were at decreased risk of liver disease progression and mortality in previous studies [12, 22]. In a study of HIV/HCV-coinfected women, black women were at decreased risk of liver-related mortality compared with white- or Hispanic-coinfected women [24].

Although end-stage liver disease (ESLD) is a common cause of death in people with HIV [25], data on the contribution of HIV infection to progression of liver disease in HCV-infected individuals with an IDU history have been mixed [10, 12, 14, 16, 17, 19, 23]. It appears that the association between HIV/HCV coinfection and liver disease progression may be mediated by level of immune suppression [11, 13–16, 20, 26–28] and/or antiretroviral therapy (ART) use [11, 26, 27].

To clarify the risk of HCV-associated clinical liver disease progression among IDUs, we analyzed data from an observational cohort study of HCV-infected drug users in a diverse urban population. We hypothesized that the rate of liver disease progression and liver-related death would be increased in HIV/HCV-coinfected individuals compared with HCV-monoinfected patients and would vary by the degree of HIV-related immune suppression.

METHODS

Design

The Hepatitis C, HIV and Related Morbidity (CHARM) cohort was a prospective cohort study consisting of HCV-infected individuals with and without HIV infection. Details regarding the cohort have been previously published [28, 29].

Subjects

Subjects were recruited from clinics at Boston Medical Center (BMC) and the Boston Veteran’s Administration ([VA] Boston, MA). Boston Medical Center subjects were recruited between January 2000 and May 2008, and Boston VA patients were recruited between February 2001 and October 2002. Informed consent was obtained from all participants, and the BMC and Boston VA Institutional Review Boards approved this protocol.

Measures

At enrollment, subjects completed a detailed baseline questionnaire focused on demographic, behavioral, and medical history and underwent a physical exam and blood draw. A chart review was conducted to collect information on HIV/acquired immune deficiency syndrome and liver disease medical history, medical and psychiatric comorbidities, laboratory data, and medication usage including ART and hepatitis C treatment.

Regularly scheduled study visits, which coincided with routine medical visits when possible, occurred initially at 12-month intervals and increased to 6-month intervals as the study progressed. Information was collected on predictors and covariates of interest including drug and alcohol use and receipt of ART. The Alcohol Use Disorders Identification Test [30] and Addiction Severity Index [31] were used to assess hazardous drinking behavior and illicit substance use. Annual chart reviews were conducted for medical information including CD4 count and HIV viral load measurements.

Clinical liver disease progression was considered to be clinical progression or death due to liver disease. Clinical progression was defined as a new diagnosis of HCV-associated encephalopathy, variceal bleeding, ascites, or hepatocellular carcinoma. Liver-related deaths included end-stage hepatic failure and death due to esophageal bleeding, spontaneous bacterial peritonitis, or progressive encephalopathy. Deaths due to other causes where liver disease was believed to be a definite or probable contributor were also included as a liver-related death. Subjects with clinical progression prior to liver-related death were censored at the time of the initial event. Deaths were identified using Massachusetts and National Death Index searches. Deaths were adjudicated by a panel of infectious diseases specialists and gastroenterologists, who independently reviewed available death records and assigned cause of death and contribution of HCV and liver disease by consensus.

Statistical Analysis

Subjects were observed until they died, became incarcerated, declined to continue to participate, or were lost to follow-up. For this analysis, subjects were censored at the time of diagnosis of clinical liver disease progression or at last time known to be alive up to 1 year after last study visit through June 30, 2010. We used unadjusted and multivariate Cox regression models to assess the association between time to liver disease progression and previously identified predictors of progression of liver disease and potentially important covariates. For this analysis, all variables were assessed as time-constant predictors using the information obtained at the baseline interview and chart review. For HIV/HCV-coinfected individuals, we examined baseline and nadir CD4 count, baseline HIV viral load, and ART use at baseline. The multivariate model was constructed using stepwise forward selection with variables chosen based on the unadjusted model results. Variables with a P value of ≤.10 were included in the final multivariate model. All analyses were performed in SAS (version 9.1; Cary, NC).

