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MAJOR ARTICLE

Clinical Liver Disease Progression Among Hepatitis C-Infected Drug Users With CD4 Cell Count Less Than 200 Cells/mm^3 Is More Pronounced Among Women Than Men

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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 coinfected 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/mm^3 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/mm^3 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].

Risk factors for progression of liver disease among persons with blood-product-associated HCV have been well described and include HIV/HCV coinfection [6–8], older age at HCV infection [7, 8], longer duration of HCV infection [9], alcohol abuse [7–9], and hepatitis B infection [7]. However, the extent to which such factors are important among persons with IDU-associated HCV infection is less clear. In studies of HCV infection that included persons with IDU-associated HCV, clinical liver disease progression has been associated with increasing age [10–13], HCV infection at an older age [11, 14–17], and longer duration of both HCV infection [15, 17, 18] and IDU [12]. Increased alcohol use has also been associated with liver disease progression in HCV-infected individuals [10, 14, 15, 17–20].

Sex also appears to be associated with HCV disease progression in a number of reports. Human immunodeficiency virus/HCV-coinfected women were at increased risk of liver disease progression compared with men in one study [13]; however, a meta-analysis of people with HIV/HCV coinfection and HCV monoinfection showed faster liver disease progression in men [19]. Male sex has been associated with increased risk of fibrosis [18, 21] and liver disease progression in HCV infection [12, 22]. After adjusting for a variety of factors including age, race, HCV

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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 $\leq$.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 (%) N = 421	HCV Monoinfected Number (%) N = 143	Total Number (%) N = 564
Demographics			
Age in years: median (25%–75%)*	46 (40–51)	45 (39–49)	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[a,***] (n = 563)	333 (79)	125 (87)	458 (81)
Marital status (n = 563)			
Married or cohabitating	84 (20)	28 (20)	112 (20)
Single	232 (55)	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[a,****] (n = 561)	75 (18)	38 (27)	113 (20)
Income less than $600/mo[a,*****] (n = 506)	144 (37)	61 (54)	205 (41)
Ever incarcerated[a,******] (n = 563)	326 (78)	93 (65)	419 (74)
HCV Related History			
HCV genotype 1[a] (n = 357)	187 (75)	88 (83)	275 (77)
HCV viral load ≥800 000 copies/IU[a] (n = 388)	127 (50)	55 (41)	182 (47)
History of IDU	365 (87)	119 (83)	484 (86)
Years of IDU, median (25%–75%)[a] (n = 496)	25 (17–32)	24 (15–31)	25 (17–31)
Active IDU[a,b] (n = 482)	123 (34)	49 (41)	172 (36)
Hazardous drinking at enrollment[c]	92 (22)	28 (20)	120 (21)
Hepatitis B antigen positive[a] (n = 527)	11 (3)	2 (1)	13 (2)
Level of fibrosis[a,*******] (n = 497)			
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/mm^3, median (25%–75%)[a] (n = 416)	186 (61–306)	–	–
Baseline CD4 count, cells/mm^3: median (25%–75%)[a] (n = 417)	385 (208–557)	–	–
Serum HIV > 75 copies/mL[a] (n = 412)	321 (78)	–	–
On antiretroviral therapy at enrollment[a] (n = 420)	210 (50)	–	–

Abbreviations: CD4, CD4 T cell; FIB, fibrosis; CHARM, Hepatitis C, HIV and Related Morbidity; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; IU, international units.

[a] Information not available for all subjects.

[b] Active IDU = IDU within 6 months of enrollment.

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

*P = .04; **P = .005; ***P = .03; ****P = .03; *****P < .001; ******P = .003; *******P = .006. Categorical variables assessed with χ^2 test and continuous variables assessed with Wilcoxon rank-sum test.

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

Outcome	HIV/HCV Coinfected N = 421	HCV Monoinfected N = 143	Total Number N = 564
Liver related death[a]	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[a]	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.

