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Barriers to Treatment of Hepatitis C in HIV/HCV-Coinfected Adults with Alcohol Problems

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Abstract

Background—Alcohol use and human immune deficiency virus (HIV) infection are both associated with accelerated progression of hepatitis C virus (HCV) disease and reduced response rates to interferon therapy. In this study, we assessed the prevalence of barriers to interferon treatment in a population of HIV/HCV-coinfected patients with current or past alcohol problems and the extent to which they received treatment to address the barriers.

Methods—This is a cross-sectional, descriptive analysis of baseline data from a prospective study assessing the impact of HCV and alcohol use on HIV disease progression. Using consensus guidelines, subjects were categorized as having absolute, relative, or no contraindications to interferon therapy for HCV. Absolute contraindications to treatment included heavy alcohol use, decompensated liver disease, CD4 cell count <100 cells/ μ L, recent needle sharing, and suicidal ideation. Relative contraindications included moderate alcohol use, recent injection drug use, depressive symptoms, and CD4 cell count from 100 to 199 cells/ μ L.

Results—Of 401 HIV-infected subjects, 200 were HCV RNA-positive. Fifty-three percent had an absolute contraindication to interferon therapy, 35% a relative but no absolute contraindication, and only 12% had no contraindication. Of those with an absolute contraindication, 61% reported heavy drinking and the majority (88%) had multiple contraindications. These contraindications were present despite the fact that over 50% were in receipt of substance abuse and mental health treatment.

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Conclusions—Continued alcohol and drug use as well as depressive symptoms are the major barriers to interferon therapy in HCV/HIV-coinfected subjects and these barriers persist despite high treatment rates for these problems. Therefore, more intensive treatments of alcohol, drug, and mental health issues are needed to improve HCV treatment eligibility in HCV/HIV-coinfected persons.

Keywords

Alcohol; Hepatitis C; Interferon; HIV

APPROXIMATELY 30% OF human immune deficiency virus (HIV)-infected persons are coinfecting with hepatitis C virus (HCV), and a substantial proportion also have alcohol problems (Campbell et al., 2006; Galvan et al., 2002; Samet et al., 2004; Sherman et al., 2002). Both HIV coinfection and alcohol use are associated with more rapidly progressive liver disease and reduced response to interferon-based treatment (Bhattacharya and Shuhart, 2003; Di Martino et al., 2001; Poynard et al., 1997; Torriani et al., 2004). Impaired response to interferon in those who use alcohol limits opportunities to control liver-related morbidity and mortality (Blackard et al., 2004; Carrat et al., 2004; Edlin, 2002; Mochida et al., 1996; Ohnishi et al., 1996; Okazaki et al., 1994; Rockstroh et al., 2005; Torriani et al., 2004). Furthermore, only about 30% of HIV-coinfected populations are eligible for interferon therapy because of ongoing drug and alcohol use, psychiatric disease, poor adherence to medical therapy, or underlying medical contraindications (Adeyemi et al., 2004; Falck-Ytter et al., 2002; Fleming et al., 2003). However, the barriers to interferon treatment, including the associated psychological and medical issues in individuals with alcohol problems, have not been well delineated.

Strategies aimed at improving the effectiveness of interferon-based treatment will require expansion of the population eligible for treatment and maximizing treatment responses in those who receive therapy. Aggressive management of drug dependence and psychiatric disease has been shown to increase the proportion of individuals eligible for interferon therapy (Backmund et al., 2001; Sylvestre, 2002; Taylor, 2005) but there have been no studies assessing the impact of treatment of alcohol problems on treatment eligibility. A better understanding of barriers in people with alcohol and other drug problems and associated mental health disorders may help to target interventions aimed at increasing receipt of pharmacotherapy for hepatitis C. The aim of this study was to assess the barriers to receipt of interferon therapy for HCV infection in an HIV-infected population with alcohol problems, many of whom have access to substance use and mental health treatment.

MATERIALS AND METHODS

Study Design

This is a cross-sectional analysis of baseline data from a prospective observational cohort study [HIV-Longitudinal Interrelationships of Viruses and Ethanol (HIV-LIVE)]. The study enrolled 401 HIV-infected patients with current or past alcohol problems. The major recruitment sites were the Diagnostic Evaluation Unit at Boston Medical Center (BMC; Samet et al., 1995) and the HIV Primary Care and Consultation Clinics at Beth Israel Deaconess Medical Center (BIDMC). Other subjects were recruited from BMC's primary care practices, referrals by other study subjects, and flyers posted at homeless shelters and HIV/AIDS social service agencies in the Boston area. Persons responding to the flyers were assessed by telephone for alcohol problems using the CAGE questionnaire and then invited for an in-person interview to complete the screening process. Recruitment began in August 2001 and ended in July 2003.

