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Hepatitis C Infection Is Associated with Depressive Symptoms in HIV-Infected Adults with Alcohol Problems

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Abstract

OBJECTIVES—Depression is common in persons with HIV infection and with alcohol problems, and it has important prognostic implications. Neurocognitive dysfunction has been reported with chronic hepatitis C virus (HCV) infection. We hypothesized that HCV infection is associated with more depressive symptoms in HIV-infected persons with a history of alcohol problems.

METHODS—We performed a cross-sectional analysis of baseline data from a prospective cohort study of 391 HIV-infected subjects with a history of alcohol problems, of whom 59% were HCV antibody (Ab) positive and 49% were HCV RNA-positive. We assessed depressive symptoms (Center for Epidemiologic Studies Depression [CES-D]) and past month alcohol consumption. In the primary analysis, we evaluated whether there were more depressive symptoms in HCV Ab-positive and RNA-positive subjects in unadjusted analyses and adjusting for alcohol consumption, gender, age, race, CD4 count, homelessness, drug dependence, and medical comorbidity.

RESULTS—Mean CES-D scores were higher in subjects who were HCV Ab-positive compared with those who were HCV Ab-negative (24.3 *vs* 19.0; $p < 0.001$). In adjusted analyses, the difference in CES-D scores between HCV Ab-positive and Ab-negative subjects persisted (24.0 *vs* 19.0; $p < 0.001$). Unadjusted mean CES-D scores were also significantly higher in HCV RNA-positive subjects compared with those who were RNA-negative, and the difference remained significant (24.6 *vs* 19.3; $p < 0.001$) in adjusted analyses.

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CONFLICT OF INTEREST

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CONCLUSIONS—HCV/HIV coinfected persons with a history of alcohol problems have more depressive symptoms than those without HCV, and this association is unexplained by a variety of population characteristics. These data suggest that HCV may have a direct effect on neuropsychiatric function.

INTRODUCTION

Depression in HIV-infected patients is a common but under-diagnosed condition with important prognostic implications (1). Depressive symptoms have been associated with poor medication adherence, more rapid HIV disease progression, and increased mortality (2). Better understanding of the factors contributing to depression and its detrimental effect on the course of HIV infection may be gained by studying the effect of significant comorbidities.

Alcohol use and hepatitis C virus (HCV) infection are also common in HIV-infected patients, particularly those with a history of injection drug use. Alcohol use is clearly associated with depression and may exacerbate it (3,4). Chronic HCV infection has been associated with neurocognitive symptoms, perhaps mediated by a direct effect on the central nervous system (5). Interferon, a component of the treatment regimen for HCV infection, can worsen depressive symptoms (6).

In order to better understand the relation between HCV infection and depressive symptoms in the context of HIV disease, we studied a cohort of HIV-infected patients with a history of alcohol problems. We tested the hypothesis that HCV infection is associated with more depressive symptoms in these HIV-infected subjects.

METHODS

Subject Recruitment

Study subjects were participants in the HIV-LIVE (HIV-Longitudinal Interrelationships of Viruses and Ethanol) study, a prospective, observational cohort study of HIV-infected patients with past or current alcohol problems. The present study is a cross-sectional analysis of data collected at entry into the HIV-LIVE cohort.

A total of 401 subjects were recruited from several different sources including: (1) a previous cohort study of people with HIV and alcohol problems (N = 154, 38%) (7); (2) the Diagnostic Evaluation Unit (DEU), an intake clinic for HIV-infected patients at Boston Medical Center (BMC) (N = 88, 22%) (8); (3) the HIV Primary Care and Specialty Clinics at Beth Israel Deaconess Medical Center (BIDMC) (N = 31, 8%); and (4) additional health care centers, homeless shelters, drug treatment programs, other studies, subject referrals, and flyers (N = 128, 32%). Enrollment began in August 2001, and ended in July 2003.

Eligibility criteria for the study included the following:

1. Documented HIV Ab test by ELISA and confirmed by Western blot (medical record or tested at enrollment).
2. Two or more affirmative responses to the CAGE alcohol screening questionnaire (9,10) or physician-investigator diagnosis of alcoholism.
3. Ability to speak English or Spanish.
4. At least one contact person who was likely to know the subject's whereabouts.

Exclusion criteria included: (1) scoring <21 on the 30-item Folstein Mini-Mental State Examination (MMSE) (11); and (2) a trained interviewer assessment that the patient was incapable of comprehending informed consent or of answering the interview questions.