RESULTS

There were 653 subjects enrolled and 564 (86%) are included in this analysis: 529 (94%) from BMC and 35 (6%) from the Boston VA. Five persons were excluded because they did not complete a baseline questionnaire, and 84 (13%) had no follow-up information available (See Supplemental Figure 1). The median length of follow-up for subjects included in this analysis was 3.0
Table 1. Baseline Characteristics of CHARM Cohort Participants

| Characteristic                      | HIV/HCV Coinfected Number (%) Total Number (%) | HCV Monoinfected Number (%) Total Number (%) |
|-------------------------------------|-----------------------------------------------|-----------------------------------------------|
|                                     | N = 421                                        | N = 143                                        | N = 564                                        |
|                                     |                                                 |                                                 |                                                 |
| Demographics                        |                                                |                                                |                                                 |
| Age in years; median (25%–75%)      | 46 (40–51)                                     | 46 (40–50)                                    | 46 (40–50)                                    |
| Male **                             | 298 (71)                                       | 83 (58)                                       | 381 (68)                                       |
| Race/ethnicity                      |                                                |                                                |                                                 |
| White                               | 113 (27)                                       | 49 (34)                                       | 162 (29)                                       |
| Black                               | 197 (47)                                       | 66 (46)                                       | 263 (47)                                       |
| Hispanic                            | 107 (25)                                       | 26 (18)                                       | 133 (24)                                       |
| Other                               | 4 (1)                                          | 2 (1)                                         | 6 (1)                                          |
| Born in United States***            | 333 (79)                                       | 125 (87)                                      | 458 (81)                                       |
| Marital status (n = 563)            |                                                |                                                |                                                 |
| Married or cohabitating             | 84 (20)                                        | 28 (20)                                       | 112 (20)                                       |
| Single                              | 232 (65)                                       | 81 (57)                                       | 313 (56)                                       |
| Separated, Divorced, or Widowed     | 104 (25)                                       | 34 (24)                                       | 138 (25)                                       |
| Less than high school education     | 189 (45)                                       | 61 (43)                                       | 250 (44)                                       |
| Currently employed**                | 75 (18)                                        | 38 (27)                                       | 113 (20)                                       |
| Income less than $600/month**       | 144 (37)                                       | 61 (54)                                       | 205 (41)                                       |
| Ever incarcerated******             | 326 (78)                                       | 93 (65)                                       | 419 (74)                                       |
| HCV Related History                 |                                                |                                                |                                                 |
| HCV genotype 1* (n = 357)           | 187 (75)                                       | 88 (83)                                       | 275 (77)                                       |
| HCV viral load >800 000 copies/UL* (n = 388) | 127 (50) | 55 (41) | 182 (47) |
| History of IDU                      | 365 (87)                                       | 119 (83)                                      | 484 (86)                                       |
| Years of IDU, median (25%–75%)      | 25 (17–32)                                     | 24 (15–31)                                    | 25 (17–31)                                    |
| Active IDU**                        | 123 (34)                                       | 49 (41)                                       | 172 (38)                                       |
| Hazardous drinking at enrollment†   | 92 (22)                                        | 28 (20)                                       | 120 (21)                                       |
| Hepatitis B antigen positive*       | 11 (3)                                         | 2 (1)                                         | 13 (2)                                         |
| Level of fibrosis*                  | 11 (3)                                         | 2 (1)                                         | 13 (2)                                         |
| Mild (FIB-4 score: <1.45)           | 159 (41)                                       | 63 (57)                                       | 222 (45)                                       |
| Moderate (FIB-4 score: 1.45–3.25)   | 149 (39)                                       | 26 (23)                                       | 175 (35)                                       |
| Advanced (FIB-4 score: >3.25)       | 78 (20)                                        | 22 (20)                                       | 100 (20)                                       |
| HIV History                         |                                                |                                                |                                                 |
| CD4 nadir, cells/mm³, median (25%–75%) (n = 416) | 186 (61–306) | – | – |
| Baseline CD4 count, cells/mm³, median (25%–75%) (n = 417) | 385 (208–557) | – | – |
| Serum HIV > 75 copies/mL (n = 412) | 321 (78)                                       | –                                             | –                                             |
| On antiretroviral therapy at enrollment† (n = 420) | 210 (60) | – | – |