Eligibility criteria for the HIV-LIVE cohort included the following: (1) documented HIV antibody test by ELISA and confirmed by Western blot (medical record or tested at enrollment);

(2) two or more positive responses to the CAGE questionnaire (Buchsbaum et al., 1991; Mayfield et al., 1974; Samet et al., 2004) or physician-investigator diagnosis of lifetime alcohol abuse or dependence; (3) ability to speak English or Spanish; and (4) at least 1 contact person who knew the subject's whereabouts. Exclusion criteria were a score of <21 on the 30-item Folstein Mini-Mental State Examination (Folstein et al., 1975; Smith et al., 2006) or a trained interviewer assessment that the patient was incapable of comprehending informed consent or answering the interview questions. Eligible subjects were asked to provide written informed consent before enrollment. The Institutional Review Boards of BMC and BIDMC approved this study. HCV RNA-positive subjects from the HIV-LIVE cohort were deemed eligible for the current analysis.

Subject Assessments

A trained research associate interviewed all subjects. A standardized interview included questions on demographics, HIV risk behaviors, alcohol consumption, and ART use in the past 30 days. Current alcohol consumption (past 30 days) was assessed using a validated calendar method (Sobell et al., 1982, 1992). The Composite International Diagnostic Interview (CIDI) Alcohol Module (Robins et al., 1988) was administered to determine current (past 6 months) and lifetime diagnoses of alcohol abuse and dependence. Recent (past 6 months) drug use and current (past 12 months) diagnosis of drug dependence was assessed at enrollment using the CIDI. Laboratory data, including liver-related blood tests, CD4 cell counts, HCV antibody, HCV RNA, and HIV viral load, were obtained by review of medical records. If complete data were not available, testing was performed at the time of the study visit. Attendance, including number and type of visit, at drug and alcohol rehabilitation programs and for routine medical care, HIV care, and psychiatric care was recorded.

Definitions of Contraindications to Interferon Therapy

Barriers to interferon therapy were defined based upon current clinical practice guidelines and the recent recommendations of the International Panel on the Treatment of HCV/HIV coinfecting Persons (Carlos Martin et al., 2004). Absolute contraindications to interferon therapy were defined as current (past 30 days) heavy alcohol use (>14 drinks per week on average or >4 drinks in 1 day for men, >7 drinks per week, or >3 drinks in a day for women), recent (past 6 months) injection drug use with needle sharing, CD4 cell count of less than 100 cells/ μ L, decompensated liver disease defined as a Child-Pugh score of ≥ 7 , and suicidal ideation or attempt in the past 6 months. Relative contraindications were defined as current moderate alcohol use (less than heavy use but not abstinent), current injection drug use without needle sharing, CD4 cell count from 100 to 199 cells/ μ L, and significant depressive symptoms (CES-D ≥ 16 ; Burack et al., 1993).

Analyses

For analytic purposes, all HCV RNA-positive subjects were considered potentially eligible for interferon therapy. Only subjects with complete data for all of the contraindications to therapy were included in the analyses describing the proportion of the study group with contraindications to treatment. Descriptive statistics were used to characterize the sample. Chi-square tests were used to assess bivariate associations between subject characteristics and the presence of at least 1 absolute contraindication.

RESULTS

Demographic Data

Of 401 HIV-infected subjects with current or past alcohol problems, 236 were HCV antibody-positive, of whom 232 had HCV RNA test results; 86% (200/236) of these had detectable HCV

RNA and were therefore candidates for interferon therapy. This sample ($n = 200$, Table 1) was predominantly male (73%) and of diverse racial/ethnic background: blacks 38%, whites 34%, Hispanics 22%, and others 6%. The mean age was 44 years (range 20–69). The vast majority reported having injected drugs in the past. About one-quarter were homeless and a similar proportion had been incarcerated. Almost all had been seen recently for medical care; 20% had had a liver biopsy, and 8% had received interferon therapy.

Prevalence of Contraindications to Interferon Therapy

The number of subjects with each contraindication to interferon is shown in Table 2. Depressive symptoms, a relative contraindication to therapy, had a prevalence of 70%, while any current alcohol use (37%) and any recent injection drug use (23%) were the other major barriers to interferon. HIV-related immune suppression ($CD4 < 200$) and advanced liver disease were barriers in 21 and 7%, respectively. Thirty-five percent of the study population reported a prior suicide attempt and 9% recent suicidal ideation (Table 1). Rates of treatment for mental health and substance abuse in the previous 6 months were substantial; over 50% had received mental health treatment and/or a prescription for a psychiatric medicine. Fifty percent had received substance abuse treatment and two-thirds had attended AA meetings.

