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Substance abuse treatment and receipt of liver specialty care among persons coinfected with HIV/HCV who have alcohol problems

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Abstract

We examined the association of substance abuse treatment with access to liver specialty care among 231 persons coinfected with HIV and hepatitis C virus (HCV) with a history of alcohol problems who were recruited and followed up in the HIV-Longitudinal Interrelationships of Viruses and Ethanol cohort study from 2001 to 2004. Variables regarding demographics, substance use, health service use, clinical variables, and substance abuse treatment were from a standardized research questionnaire administered biannually. We defined substance abuse treatment services as any of the following in the previous 6 months: 12 weeks in a halfway house or residential facility, 12 visits to a substance abuse counselor or mental health professional, day treatment for at least 30 days, or any participation in a methadone maintenance program. Liver specialty care was defined as a visit to a liver doctor, a hepatologist, or a specialist in treating hepatitis C in the past 6 months. At study entry, most of the 231 subjects (89%, $n = 205$) had seen a primary care physician, 50% had been exposed to substance abuse treatment, and 50 subjects (22%) had received liver specialty care. An additional 33 subjects (14%) reported receiving liver specialty care during the follow-up period. In the multivariable model, we observed a clinically important although not statistically significant association between having been in substance abuse treatment and receiving liver specialty care (adjusted odds ratio = 1.38; 95% confidence interval = 0.9–2.11). Substance abuse treatment systems should give attention to the need of patients to receive care for prevalent treatable diseases such as HIV/HCV coinfection and facilitate its medical care to improve the quality of care for individuals with substance use disorders. The data illustrate the need for clinical care models that give explicit

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attention to the coordination of primary health care with addiction and hepatitis C specialty care while providing ongoing support to engage and retain these patients with complex health needs.

Keywords

Substance abuse; Hepatitis C virus; Liver specialty care; Substance abuse treatment

1. Introduction

The prevalence of hepatitis C virus (HCV) among injection drug users with HIV infection is close to 90% (Sulkowski & Thomas, 2003). It is well known that HIV coinfection accelerates the progression of HCV liver disease (Sulkowski, Mast, Seeff, & Thomas, 2000), and a meta-analysis estimated that the risk of cirrhosis due to HIV coinfection is twofold (Graham et al., 2001). As HIV becomes a chronic disease due to the success of highly active antiretroviral therapy (Hogg et al., 1999;Palella et al., 1998), HCV liver disease is increasingly becoming a significant cause of morbidity and death among these individuals (Bica et al., 2001;Clanon, Mueller, & Harank, 2005;Monga et al., 2001). The current standard of care for chronic HCV infection is pegylated interferon and ribavirin, which can achieve sustained viral response of approximately 42–82%, depending on genotype. This is a substantial improvement over previous interferon monotherapy response rates of 6–20% (Desmond et al., 2006;National Institutes of Health [NIH], 2002). Unfortunately, the treatment given to persons coinfected with HIV/HCV is less effective (17–83%) at this time, but optimism about therapeutic options is warranted (Chung et al., 2004;Perez-Olmeda et al., 2003;Sulkowski, 2006). Because HCV treatment requires extensive evaluation and monitoring (Sulkowski, 2006), it is typically provided by specialists after primary care physician referral.

Active drug and alcohol use may pose challenges regarding the access to and the provision of HCV specialty care for individuals coinfected with HIV/HCV (Edlin et al., 2001). Heavy alcohol use is particularly harmful in the setting of chronic HCV infection, and it has been shown to reduce the success of HCV treatment (Corrao & Arico, 1998;Pessione et al., 1998;Thomas et al., 2000). In one study of patients infected with HCV in an opiate dependence treatment program, only 30% had been evaluated for HCV treatment and 34% were aware of HCV treatment underscoring the limited understanding of their disease and HCV treatment options (Walley, White, Kushel, Song, & Tulsky, 2005).