Table 2. Initial Clinical Liver Disease Progression Event (n = 55)

| Outcome                                   | HIV/HCV Coinfected Number (%) | HCV Monoinfected Number (%) | Total Number (%) |
|-------------------------------------------|-------------------------------|-----------------------------|------------------|
| Liver related death*                      | 24                            | 5                           | 29               |
| Progressive liver failure                 | 14                            | 2                           | 16               |
| Ascites                                   | 3                             | 1                           | 4                |
| Spontaneous bacterial peritonitis         | 2                             | 0                           | 2                |
| Encephalopathy                            | 3                             | 1                           | 4                |
| Variceal bleed                            | 3                             | 2                           | 5                |
| Hepatoma                                  | 1                             | 1                           | 2                |
| Liver disease was a major contributing factor | 5                         | 1                           | 6                |

Clinical progression of liver disease*     | 20                            | 6                           | 26               |
New ascites                                | 9                             | 3                           | 12               |
New spontaneous bacterial peritonitis       | 2                             | 0                           | 2                |
New encephalopathy                         | 7                             | 2                           | 9                |
New variceal bleed                         | 1                             | 1                           | 2                |
Hepatoma                                   | 3                             | 1                           | 4                |

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

* Subgroups add up to more than total because some individuals were diagnosed with multiple conditions during a single time period.

years (interquartile range [IQR], 1.7–6.4 years), with a median follow-up of 2.9 years for HIV/HCV-coinfected subjects (IQR, 1.4–5.7 years) and 4.9 years for HCV-monoinfected participants (IQR, 2.0–7.0 years).

The baseline characteristics of the 564 HCV-infected subjects stratified by HIV status are shown in Table 1. The median age of subjects was 46 years, and 99% reported a history of drug use including 86% with IDU. For the 74 subjects (13%) who denied IDU, the noninjection drugs reported included marijuana (93%), cocaine (73%), heroin (22%), and other drugs (3%). Forty-seven subjects (9%) reported history of HCV treatment. Coinfected subjects were less likely to have mild fibrosis as measured by FIB-4 (FIB-4) score [32], to be born in the United States, to be employed, and to have an income under $600 per month.

There were 55 individuals with clinical liver disease progression during follow-up (10%) including 26 instances of clinical progression and 29 liver disease-related deaths (Table 2). The rate of liver disease progression overall was 25.3 events per 1000 person-years of follow-up, with 28.9 events per 1000 person-years in persons with HIV/HCV coinfection and 16.9 events per 1000 person-years in those with HCV monoinfection.

In unadjusted analysis, persons with hepatitis B antigen positivity, moderate or advanced (vs mild) liver fibrosis, and HIV infection with CD4 count <200 cells/mm³ (vs HCV monoinfection)
### Table 3. Unadjusted Predictors of Clinical Liver Disease Progression Among All Subjects in the CHARM Cohort (n = 564)