If an eligible individual agreed to participate in this study, a research associate scheduled an appointment for the first interview at BMC's General Clinical Research Center (GCRC) or BIDMC's Clinical Research Center (CRC). All subjects who met the eligibility criteria and wished to participate in the study provided written informed consent prior to enrollment. The Institutional Review Boards of BMC and BIDMC approved this study. Additional privacy protection was secured by the issuance of a Certificate of Confidentiality by the Department of Health and Human Services to protect subjects from release of their research data even under a court order or subpoena.

Subject Assessment

After enrollment, subjects received an interviewer-administered assessment. The assessment included questions on the following: demographics; depressive symptoms (Center for Epidemiologic Studies Depression [CES-D] scale) (12); medical comorbidity by a validated interview measure (13); current and lifetime alcohol use and dependence (Composite International Diagnostic Interview [CIDI]) (14); current drug dependence (CIDI Short Form); and HIV risk behaviors (Risk Assessment Battery [RAB], modified version) (15). Past month alcohol consumption was assessed using a validated calendar method (16). Heavy alcohol consumption was defined as more than 14 drinks per week or more than 4 drinks on any one occasion for men aged 65 yr and younger; or more than 7 drinks per week or more than 3 drinks on any one occasion for women and anyone over the age of 65 yr. Moderate use was defined as 1 or more drinks in the past 30 days but less than the "heavy" category. Abstinent was defined as no drinks in the past 30 days. Homelessness was defined as having spent at least one night either on the street or in a shelter in the 6 months prior to the interview.

All subjects in this cohort were Ab tested for HCV infection. Those who were Ab-positive had HCV testing by RNA measurement using polymerase chain reaction testing to verify the presence of active infection.

Primary Outcome

The primary study outcome was depressive symptoms, which were assessed using the CES-D (12). The CES-D is a short self-report tool intended to assess depressive symptoms in the general population. It consists of 20 questions concerning mood and behavior over the past week with results reported as rarely or none of the time (<1 day), some or a little of the time (1–2 days), occasionally or a moderate amount of the time (3–4 days), or most or all of the time (5–7 days). CES-D scores can range from 0 to 60. Higher CES-D scores reflect the presence of more depressive symptoms.

Primary Independent Variable

The main independent variable was HCV status, which was defined in two ways: (1) HCV Ab-positive *versus* Ab-negative and (2) HCV RNA-positive *versus* RNA-negative. Examination of the independent variable in this manner was deemed important to identify a potential biologic effect of HCV infection on depressive symptoms. For the purpose of the analysis, HCV Ab-negative subjects were assumed to be HCV RNA-negative (17).

Statistical Analyses

χ^2 and Wilcoxon rank sum tests were used to compare subject characteristics by HCV serologic status. Multiple linear regression models were used to assess the cross-sectional association between HCV infection and depressive symptoms. Separate analyses were performed for each method of defining HCV status. Covariates examined included alcohol consumption (abstinent *vs* moderate *vs* heavy) (18), gender, age, race (black *vs* white *vs* Hispanic *vs* other), CD4 cell count, homelessness (yes *vs* no), diagnosis of drug dependence (yes *vs* no), and medical

comorbidity. Self-reported information was available on whether subjects ever used injection drugs. However, this variable was highly correlated with HCV infection status, whereas drug dependence diagnosis was not. Thus, drug dependence diagnosis was included as the covariate in regression analyses to avoid potential collinearity.

Secondary analyses were conducted modeling CES-D as a binary outcome (CES-D ≥ 23 *vs* CES-D < 23) and also modeling CES-D as a continuous outcome excluding those questions (1,5,7,11,20) that reflect somatic symptoms. Additional analyses were conducted to assess the following potential confounders: MMSE; ever received interferon therapy; educational level (high school *vs* not); employment status (yes *vs* no); income level (above *vs* below median); and current injection drug use (within 6 months). To assess the potential bias from including subjects who were previously on interferon therapy, the primary analysis was repeated excluding those subjects.

All analyses were conducted using two-sided significance tests defining $p < 0.05$ as statistically significant. Analyses were performed using SAS software (version 8.2; SAS Institute, Cary, NC).