The 2002 NIH Consensus Statement on HCV infection recommended increased availability of HCV treatment to patients with high likelihood of acquiring or spreading this disease, such as injection drug users (NIH, 2002), but translating this to improved delivery of treatment is challenging. There has been increasing attention to HCV prevention and treatment among drug treatment programs, given the high prevalence among their clientele (Astone, Strauss, Hagan, & Jarlais, 2004;Munoz-Plaza, Strauss, Astone, Jarlais, & Hagan, 2004;Vassilev, Strauss, Astone, Friedmann, & Jarlais, 2004). From an overall health care management perspective, primary care providers may view patients coinfected with HIV/HCV with alcohol problems who are actively participating in substance abuse treatment as having their addiction issues addressed and, thus, more likely to be able to tolerate the HCV therapy and adhere to the close monitoring. This, in turn, may result in primary care physicians being more likely to refer such individuals to liver specialty care.

However, it is not clear whether HCV infection, a consequence of injection drug use, is effectively integrated into substance abuse treatment programs. To explore this issue, we tested the following hypothesis in an observational cohort of persons coinfected with HIV/HCV who have alcohol problems, most of whom with existing primary care: Participation in substance

abuse treatment improves the likelihood of being evaluated by liver specialty care providers. In assessing this association of substance abuse treatment with one measure of desired quality health care (i.e., attention to HCV infection), we sought evidence of effective current collaboration of addiction treatment and general medical care.

2. Materials and methods

2.1. Study design and population

We analyzed data from participants of the HIV-Longitudinal Interrelationships of Viruses and Ethanol (LIVE) prospective cohort, which is an observational study of persons with HIV infection who have alcohol problems. Patients who were infected with HIV and had a history of alcohol problems were identified by explicit eligibility criteria: a documented HIV antibody by ELISA confirmed by Western blot; two or more affirmative responses to the Cut Down, Annoyed, Guilty, and Eye Opener (CAGE) alcohol screening questionnaire for lifetime alcohol abuse or dependence (Buchsbaum, Buchanan, Centor, Schnoll, & Lawton, 1991) or coinvestigator physician diagnosis of an alcohol disorder; ability to speak English or Spanish; and at least one contact person who was likely to know their whereabouts. The only exclusion criterion was a score of <21 on the 30-item Folstein Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) or trained interviewer assessment that the patient was incapable of comprehending informed consent or answering the interview questions.

From August 2001 to July 2003, subjects were recruited using multiple methods and from several sources. These included medical clinics responsible for the evaluation of patients with HIV infection presenting for medical care: the HIV Diagnostic Evaluation Unit at Boston Medical Center (BMC; Samet et al., 1995) and the HIV Consult Clinic and the Primary Care Clinic at Beth Israel Deaconess Medical Center (BIDMC). Other subjects were recruited from the following locations: BMC primary care practices, referrals by friends, and posted flyers at homeless shelters and HIV/AIDS social service agencies in the Boston area. Persons responding to the flyers were administered a preliminary screening over the telephone (CAGE questionnaire) and, if eligible, were invited for an interview to complete the screening process.

If a patient at these clinical sites or from other referral sources agreed to participate, a study research associate scheduled an appointment for the first interview at BMC's General Clinical Research Center or BIDMC's Clinical Research Center. All subjects provided written informed consent in the Clinical Research Centers prior to enrollment. The Institutional Review Boards of BMC and BIDMC approved this study. A subject's privacy was made more secure through the issuance of a Certificate of Confidentiality by the Department of Health and Human Services; that is, it protects the release of a subject's research data even if a court order or subpoena is issued.

The HIV-LIVE study recruited 401 subjects. However, the current analyses focus on receipt of liver specialty care in just 231 (58%) subjects coinfected with HIV and HCV.