| Predictor                                      | Events (n = 55) | Person Years | Hazard Ratio (95% CI) | P Value |
|------------------------------------------------|-----------------|--------------|-----------------------|---------|
| **Age, years**                                 |                 |              |                       |         |
| <40                                            | 10              | 487.3        | Reference             | –       |
| 40 to 49                                       | 30              | 1113.7       | 1.32 (1.65–2.70)      | NS      |
| ≥50                                            | 15              | 572.1        | 1.24 (1.56–2.75)      | NS      |
| **Sex**                                        |                 |              |                       |         |
| Female                                         | 15              | 802.6        | Reference             | –       |
| Male                                           | 40              | 1370.5       | 1.49 (1.82–2.70)      | NS      |
| **Race/ethnicity**                             |                 |              |                       |         |
| White                                          | 16              | 571.4        | Reference             | –       |
| Black                                          | 27              | 1095.0       | 0.91 (1.49–1.70)      | NS      |
| Hispanic                                       | 12              | 486.3        | 0.88 (4.2–1.87)       | NS      |
| Other                                          | 0               | 20.5         | –                     | –       |
| **Location of birth**                          |                 |              |                       |         |
| United States                                  | 45              | 1791.1       | Reference             | –       |
| Outside United States                          | 10              | 374.6        | 1.04 (1.53–2.07)      | NS      |
| **Marital status**                             |                 |              |                       |         |
| Married or cohabitating                        | 12              | 408.6        | Reference             | –       |
| Single                                         | 33              | 1266.2       | 0.92 (1.47–1.78)      | NS      |
| Separated, Divorced or Widowed                 | 10              | 494.0        | 0.89 (1.39–1.99)      | NS      |
| **Employed at baseline**                       |                 |              |                       |         |
| Yes                                            | 9               | 471.1        | 0.71 (3.35–1.46)      | NS      |
| No                                             | 46              | 1694.0       | Reference             | –       |
| **Income <$600 per month**                     |                 |              |                       |         |
| Yes                                            | 18              | 884.8        | 0.73 (4.11–3.30)      | NS      |
| No                                             | 32              | 1071.7       | Reference             | –       |
| **Ever incarcerated**                          |                 |              |                       |         |
| Yes                                            | 42              | 1599.9       | 1.15 (1.62–2.15)      | NS      |
| No                                             | 13              | 572.3        | Reference             | –       |
| **HCV genotype**                               |                 |              |                       |         |
| Type 1                                         | 32              | 1090.0       | 1.90 (1.67–3.58)      | NS      |
| Other or Not Indicated                         | 4               | 275.4        | Reference             | –       |
| **HCV viral load, copies/IU**                  |                 |              |                       |         |
| <800 000                                      | 22              | 943.6        | Reference             | –       |
| ≥800 000                                      | 22              | 773.2        | 1.20 (1.67–2.17)      | NS      |
| **History of IDU**                             |                 |              |                       |         |
| Yes                                            | 48              | 1896.7       | 1.04 (1.47–2.31)      | NS      |
| No                                             | 7               | 276.5        | Reference             | –       |
| **Length of IDU, years**                       |                 |              |                       |         |
| <20                                           | 12              | 618.9        | Reference             | –       |
| 20 to <30                                      | 14              | 665.4        | 1.08 (1.50–2.34)      | NS      |
| ≥30                                           | 21              | 612.7        | 1.69 (1.83–3.43)      | NS      |
| **Active IDU**                                 |                 |              |                       |         |
| Yes                                            | 14              | 682.6        | 0.75 (4.04–1.41)      | NS      |
| No                                             | 34              | 1211.7       | Reference             | –       |
| **Hazardous drinking**                         |                 |              |                       |         |
| Yes                                            | 13              | 460.0        | 1.14 (6.61–2.12)      | NS      |
| No                                             | 42              | 1713.1       | Reference             | –       |
| **Hepatitis B antigen positive**               |                 |              |                       |         |
| Yes                                            | 3               | 32.7         | 3.29 (1.02–10.60)     | <.05    |
| No                                             | 49              | 1953.7       | Reference             | –       |
| **Level of fibrosis**                          |                 |              |                       |         |
| Mild (FIB-4 score: <1.45)                      | 3               | 681.8        | Reference             | –       |
| Moderate (FIB-4 score: 1.46–3.29)              | 13              | 722.9        | 5.19 (1.48–18.23)     | .01     |
| Advanced (FIB-4 score: >3.25)                  | 34              | 331.2        | 28.91 (8.88–94.16)    | <.001   |

Abbreviations: CD4, CD4 T cell; CHARM, Hepatitis C, HIV and Related Morbidity; CI, confidence interval; FIB, fibrosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; IU, international units; NS, not significant.

a Information not available for all 564 subjects.

b Active IDU = IDU within 6 months of enrollment.

c Alcohol Use Disorders Identification Test (AUDIT) score ≥8.

had a higher hazard of liver disease progression (Table 3). There was a significant interaction between sex and HIV status; thus, the adjusted models presented are stratified by sex. Fibrosis score was the strongest predictor of liver disease progression; however, because this parameter is on the pathway to disease progression, we excluded it from models constructed to identify clinical predictors of disease progression.

There was a trend towards an increased risk of liver disease progression for white (vs non-white) women, but there was no difference in liver disease progression between white and non-white men. There also appeared to be a differential effect of HIV and CD4 count between men and women; the HIV/HCV-coinfected women in the lowest CD4 count group showed 9.99 times the risk of liver disease progression compared with monoinfected women, whereas HIV/HCV-coinfected men had 2.86 times the risk of liver disease progression compared with monoinfected men (Table 4).