RESULTS

Of the 401 HIV-infected subjects with current or past alcohol problems enrolled in the HIV-LIVE cohort, 391 had available HCV Ab test results. Of these 391 subjects, 231 (59%) were HCV Ab-positive (Fig. 1). Of the 213 HCV Ab-positive subjects who were tested for RNA, 183 (86%) had a detectable level. One additional subject did not have available HCV Ab results, but tested HCV RNA-negative and was included only in the HCV RNA analyses. Only one HCV-infected subject in the study was receiving interferon therapy at baseline, and only 17 of 231 (7.4%) HCV Ab-positive subjects had received interferon therapy ever. Of those 17 subjects, 10 had received it for more than 3 months, and 6 had received it for more than 6 months.

Characteristics of the cohort reflected the urban setting of this study: 75% were men with a median age of 42 yr; 41% were black, 33% white, and 19% Hispanic; 25% were homeless; and 43% met criteria for current drug dependence (past 12 months). Thirty-two percent reported heavy alcohol consumption, 11% had moderate alcohol consumption, and 58% were abstinent in the past 30 days. The median CD4 cell count was 402/mm^3 (interquartile range 241–624/mm^3), and the median HIV log RNA was 2.9 copies/mL (interquartile range 0.0–4.1 copies/mL). The median number of medical comorbidities was 1 (interquartile range 0–6).

Characteristics of subjects who were HCV Ab-positive *versus* those who were HCV Ab-negative are listed in Table 1. HCV Ab-positive subjects were more likely to be men, older, homeless, abstinent from alcohol, have injection drug use as their primary HIV-risk behavior, and have a lower MMSE score. HCV Ab-positive subjects also had a lower median CD4 cell count and more medical comorbidity.

Unadjusted mean CES-D scores were higher in the 231 subjects who were HCV Ab-positive compared with the 160 who were Ab-negative (24.3 *vs* 19.0; $p = 0.001$) (Table 2). In adjusted analyses, the difference in CES-D scores between HCV Ab-positive and Ab-negative subjects remained significant (24.0 *vs* 19.0; $p = 0.001$). Unadjusted mean CES-D scores were significantly higher in the 183 HCV RNA-positive subjects compared with the 191 who were RNA-negative (24.8 *vs* 19.2; $p < 0.001$) (Table 3). The difference in CES-D scores remained significant (24.6 *vs* 19.3; $p < 0.001$) in adjusted analyses.

In order to assess the effect of using a clinically relevant CES-D threshold, we repeated our primary analysis with CES-D < 23 *vs* CES-D ≥ 23 as the dependent variable and still found a

significant association between HCV status and depressive symptoms (HCV RNA, adjusted analysis: OR 2.78 [1.73, 4.49]). In order to determine whether somatically focused CES-D questions may have influenced the results, we repeated our primary analysis excluding those five questions and still found a comparable significant association between HCV status and depressive symptoms (Table 4).

In order to assess whether MMSE was a confounder, we repeated our primary analysis adjusting for MMSE score and still found a significant association between HCV status and depressive symptoms (Table 4). In order to determine whether prior interferon therapy may have affected the results, we repeated our primary analysis excluding subjects who had ever received interferon therapy and still found a significant association between HCV status and depressive symptoms (Table 4).

We also examined whether sociodemographic factors may have influenced the results. Our primary analysis was repeated adjusting for educational level, employment status, and income level and still showed a significant difference in CES-D scores by HCV status (Table 4). In addition, we repeated our primary analysis adjusting for self-reported current injection drug use and still found a significant difference in CES-D scores by HCV status (Table 4).

DISCUSSION

In this cohort of HIV-infected subjects with current or past alcohol problems, depressive symptoms were significantly more frequent in those coinfected with HCV. Other population characteristics, including alcohol consumption, gender, age, race, CD4 count, homelessness, drug dependence, and medical comorbidity, did not account for this observed difference. Significant differences in depressive symptoms between HCV-infected and uninfected subjects were still noted when using a clinically relevant CES-D threshold, excluding CES-D questions with somatic content, adjusting for MMSE score, excluding subjects who had ever received interferon therapy, and adjusting for additional sociodemographic factors and current injection drug use.

Depression is common in patients with chronic HCV infection, and most authors have attributed it to a psychological response to a chronic progressive medical condition or drug use itself (19–26). In one blinded study of 309 injection drug users, 57.2% of subjects with HCV infection had significant depressive symptomatology based on CES-D test results compared with 48.2% of HCV-negative controls (27). None of the HCV-infected subjects were receiving interferon therapy. However, another study comparing 295 injection drug users who were HIV +/HCV− (N = 81), HIV−/HCV+ (N = 62), and HIV−/HCV− (N = 152) found no differences in psychological morbidity on several affective scales among these groups (28).