2.2. Data collection

After enrollment, all subjects received an interviewer-administered baseline assessment. The baseline instrument included questions on the following: demographics, Short Form Health Survey (Ware, Kosinski, & Keller, 1996), depressive symptoms (Center for Epidemiologic Studies Depression Scale [CES-D]; Andresen, Malmgren, Carter, & Patrick, 1994), psychological status (questions from the Addiction Severity Index; McLellan et al., 1985), health status, medication use, health care and addiction services use, alcohol and drug use quantity, current and lifetime alcohol abuse and dependence (Composite International Diagnostic Interview [CIDI]; Robins et al., 1988), HIV risk behaviors (modified version of the

Risk Assessment Battery; Navaline et al., 1994), trauma history, social support, and social networks. All subjects in this cohort were tested for HCV infection through measurement of HCV antibody; HCV RNA testing was sought for all HCV-antibody-positive persons. Follow-up was conducted over 3 years at 6-month intervals and included a reassessment of the domains covered at baseline. Subjects received a cash compensation of US$20 at baseline and US$25–30 at the follow-up time points. Results from follow-up assessments as of February 25, 2004, were utilized in these analyses.

2.3. Outcome variable

Receipt of liver specialty care in the previous 6 months was modeled as a dichotomous response. Typically, primary care physicians provide referrals for liver specialty care. Subjects were asked "How many times did you see each of the following health care professionals during the past six months?" Receipt of liver specialty care was defined as having an affirmative response to being seen by a "liver doctor, hepatologist, or specialist in treating Hepatitis C."

2.4. Primary independent variable

Substance abuse treatment services was a dichotomous variable indicating whether the subject received any of the following services in the past 6 months: at least 12 weeks in a halfway house or residential facility, at least 12 visits to a substance abuse counselor or mental health professional, day treatment for at least 30 days, or any participation in a methadone maintenance program (Palepu, Horton, Tibbetts, Meli, & Samet, 2005;Palepu, Raj, et al., 2005;Palepu et al., 2004). Information on substance abuse treatment services was obtained from patient self-report at each study interview.

2.5. Other independent variables

Other specific variables assessed included age; gender; race (Black, White, or other—the latter subjects were mostly Hispanic); an indicator of whether the subject had participated in a previous cohort study of subjects with HIV infection who have alcohol problems; depressive symptoms (yes vs. no) as measured by the 20-item CES-D (Andresen et al., 1994), where a higher cutoff score of $\geq$21 was used to denote depressive symptoms in persons with chronic diseases rather than the standard score of 16 that has been used for the general population; any liver complications (i.e., jaundice, ascites, esophageal varices, hepatic encephalopathy, or gastrointestinal bleeding) in the previous 6 months; current receipt of highly active antiretroviral therapy; ever been treated for psychiatric disorders; drug injection in the past 6 months; abstinent from alcohol in the past 30 days; alcohol dependence in the past 6 months as defined by the CIDI short form (Robbins et al., 2003); average alanine aminotransferase (ALT); the number of months since baseline time point; and CD4 cell count.

2.6. Analysis

Two-sample *t* tests and chi-square tests were used to assess bivariable relationships between demographics, behavioral and clinical data, and the outcome accessing liver specialty care at baseline. We used generalized estimating equations (GEE) logistic regression models to examine the association between substance abuse treatment and accessing liver specialty care, adjusting for potential confounding factors: gender, age, race, liver complications, current receipt of antiretroviral therapy, depressive symptoms, ever been treated for psychiatric disorders, drug injection in the past 6 months, 30-day alcohol abstinence, recent alcohol dependence and ALT level, CD4 cell count, rollover, and the number of months since baseline time point. The GEE approach was used to adjust for the correlation due to analyzing repeated measures from the same subject over time (Liang & Zeger, 1986;Zeger & Liang, 1986). The empirical standard errors from the GEE approach were used for all analyses. All of the predictor variables except for gender, age, race, rollover, and treatment for psychiatric disorders were

allowed to vary with time. We examined the potential for collinearity in multivariate models by assessing the correlation between pairs of independent variables and verified that no pair of variables included in the same regression model was highly correlated (i.e., no correlation was greater than .40). Although the outcome and most covariates were assessed semiannually, ALT was collected once yearly. Thus, we used the average ALT value of the most recent and subsequent measures to impute values for missing time points. All analyses were carried out using SAS version 8.2 (SAS Institute, Cary, NC).