### DISCUSSION

Our results suggest that advanced HIV-associated immune suppression, and not HIV infection alone, is the primary risk factor for clinical liver disease progression in HIV/HCV-coinfected drug users. Our results also show that there may be a sex difference in the role of advanced immune suppression. This analysis builds on a previous analysis of HIV/HCV-coinfected CHARM participants that showed that, among HIV-infected persons, low nadir, baseline, and current CD4 counts were associated with increased risk of liver disease progression; however, because this parameter is on the pathway to disease progression, we excluded it from models constructed to identify clinical predictors of disease progression.

Our finding of an association between HIV status, stratified by level of immune suppression, and liver disease progression is in contrast to some previous studies including a large meta-analysis that showed no increased risk of liver disease progression in people with HIV infection [10, 12, 19]; however, those studies did not report on level of immune suppression. Two studies that found an association between HIV and risk of liver disease progression also showed that severe immune...
suppression was associated with liver disease progression [14, 16]. In a cohort of male HIV/HCV-coinfected individuals that examined the relationship between initiation of ART and hepatic decompensation, lower CD4 count was also associated with increased risk of decompensation [27]. Lack of CD4 count recovery in ART-initiators was associated with increased risk of liver disease progression in HIV/HCV-coinfected CHARM subjects [28]. In another cohort of HIV/HCV-coinfected individuals, lower CD4 count was associated with increased risk of ESLD diagnosis, hepatocellular carcinoma diagnosis, and all-cause mortality [11]. The mechanism for increased risk of clinical liver disease progression in people with HIV may be related to liver fibrosis, because risk of liver fibrosis appears to be increased for people with HIV/HCV coinfection compared with those with HCV monoinfection despite ART use [33]. Although one study found no association between current or nadir CD4 count and risk of liver fibrosis in HIV/HCV-coinfected individuals [34], other studies have shown that decreased current or nadir CD4 counts are associated with higher risk of liver fibrosis [35, 36].

The rate of liver disease progression seen in our cohort was high (25.3 events per 1000 person-years of follow-up) versus 3.1 [10] and 8.1 [19] per 1000 person-years in other studies of HIV/HCV-coinfected and HCV-monoinfected study populations. Thus, we may have been able to detect an association between immune suppression and liver disease progression not seen by others because our subjects had a higher risk of progression to liver disease. In previous studies limited to HIV/HCV-coinfected individuals, the rate of liver disease progression was less than half that of our HIV/HCV-coinfected cohort (13.1 [11] and 14 [27] per 1000 person-years). The rate of liver disease progression in our cohort was more similar to the rate of events seen in those HIV/HCV-coinfected individuals with more advanced fibrosis [11]. It may be that our cohort had a higher degree of liver fibrosis at entry compared with other cohorts; however, our FIB-4 scores do not suggest that this was the case. Our study site is a large urban tertiary care center so it is possible that there was referral bias with sicker individuals seeking care. It is also possible that there was differential loss to follow-up with individuals with less severe liver disease being lost to follow-up, whereas the individuals with more advanced liver disease remained in care. In addition, only 50% of our HIV-infected subjects were on ART at baseline, versus 69% in another urban cohort [11]. Lower ART use could have accounted for some of the higher rate of clinical liver disease progression seen in our population; however, our proportion of HIV-infected individuals on ART at baseline is not surprising given the time frame of enrollment (2000–2008).

We also observed differential risks for liver disease progression between men and women. Men had an approximately 50% increased rate of liver disease progression compared with women, although this risk was not statistically significant \((P = .19)\). Human immunodeficiency virus/HCV-coinfected men with a CD4 count above 200 cells/mm\(^3\) appeared to have a similar hazard of liver disease progression compared with HCV-monoinfected men. In contrast, HIV/HCV-coinfected women with a CD4 count between 200 and \(<350\) cells/mm\(^3\) had 2.6 times the risk of liver disease progression compared with HCV-monoinfected women; however, it should be noted that the sample size in our female stratified analysis was relatively small, and these results did not achieve statistical significance. Prior studies have shown different results regarding the relationship between sex and liver disease progression and fibrosis: some data showed increased risk for men \([18, 19, 21, 22]\); some data showed increased risk for women \([13]\); and several older studies showed no association between liver disease progression and sex \([14, 23]\). We are not aware of prior research showing a differential effect of immune suppression on risk of liver disease progression between men and women. It is possible that some of the contradictory findings regarding the role of sex in liver disease progression could be related to our finding of a differential role of immune suppression between men and women; however, much of the prior research examining sex has been conducted in predominantly male populations \([13, 14, 19, 23]\).