Of the 200 coinfecting study participants, complete data were obtained in 168 (84%). Fifty-three percent of subjects had at least 1 absolute contraindication to interferon therapy, 35% had at least 1 relative but no absolute contraindication, and only 12% identified no contraindication (Fig. 1). Heavy drinking (61%), recent injection drug use with needle sharing (19%), advanced immunosuppression (19%), suicidal ideation (17%), and advanced liver disease (16%) were all important absolute contraindications (Fig. 1). Of note, only 19% of subjects with 1 absolute contraindication had no other contraindication to interferon therapy, 30% had at least 2 absolute contraindications, and 51% had 1 absolute contraindication with 1 or more relative contraindications.

Bivariate Associations with the Presence of an Absolute Contraindication

In bivariate analyses, race, particularly white race, not using antiretroviral therapy, failure to seek routine medical care, and less than weekly attendance at AA meetings were all associated with the presence of an absolute contraindication to interferon (Table 3). The association between homelessness and absolute contraindication was of borderline statistical significance. Age, gender, employment, incarceration, and receipt of substance abuse and mental health treatment were not associated with an absolute contraindication to HCV therapy.

DISCUSSION

Using current published guidelines for treatment eligibility, over half of HCV/HIV-coinfecting subjects with current or past alcohol problems had absolute contraindications to interferon therapy. Over one-third had relative contraindications, and only 12% had no contraindication. Heavy alcohol use was the single most important contraindication to interferon therapy. However, it was frequently associated with multiple other barriers to treatment, including depressive symptoms, and recent drug injection use as well as poorly controlled HIV infection and decompensated liver disease. The observation that a high proportion of those with an absolute contraindication to therapy also had multiple other barriers to treatment has important implications for the management of these individuals and limits opportunities to increase treatment eligibility.

A second important observation of the current study was the finding that many of the substance abuse and mental health barriers to treatment were present despite a high proportion of subjects having received substance abuse and mental health treatment. Furthermore, when we assessed

for factors that were predictive of treatment ineligibility, we found that white race, homelessness, nonreceipt of HAART, noncompliance with routine medical care, and attendance at few AA meetings were all associated with treatment ineligibility. These data suggest that attempts to improve interferon treatment rates in a population with alcohol problems will likely require a multidisciplinary approach that includes substance abuse, mental health, and medical care including receipt of effective HIV pharmacotherapy. Furthermore, increasing interferon treatment eligibility will require more intensive and more efficacious management of alcohol and mental health care than was available to this study population.

The findings of this study reveal an even more disappointing state of the provision of effective HCV treatment for patients with HIV coinfection and alcohol problems than were previously reported, where it was estimated that 25% to 30% of HCV-positive individuals are eligible for interferon treatment (Adeyemi et al., 2004; Falck-Ytter et al., 2002; Fleming et al., 2003; Restrepo et al., 2005). To add to this challenge, the impact of HCV treatment is further limited by poor patient acceptance due to concerns about limited treatment efficacy and adverse medication effects, particularly in coinfecting patients (Blackard et al., 2004; Carrat et al., 2004; Fried et al., 2002; Hadziyannis et al., 2004; Manns et al., 2001; Rockstroh et al., 2005; Torriani et al., 2004).

There have been no prior studies evaluating HCV treatment eligibility in patients with alcohol problems despite the fact that more than 50% of people coinfecting with HCV and HIV have alcohol problems (Samet et al., 2004). The importance of continued alcohol use is not only related to its adverse effect on the progression of liver disease but also to the observation that alcohol use is associated with reduced response rates to interferon, an effect that can persist even after abstinence (Edlin, 2002; Harris et al., 2001; Hezode et al., 2003; Mochida et al., 1996; Ohnishi et al., 1996; Okazaki et al., 1994; Poynard et al., 1997; Safdar and Schiff, 2004; Tabone et al., 2002). For these reasons, current guidelines recommend that abstinence be achieved before beginning interferon therapy, especially with HIV/HCV-coinfecting patients who also have diminished interferon response rates and more rapidly progressive liver disease (Peters and Terrault, 2002).