Several studies have described an association between chronic HCV infection and neurocognitive dysfunction that appears independent of liver disease severity. Forton *et al*. used a computer-based cognitive battery to demonstrate selective impairments of attention, concentration, and psychomotor speed in patients without significant disease on liver biopsy (5). Fatigue, depression, or a history of drug abuse did not account for these findings. Hilsabeck *et al*. described neuropsychological impairment in 49% of HCV-infected patients without cirrhosis (29). McAndrews *et al*. evaluated a cohort of HCV-infected subjects, screened to exclude relevant comorbidities, with neuropsychological tests (30). Compared to controls, subjects with HCV infection were observed to have somewhat poorer learning ability. Ryan *et al*. compared coinfected subjects with advanced HIV disease to subjects without HCV infection using neurocognitive testing and psychiatric interviews (31). Forty-two percent of each group met criteria for major depression, but coinfected subjects exhibited diminished neurocognitive capabilities.

Neuroradiologic and neurophysiologic studies have indicated the possibility of an underlying biological mechanism for neurocognitive dysfunction in HCV-infected patients (32,33). Forton *et al*. showed altered brain metabolism using proton magnetic resonance spectroscopy in patients with chronic HCV infection (32). Kramer *et al*. demonstrated mild abnormalities on neuroelectrophysiologic testing in this patient population not attributable to drug or alcohol use or cirrhosis (33). HCV genomic sequences have also been detected in postmortem brain tissues along with evidence of viral replication (34,35). Thus, in addition to epidemiological evidence for an association between HCV infection and depressive symptoms, neuropsychological testing and physiological data from neuroimaging provide support for a potential biologic basis for this observation.

Depression affects half of the HIV-infected population at some time in the course of their disease, occurring twice as frequently as in seronegative persons (1,36–39). However, because of the clinical focus on other complications, it may not always be diagnosed (39,40). Depression in this patient population has been associated with decreased adherence to medical therapy (41) and increased mortality (2,42). Recognition that HIV-infected patients who also have hepatitis C may be prone to more depressive symptoms has important management implications.

This study has several limitations. While the CES-D is a well-validated scale for depressive symptoms, use of other instruments, such as the Beck Depression Inventory, might have yielded different results. Interpretations of the importance of differences in CES-D scores vary. However, the observed differences in this study have generally been considered clinically important (2). Whether these study findings are applicable to other populations with chronic HCV infection would need to be confirmed. The cross-sectional, observational nature of this study limits our ability to establish a causal link between HCV infection and depressive symptoms. In addition, we cannot distinguish between the effects of injection drug use and HCV serostatus on depressive symptoms. An alternative, but less compelling, explanation for these findings would be that depressed persons are more likely to inject drugs, which leads to HCV infection.

In summary, HCV infection appears to be associated with more depressive symptoms in patients with HIV infection who have a history of alcohol problems. Recent literature suggests that HCV infection has a direct effect on the central nervous system, which may be responsible for this observation.

Clinicians should be alert for depressive symptoms in HIV/HCV coinfected patients and initiate treatment for depression when appropriate. Institution of antidepressant therapy may enhance medical adherence, which is key to successful antiretroviral management, and the patient's ability to tolerate treatment for HCV infection. Researchers should focus future efforts on understanding the potential biologic reasons for the association observed in this study. Further research may better delineate the contributions of HCV and other factors in the development of depressive symptoms in HIV-infected patients.

STUDY HIGHLIGHTS

What is Current Knowledge

- Depression is common in HIV-infected persons and persons with alcohol problems and has important prognostic implications.
- Neurocognitive dysfunction has been reported with chronic hepatitis C virus (HCV) infection.

What is New Here

- HCV/HIV co-infected persons with a history of alcohol problems have more depressive symptoms than those without HCV.
- This association is unexplained by a variety of population characteristics.
- HCV may have a direct effect on neuropsychiatric function.