In a study of sex differences and liver fibrosis in HIV/HCV-coinfected individuals, male sex was an independent risk factor for fibrosis and cirrhosis; however, men in that study had more risk factors for fibrosis compared with women, including alcohol abuse, higher HCV viral load, and longer duration of HCV infection \([37]\). A study conducted in women showed that increased CD4 count was associated with decreased risk of liver-related mortality in univariate but not multivariate analysis \([24]\).

We found that white women had a marginally significant increased risk of liver disease progression compared with black and Hispanic women \((P = .07)\); however, there was no significant difference in liver disease progression for white men compared with non-white men. Some prior studies have not shown a relationship between race and liver disease progression \([10, 11]\), whereas other studies have found such an association. One study of injection drug users showed that men and non-black individuals were at increased risk for ESLD; and after adjusting for sex, age, duration of drug use, and HCV viral load, non-black injection drug users had 2.76 times the odds of ESLD mortality compared with black injection drug users \([12]\). Another study conducted in women showed that black HIV/HCV-coinfected women had decreased risk of liver-related mortality compared with white- or Hispanic-coinfected women \([24]\). The reason for our finding of a differential effect of race on liver disease progression stratified by sex is unclear. There may be possible genetic factors associated with decreased risk of liver disease progression in blacks.

We also observed a substantial but not statistically significant association between hepatitis B antigen positivity and risk of
liver disease progression in our cohort. The number of people who were hepatitis B antigen positive in our cohort was small, so this variable was not retained in the multivariate analysis. However, the presence of an additional active viral hepatitis infection has been associated with increased risk of liver disease progression in previous studies [38, 39].

A number of factors previously associated with liver disease progression in HCV-infected individuals such as age [10–13], duration of HCV infection [15, 17, 18], current IDU [12], and hazardous alcohol use [10, 14, 15, 17–20] were not associated with clinical liver disease progression in our cohort. The reason for the lack of these associations is unclear. Our cohort was relatively young, although the duration of IDU (as a proxy for duration of HCV infection) was 25 years. It may be that our outcome of clinically diagnosed liver events missed less obvious liver disease progression, and that measurement of liver disease progression based on liver biopsy or noninvasive fibrosis marker would have shown a stronger association with hazardous alcohol use, age, or duration of HCV infection. The duration of follow-up was relatively short for development of clinical liver progression, which may have obscured the association between age and liver disease progression. In addition, we assessed baseline factors, and it is possible that some of these factors may have become significant in a time-dependent analysis. However, the short duration of follow-up would tend to minimize such effects.

Our study had a number of limitations. The limited number of clinical liver events led to wide confidence intervals and difficulty drawing definitive conclusions. In addition, the HCV-monoinfected subjects had 2 additional years of follow-up on average. The differential length of follow-up may be due to the fact that HIV/HCV-coinfected individuals had liver disease events that occurred earlier. It could also be that HIV/HCV-coinfected subjects were lost to follow-up sooner because of competing risks such as being sicker due to non-HCV-related factors or because of differential social issues or other barriers to follow-up. Our rigorous review of the state and national death registries makes missed cases of death less likely. Because there was a high rate of clinical liver disease progression in both groups, it seems unlikely that we missed many cases of liver disease progression due to ascertainment bias. Our analysis was limited to baseline characteristics, and it is possible that the risk of liver disease progression varied over time for factors such as ART use, CD4 count, alcohol use, and IDU. Failure of CD4 count recovery over time has been associated with liver disease progression in HIV/HCV-coinfected CHARM participants [28], and initiation and duration of ART was associated with decreased risk of liver disease progression in another HIV/HCV-infected cohort [27].