[a] 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 at baseline, and 210 (50%) of HIV-infected subjects were on ART at enrollment. Participants with HIV/HCV coinfection were older, more likely to be male, and to have a history of incarceration at study entry compared with those with monoinfection. Coinfected subjects were less likely to have mild fibrosis as measured by fibrosis-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/mm^3 (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 (.65–2.70)	NS
≥50	15	572.1	1.24 (.56–2.75)	NS
Sex				
Female	15	802.6	Reference	–
Male	40	1370.5	1.49 (.82–2.70)	NS
Race/ethnicity				
White	16	571.4	Reference	–
Black	27	1095.0	0.91 (.49–1.70)	NS
Hispanic	12	486.3	0.88 (.42–1.87)	NS
Other	0	20.5	–	–
Location of birth[a]				
United States	45	1791.1	Reference	–
Outside United States	10	374.6	1.04 (.53–2.07)	NS
Marital status[a]				
Married or cohabitating	12	408.6	Reference	–
Single	33	1266.2	0.92 (.47–1.78)	NS
Separated, Divorced or Widowed	10	494.0	0.69 (.30–1.59)	NS
Employed at baseline[a]				
Yes	9	471.1	0.71 (.35–1.46)	NS
No	46	1694.0	Reference	–
Income <$600 per month[a]				
Yes	18	884.8	0.73 (.41–1.30)	NS
No	32	1071.7	Reference	–
Ever incarcerated[a]				
Yes	42	1599.9	1.15 (.62–2.15)	NS
No	13	572.3	Reference	–
HCV genotype[a]				
Type 1	32	1090.0	1.90 (.67–5.38)	NS
Other or Not Indicated	4	275.4	Reference	–
HCV viral load, copies/IU[a]				
<800 000	22	943.6	Reference	–
≥800 000	22	773.2	1.20 (.67–2.17)	NS
History of IDU				
Yes	48	1896.7	1.04 (.47–2.31)	NS
No	7	276.5	Reference	–
Length of IDU, years[a]				
<20	12	618.9	Reference	–
20 to <30	14	665.4	1.08 (.50–2.34)	NS
≥30	21	612.7	1.69 (.83–3.43)	NS
Active IDU[a,b]				
Yes	14	682.6	0.75 (.40–1.41)	NS
No	34	1211.7	Reference	–
Hazardous drinking[c]				
Yes	13	460.0	1.14 (.61–2.12)	NS
No	42	1713.1	Reference	–
Hepatitis B antigen positive[a]				
Yes	3	32.7	3.29 (1.02–10.60)	<.05
No	49	1953.3	Reference	–
Level of fibrosis[a]				
Mild (FIB-4 score: <1.45)	3	861.8	Reference	–
Moderate (FIB-4 score: 1.45–3.25)	13	722.9	5.19 (1.48–18.23)	.01
Advanced (FIB-4 score: >3.25)	34	331.2	28.91 (8.88–94.16)	<.001
HIV status, baseline CD4 count[a]				
Hepatitis C monoinfected	11	650.4	Reference	–
HIV$^+$, ≥350 cells/mm^3	17	856.8	1.11 (.52–2.37)	NS
HIV$^+$, 200 to <350 cells/mm^3	8	395.3	1.15 (.46–2.88)	NS
HIV$^+$, <200 cells/mm^3	19	260.5	3.97 (1.88–8.39)	<.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 [28].

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

Table 4. Multivariate Predictors of Clinical Liver Disease Progression Stratified by Sex

Predictor	Male n = 380, 40 Events Hazard Ratio (95% CI)	*P* Value	Female n = 180, 15 Events Hazard Ratio (95% CI)	*P* Value
White race[a]	0.89 (.43–1.82)	NS	2.84 (.93–8.68)	.07
HIV status by baseline CD4 T-cell count[b]				
Hepatitis C monoinfected	Reference	–	Reference	–
HIV$^+$, ≥350 cells/mm^3	0.72 (.30–1.76)	NS	3.92 (.74–20.74)	NS
HIV$^+$, 200 to <350 cells/mm^3	0.87 (.31–2.47)	NS	2.63 (.36–19.01)	NS
HIV$^+$, <200 cells/mm^3	2.86 (1.23–6.65)	.01	9.99 (1.84–54.31)	.008

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; NS, not significant.

[a] Compared with all non-white subjects.

[b] Information not available for all 564 subjects.

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 coinfected 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/mm^3, 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/).

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