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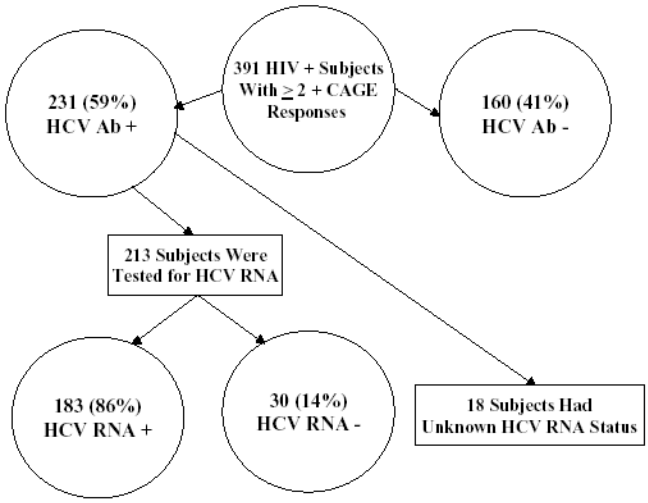

Figure 1.
Hepatitis C serologic status of a cohort of HIV-infected subjects with current or past alcohol problems.

Table 1

Characteristics of HIV-Infected Subjects with Current or Past Alcohol Problems

Characteristic	HCV Ab-Positive (N = 231)	HCV Ab-Negative (N = 160)
Male, N (%)*	165 (71%)	130 (81%)
Median (IQR) age*	44.4 (39.7, 48.1)	39.9 (35.6, 45.7)
Race, N (%)		
Black	87 (38%)	75 (47%)
White	77 (33%)	52 (33%)
Hispanic	53 (23%)	21 (13%)
Other	14 (6%)	12 (7%)
Homelessness, N (%)*	69 (30%)	29 (18%)
Drug dependence, N (%)	101 (44%)	65 (41%)
Alcohol consumption, N (%)*		
Abstinent	145 (63%)	78 (49%)
Moderate	18 (8%)	23 (14%)
Heavy	68 (29%)	58 (37%)
Primary HIV risk behavior, N (%)*		
Injection drug use	156 (75%)	12 (8%)
Men sex with men	9 (4%)	75 (50%)
Other	44 (21%)	64 (42%)
Median (IQR) CD4 cell count*	362 (232, 546)	472 (291, 698)
Median (IQR) HIV log RNA	3.0 (0, 4.1)	2.9 (0, 4.1)
Median (IQR) medical comorbidity*	2 (0, 6)	1 (0, 6)
Receiving interferon therapy, N (%)	1 (0.4%)	0 (0.0%)
Mean (SD) MMSE score*	26.94 (2.34)	27.64 (2.14)

* $p < 0.05$.

IQR = interquartile range; SD = standard deviation.

Table 2

Bivariate and Multivariable Analysis of the Impact of HCV Antibody Status on Depressive Symptoms

	Mean Depressive Symptoms (SE) Unadjusted	Mean Depressive Symptoms (SE) Adjusted*
HCV Ab-positive (N = 231)	24.3 (0.88)	24.0 (0.86)
HCV Ab-negative (N = 160)	19.0 (0.90)	19.0 (1.04)
P-value	<0.001	<0.001

Bivariate and multivariable analysis of the impact of HCV antibody status on depressive symptoms is measured by CES-D score.

*Adjusted for alcohol consumption, gender, age, race, CD4 count, homelessness, drug dependence, and medical comorbidity.

Table 3

Bivariate and Mutivariable Analysis of the Impact of HCV RNA Status on Depressive Symptoms

	Mean Depressive Symptoms (SE) Unadjusted	Mean Depressive Symptoms (SE) Adjusted*
HCV RNA-positive (N = 183)	24.8 (1.00)	24.6 (0.95)
HCV RNA-negative (N = 191)	19.2 (.85)	19.3 (0.92)
P-value	<0.001	<0.001

Bivariate and mutivariable analysis of the impact of HCV RNA status on depressive symptoms is measured by CES-D score.

*Adjusted for alcohol consumption, gender, age, race, CD4 count, homelessness, drug dependence, and medical comorbidity.

Table 4

Adjusted Mean Difference in CES-D Score in Secondary Analyses

Secondary Analysis	HCV Ab+ *vs* Ab−	HCV RNA + *vs* RNA−
CES-D without somatic questions as the dependent variable	3.4	3.8
Primary model adjusting for MMSE	4.7	4.9
Primary model excluding interferon users	5.2	5.2
Primary model adjusting for educational level	4.0	4.5
Primary model adjusting for employment status	4.3	4.6
Primary model adjusting for income level	4.2	4.6
Primary model adjusting for current drug use	5.1	5.3

Primary model examines CES-D as continuous variable and is adjusted for alcohol consumption, gender, age, race, CD4 count, homelessness, drug dependence, and medical comorbidity.

All adjusted mean differences $p < 0.05$.