3. Results

Of the 231 subjects coinfected with HIV/HCV in the study sample, half (116/231) were engaged in substance abuse treatment at the initial observation, of whom 47 (20%) were in a methadone treatment program. Among the 115 subjects who were not engaged in substance abuse treatment at the initial observation, 39 (34%) subjects entered substance abuse treatment during the study period.

There were 50 (22%) subjects who received liver specialty care and 205 (89%) subjects who reported having seen a primary care physician at the baseline interview. An additional 33 (14%) subjects reported receiving liver specialty care during the 3-year follow-up period. In this research study, the subjects were followed up every 6 months for up to six visits, and the median number of observations per subject was 3. For the current analysis, the proportion of subjects who completed one, two, three, four, five, and six observations during the 3-year follow-up period was 5%, 17.2%, 21.1%, 24.7%, 30.2%, and 1.7%, respectively. Overall, the 231 subjects contributed 696 observations to the longitudinal analysis; however, due to incomplete data, 76 subjects were dropped.

The baseline characteristics of the 231 subjects coinfected with HIV/HCV are presented in Table 1. In the bivariable analyses based on the baseline assessments only, subjects who were currently receiving highly active antiretroviral therapy, who had liver complications in the previous 6 months, and who were abstinent from alcohol in the past 30 days were more likely to have accessed liver specialty care.

In the longitudinal multivariable model (Table 2), we observed a clinically important although not statistically significant association between substance abuse treatment and accessing liver specialty care (adjusted odds ratio [OR] = 1.38; 95% confidence interval [CI] = 0.9–2.11). Liver complications (adjusted OR = 2.15; 95% CI = 1.02–4.54), current receipt of highly active antiretroviral therapy (adjusted OR = 2.18; 95% CI = 1.33–3.59), CD4 cell count per 100 cells/mm^3 increase (adjusted OR = 1.11; 95% CI = 1.02–1.20), and 30-day alcohol abstinence (adjusted OR = 1.55; 95% CI = 1.04–2.32) were positively associated with accessing liver specialty care.

4. Discussion

Substance abuse treatment can be an effective means of HCV education, facilitated access, or linkage and may be a motivating factor for seeking out HCV care for some patients (Strauss, Astone, Des Jarlais, & Hagan, 2005;Strauss, Astone, Hagan, & De Jarlais, 2004;Strauss, Astone, Jarlais, & Hagan, 2004). However, in our longitudinal study of persons coinfected with HIV/HCV who have alcohol problems, of whom some were receiving community-based substance abuse treatment, we were not able to detect a significant association between substance abuse treatment and receipt of specialty care for hepatitis C. We found that the presence of significant liver disease or factors associated with HCV treatment eligibility, such as tolerating antiretroviral therapy, having a higher CD4 cell count, and being recently abstinent from alcohol, were the factors associated with receipt of liver specialty care. In our system,

referrals were likely through the primary care physician where initiation and maintenance of ART for HIV infection may have been the first step in addressing the complex health needs of these patients. Among HCV monoinfected injection drug users, Strathdee et al. (2005) found that having a usual source of primary care, a high perceived threat of progressive liver disease, no evidence of alcohol dependence, and higher readiness scores for quitting drug use were all factors associated with being interested in HCV treatment. Assessing the specific impact of substance abuse treatment on receipt of liver specialty care may be difficult, given that the receipt of addiction treatment could be interpreted as a barrier to HCV therapy. Substance abuse treatment may be indicative of recent drug and alcohol use, and yet, it may also be a motivator or facilitator for patients and their primary care provider to seek further care for the patients' comorbid medical conditions. Substance abuse treatment, as a pathway to remission of substance abuse, could set the stage for addressing previously unattended chronic medical conditions. Our findings that receipt of ART and 30-day alcohol abstinence are associated with accessing liver specialty care likely reflect the hierarchy of priorities primary care providers face in managing these patients with complicated health needs. Such priorities are supported by current NIH and international guidelines (Soriano et al., 2002), where it is recommended that HIV and substance abuse are addressed prior to initiating HCV therapy.