This prospective longitudinal study also had a number of strengths. This was a large study for which follow-up information was available for 86% of enrolled subjects in an urban drug using population. We observed a higher rate of liver disease progression during follow-up than was seen in prior studies. This can be at least partially attributed to the fact that only 50% of our HIV-coinfected subjects were on ART at the start of the study. Thus, the increased risk of liver disease progression would likely be reduced by identifying coinfecting persons sooner and getting them on ART.

In addition, our cohort included a very diverse and socioeconomically disadvantaged patient population in which more than 70% of our subjects were minorities, 32% were female, and 75% were HIV/HCV-coinfected. In this regard, our population is more representative of persons at risk for HIV/HCV coinfection in the United States.

**CONCLUSIONS**

In conclusion, we found a higher rate of clinical liver disease progression in a cohort of HCV-monoinfected and HIV/HCV-coinfected drug users than has been previously reported. Risk of liver disease progression was primarily associated with HIV infection in persons with a baseline CD4 count <200 cells/mm³, and it appears that women with advanced immune suppression may be at higher risk for liver disease progression compared with men. As new oral regimens come into greater use, it will be important to see whether earlier treatment leads
to less immune suppression and correspondingly less liver disease progression in HCV/HIV-coinfected persons.

**Supplementary Material**

Supplementary material is available online at Open Forum Infectious Diseases (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

**Acknowledgments**

We thank Sheila Tumult for study management, Caleb Bass and Michael Winter for data management, and Greg Kirk for outcome adjudication.

**Financial support.** This work was funded by the National Institute of Drug Abuse at the National Institutes of Health ([NIH] grant R01 DA023054). A. S. B. was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the NIH (grant 5 K12 HD043444-07).