Recent guidelines have included current substance abuse and psychiatric disease as relative contraindications to interferon therapy or have recommended that treatment be administered on a case-by-case basis. Early studies in the management of this population had shown that the incidence of psychiatric problems, drug relapse, and early discontinuation of therapy was higher in those with addiction (Edlin, 2002; Fleming et al., 2003; Kraus et al., 2001; Schaefer et al., 2004). It is clear, however, that individuals stable on opioid replacement therapy can receive therapy safely and effectively (Sylvestre, 2005b). For instance, Sylvestre (2005b) reported that 78% of patients in methadone maintenance treatment that included counseling completed their planned 6 to 12 months course of interferon with an end-of-treatment response rate of 54%. However, responses are lower in those with recent substance abuse and psychiatric disorders (Sylvestre, 2005a). Backmund et al. (2001) have also reported successful treatment in injection drug users using a multidisciplinary approach including specialists in HCV therapy, medical, mental health, and addiction care (Taylor, 2005). Successful treatments in highly coordinated programs like these are a model for larger centers with the necessary resources. Comparable studies evaluating the effectiveness of alcohol treatment programs on interferon treatment eligibility and outcomes are not available. The observation in this study that high attendance rates in AA meetings were associated with treatment eligibility suggests that adherence to alcohol treatment programs may be associated with improved interferon treatment eligibility.

As in previous studies of substance abusing populations, we found a very high prevalence of substantial depressive and other psychiatric symptoms (Johnson et al., 1998; Loftis and Hauser,

2004). Psychiatric disease is associated with a high incidence of interferon-related depression and drug relapse (Edlin, 2002; Fleming et al., 2003; Kraus et al., 2001). In this study, depressive symptoms were present despite high rates of psychiatric care, suggesting that the availability of these services was not sufficient to mitigate HCV therapy ineligibility related to depressive symptoms.

White race and nonreceipt of HAART were associated with treatment ineligibility, and homelessness was of borderline significance. While the impact of HAART and homelessness might be expected, it is unclear why those of white race may be less eligible for interferon therapy. However, at least 2 recent studies have assessed treatment eligibility according to race or ethnicity and both, as in this study, have suggested that minorities had higher treatment eligibility rates (Bini et al., 2005; Cheung et al., 2005).

This study has several limitations. The proportion of subjects eligible for interferon therapy may have been overestimated as a number of factors that might affect treatment eligibility were not assessed. These include patient acceptance of interferon, as well as a variety of medical issues including diabetes mellitus, other autoimmune diseases, and significant cardiac, pulmonary, and renal disease (Fleming et al., 2003; Restrepo et al., 2005). Nonetheless, even if these contraindications led to reduction of our total number of eligible patients for interferon therapy, the potential impact of substance use and mental health would remain large. As this study is largely derived from a single urban center, it may be less generalizable to other populations. Both a limitation and a strength of this study is that we used strict eligibility criteria in the assessment of contraindications for HCV therapy. This assessment was based upon recent guidelines, rather than physician opinion, about individual patients. Thus, we produced 3 categories of treatment eligibility, recognizing that many persons deemed to have a relative contraindication to therapy could receive it in the appropriate clinical context. It is also true that treatment eligibility is likely to vary over time such that treatment-ineligible persons may become eligible as their clinical and social circumstances change.

In summary, almost half of all HCV/HIV-infected individuals with a history of alcohol problems have absolute contraindications that make them ineligible for interferon-based therapies; a substantial proportion have relative contraindications based on other social and psychological barriers. The single largest barrier to interferon therapy was alcohol use, while illicit drug use and mental health problems were also substantial issues. Furthermore, these barriers were present despite the high proportion of patients utilizing psychiatric and substance abuse treatment. Improvements in interferon treatment eligibility will likely require increased coordination of substance abuse and psychiatric treatment with those providing HCV and HIV clinical care, a general recommendation endorsed by a recent IOM report (committee on Crossing the Quality Chasm, 2006). In those patients who remain ineligible for interferon therapy, continued education and support to avoid alcohol use, maintain immune function, and select appropriate antiretroviral agents with reduced hepatotoxicity should be emphasized to limit liver injury. Interferon treatment eligibility should be reviewed regularly as treatment eligibility is likely to change over time. Addressing the important comorbidities, in particular alcohol, drug, and mental health problems of patients coinfecting with HIV and HCV, presents an opportunity to improve the delivery of effective HCV pharmacotherapy to this particular at-risk population.

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Fig. 1.
Sample assessed for treatment eligibility and the reasons for treatment ineligibility.