**Potential conflicts of interest.** All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

**References**

1. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144:705–14.
2. Alter MJ, Krawczak-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999;341:556–62.
3. Chak E, Talal AH, Sherman KE, et al. Hepatitis C virus infection in USA: an estimate of true prevalence. Liver Int 2011;31:1090–101.
4. Sherman KE, Rouster SD, Chung RT, Rajicic N. Hepatitis C virus prevalence among patients infected with human immunodeficiency virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. Clin Infect Dis 2002;34:831–7.
5. Centers for Disease Control and Prevention. Surveillance for viral hepatitis - United States, 2011. Viral Hepatitis Statistics and Surveillance 2013; http://www.cdc.gov/hepatitis/Statistics/2011Surveillance/Commentary.htm? HepC. Accessed 26 August 2013.
6. Graham BS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis 2001;33:562–9.
7. Ragni MV, Belle SH. Impact of human immunodeficiency virus infection on progression to end-stage liver disease in individuals with hemophilia and hepatitis C virus infection. J Infect Dis 2001;183:1112–5.
8. Posthouwer D, Makris M, Yee TT, et al. Progression to end-stage liver disease in patients with inherited bleeding disorders and hepatitis C: an international, multicenter cohort study. Blood 2007;109:3667–71.
9. Niederhaus C, Lange S, Heinig T, et al. Progress of chronic hepatitis C: results of a large, prospective cohort study. Hepatology 1998;28:1687–95.
10. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA 2000;284:450–6.
11. Limketkal BN, Mehta SH, Sutcliffe CG, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/ HCIV. JAMA 2002;308:370–8.
12. Hisada M, Chatterjee N, kalayioglu Z, et al. Hepatitis C virus load and survival among injection drug users in the United States. Hepatology 2005;42:1446–52.
13. Pineda JA, Garcia-Garcia JA, Aguilar-Guisado M, et al. Clinical progression of hepatitis C virus-related chronic liver disease in human immunodeficiency virus-infected patients undergoing highly active antiretroviral therapy. Hepatology 2007;46:622–30.
14. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus-infected and hepatitis C virus-infected patients. The Multicenter Group. Hepatology 1999;30:1054–8.
15. Benhamou Y, Di Martino V, Bochet M, et al. Factors affecting liver fibrosis in human immunodeficiency virus-infected and hepatitis C virus-infected patients: impact of protease inhibitor therapy. Hepatology 2001;34:283–7.
16. Di Martino V, Rufat P, Boyer N, et al. The influence of human immunodeficiency virus infection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. Hepatology 2001;34:1193–9.
17. Polet S, Fontaine H, Carnot F, et al. Predictive factors for development of cirrhosis in parenterally acquired chronic hepatitis C: a comparison between immunocompetent and immunocompromised patients. J Hepatol 1998;29:12–9.
18. Poynard T, Ratziu V, Charlotte F, et al. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. J Hepatol 2001;34:730–9.
19. John-Baptiste A, Krahm M, Heathcote J, et al. The natural history of hepatitis C infection acquired through injection drug use: meta-analysis and meta-regression. J Hepatol 2010;53:245–51.
20. Pineda JA, Aguilar-Guisado M, Rivero A, et al. Natural history of compensated hepatitis C virus-related cirrhosis in HIV-infected patients. Clin Infect Dis 2009;49:1274–82.
21. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997;349:825–32.
22. McCombs J, Matsuda T, Tonnu-Mihara I, et al. The risk of long-term morbidity and mortality in patients with chronic hepatitis C: results from an analysis of data from a Department of Veterans Affairs Clinical Registry. JAMA Intern Med 2014;174:204–12.
23. Soto B, Sanchez-Quijano A, Rodrigo I, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol 1997;26:5–10.
24. Sarkar M, Baccetti P, French AL, et al. Lower liver-related death in African-American women with human immunodeficiency virus/hepatitis C virus coinfection, compared to Caucasian and Hispanic women. Hepatology 2012;56:1699–705.
25. Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis 2001;33:492–7.
26. Merchant N, Giron-Gonzalez JA, Gonzalez-Serrano M, et al. Survival and prognostic factors of HIV-infected patients with HCV-related end-stage liver disease. AIDS 2006;20:49–57.
27. Anderson JP, Tchetgen Tchetgen EJ, Lo Re V Jr, et al. Antiretroviral therapy reduces the rate of hepatic decompensation among HIV- and hepatitis C virus-coinfected veterans. Clin Infect Dis 2014;58:719–27.
28. Anderson JP, Horsburgh CR, Williams PL, et al. CD4 recovery on antiretroviral therapy is associated with decreased progression to liver disease among hepatitis C virus-infected injecting drug users. Open Forum Infect Dis 2015;2:oft019.
29. Nunes D, Fleming C, Offner G, et al. Noninvasive markers of liver fibrosis are highly predictive of liver-related death in a cohort of HCV-infected individuals with and without HIV infection. Am J Gastroenterol 2010;105:1346–53.
30. Saunders JB, Axline ODG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption. Addiction 1993;88:791–804.
31. Makela K. Studies of the reliability and validity of the Addiction Severity Index. Addiction 2004;99:398–410.
32. Sterling RK, Lissen E, Clumec M, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317–25.
33. de Ledinghen V, Barreiro P,oucher J, et al. Liver fibrosis on account of chronic hepatitis C is more severe in HIV-positive than HIV-negative patients despite antiretroviral therapy. J Viral Hepat 2008;15:427–33.
34. Collazos J, Carton JA, Asensio V. Immunological status does not influence hepatitis C virus or liver fibrosis in HIV-hepatitis C virus-coinfected patients. AIDS Res Hum Retroviruses 2011;27:383–9.
35. Martin-Carbonero L, Benhamou Y, Puoti M, et al. Incidence and predictors of severe liver fibrosis in human immunodeficiency virus-infected patients with chronic hepatitis C: a European collaborative study. Clin Infect Dis 2004;38:128–33.
36. Pineda JA, Gonzalez J, Ortega E, et al. Prevalence and factors associated with significant liver fibrosis assessed by transient elastometry in HIV/hepatitis C virus-coinfected patients. J Viral Hepat 2010;17:214–9.
37. Collazos J, Carton JA, Asensio V. Gender differences in liver fibrosis and hepatitis C virus-related parameters in patients coinfected with human immunodeficiency virus. Curr HIV Res 2011;9:339–45.
38. Puoti M, Spinetti A, Ghezzi A, et al. Mortality for liver disease in patients with HIV infection: a cohort study. J Acquir Immune Defic Syndr 2000;24:211–7.
39. Thio CL, Seaburg EC, Skalsky R Jr, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet 2002;360:1921–6.

Clinical Liver Disease Progression in Drug Users • OFID • 7