Table 1
 Characteristics of HIV/HCV-Infected Persons with Current or Past Alcohol Problems (*N* = 200)

Characteristic	<i>N</i> (%)
Male	146 (73)
Race	
Black	76 (38)
White	68 (34)
Hispanic	43 (22)
Other	13 (6)
Employed	36 (18)
Homeless, past 6 mo ^a	57 (28)
Incarcerated, past 6 mo ^b	46 (23)
Injection drug use, ever	178 (89)
Injection drug use, current	47 (23)
CD4 cell count—median (IQR)(<i>n</i> = 187)	357 (106–546)
HIV RNA median (IQR)	804 (0–12914)
Undetectable	53 (29)
Antiretroviral therapy	118 (59)
HCV RNA (copies/mL)<1,000,000	83 (41)
HCV Genotype (<i>n</i> = 94)	
Genotype 1	79 (84)
Genotypes 2 or 3	13 (14)
Genotype 4	2 (2)
Child–Pugh score—median (IQR) (<i>n</i> = 175)	5 (5–6)
Suicide attempt, ever	71 (35)
Suicide attempt, past 6 mo	4 (2)
Suicidal ideation, past 6 mo (<i>n</i> = 199)	19 (9)
Mental health treatment, past 6 mo ^c	110 (55)
Prescription for psychiatric medication, past 6 mo	104 (52)
AA attendance, past 6 mo ^d	132 (66)
Substance abuse treatment, past 6 mo ^e	101 (50)
Methadone treatment, past 6 mo	41 (20)

^a ≥ 1 night on the street or in a shelter.

^b 1 night or more in jail.

^c Seen by a mental health professional.

^d Attended Alcoholic Anonymous meeting at least once in the past 6 months.

^e At least 6 weeks in a residential facility or half-way house, and/or at least 12 visits to a substance abuse or mental health professional and/or 30 days of day treatment or participation in a methadone program.

IQR, interquartile range.

Table 2

Prevalence of Contraindications to Hepatitis C Pharmacotherapy Among HIV-Coinfected Persons With Current or Past Alcohol Problems ($N = 200$)

Characteristic	Number (%; 95% CI)
Absolute contraindication	
Current heavy alcohol use ^a	59 (29, 23–36%)
Injection drug use* (past 6 mo) with needle sharing	21 (10, 6–15%)
Suicidal ideation	19 (9, 5–13%)
CD4<100*	18 (9, 5–13%)
Child–Pugh >7*	14 (7, 3–11%)
Relative contraindication	
Moderate alcohol use ^b	16 (8, 4–12%)
Injection drug use (past 6 mo) with no needle sharing	26 (13, 8–18%)
Depressive symptoms (CES-D score > 16)	140 (70, 64–76%)
CD4 cell count 100–199*	24 (12, 7–16%)

^a >14 standard drinks per week on average or >4 drinks in 1 day for men; >7 drinks per week or >3 drinks in a day for women.

^b Any alcohol use not meeting the criteria for heavy use.

* 32 subjects with missing data: 25 missing Child–Pugh score, 13 missing CD4 cell count, and 1 missing suicidal ideation.

Table 3
Characteristics of Subjects With HIV/HCV Coinfection and Current or Past Alcohol Problems Based on Eligibility for Interferon Therapy (N = 168^a)

Characteristic	Absolute contraindication to interferon (n = 89) No. (%)	Relative or no contraindication to interferon (n = 79) No. (%)	p Value
Male	70 (79%)	57 (72%)	0.37
Age (mean years)	42.9	45.0	0.63
Race			
Black	29 (33%)	36 (46%)	0.021
White	37 (41%)	19 (24%)	
Hispanic	20 (22%)	15 (19%)	
Other	3 (3%)	9 (11%)	
Employed	14 (16%)	12 (15%)	1.00
Homeless, past 6 mo	33 (37%)	18 (23%)	0.06
Incarcerated, past 6 mo	23 (26%)	19 (24%)	0.86
On HAART ^b	48 (54%)	57 (72%)	0.02
Routine Medical Visit, past 6 mo	81 (91%)	78 (99%)	0.04
AA, past 6 mo (> weekly attendance)	38 (43%)	46 (58%)	0.04
Received SAT, past 6 mo ^c	44 (49%)	38 (48%)	0.43
Received MHT, past 6 mo ^d	48 (54%)	41 (52%)	0.76

^a 168 of the 200 HIV/HCV-infected subjects had complete data on the above characteristics.
^b HAART = On at least 3 potent anti-retroviral medications at the time of subject interview.
^c Substance abuse treatment (SAT): At least 6 weeks in a residential facility or halfway house, and/or at least 12 visits to a substance abuse or mental health professional and/or 30 days of day treatment or participation in a methadone program.
^d Mental health treatment (MHT): Seen by a mental health professional.