The lack of coordination of medical care and substance abuse treatment has been cited as the most significant barrier to HCV treatment for persons with substance use disorders, rather than the more typical barriers to medical care such as health insurance or transportation (Litwin, Soloway, & Gourevitch, 2005). Litwin et al. recently described a multidisciplinary model of care that addressed substance abuse and psychiatric conditions, as well as HCV screening and treatment. This approach resulted in substantial rates of initiation of antiviral therapy, and the colocation of these services significantly improved HCV treatment access (Litwin et al., 2005). Clearly, methadone maintenance and other substance abuse treatment programs can be gateways to enhancing access to HCV treatment through screening and education (Walley et al., 2005). A few integrated models of care that address HIV, HCV, and substance abuse have been recently reported (Clanon et al., 2005;Flanigan, Taylor, & Mitty, 2005; Fleming, Tumility, Murray, & Nues, 2005; Sylvestre, 2005;Taylor, 2005). These studies highlight the importance of a multidisciplinary team approach to such patients with complex health needs. In one clinic setting, one third of the patients coinfected with HIV/HCV were eligible for treatment (Fleming et al., 2005). Reasons for ineligibility include nonadherence with clinic visits, active psychiatric disease and ongoing drug and alcohol use, advanced HIV disease, decompensated liver disease, and significant comorbid illness. Furthermore, two thirds of those who were eligible declined HCV treatment with interferon and ribivirin. In sum, only 8% (21/260) were treated for their HCV and two patients achieved sustained virological response. These studies highlight the importance of addressing the modifiable barriers to HCV treatment eligibility and adherence. Given the significant overlap of HCV and addictions, more coordination and integration of these treatment services would be desirable to address the burden of HCV–liver disease in this vulnerable population.

Our study has several limitations. We assessed HCV infection solely based on HCV antibody test and not HCV RNA (viral load). There were 10% to 15% of the HCV-antibody-positive patients who did not have detectable HCV RNA, and when we fitted the models with those who were positive for HCV RNA, the findings were unchanged. However, our study sample included all HCV-antibody-positive patients, as substance abuse treatment providers would not be expected to ask such a medical question and, in fact, some patients might not be aware of the HCV antigen status. Although our measure of substance abuse treatment may not be as stringent as that used by Laine et al. (2001), we think that it has face validity. Approximately half of our cohort was receiving substance abuse treatment services at a reasonable level of exposure. Our main explanatory and outcome measures were obtained through self-report, although validated instruments were used where possible. We were unable to explore the

precise reasons for why subjects with HIV/HCV coinfection did or did not receive liver specialty care in terms of source of referral, patient refusal, or specialist refusal. The study was observational and we cannot infer causation. This analysis was also potentially underpowered to detect a statistically significant effect of substance abuse treatment. For post hoc power calculations, assuming 18% of the subjects not receiving substance abuse treatment accessed liver specialty care (based on data from study entry), our study would have approximately 80% power to detect an OR as small as 2.0. Thus, it is likely that the study was not adequately powered to detect a small association of the observed magnitude. Finally, these findings may not be generalizable to health care systems that have differing availability of liver specialty care.

In summary, we did not observe a clear association between substance abuse treatment and receipt of liver specialty care among persons coinfected with HIV/HCV who have a history of alcohol problems. The current system of addiction treatment in our study appears to be isolated from primary care as well as liver specialty care and does not utilize the substance abuse treatment opportunity to motivate the patient to address other chronic medical problems. The patients who reported receiving liver specialty care were persons who were having their HIV disease managed, had liver disease complications, and were not actively using alcohol. These are the types of patients primary care providers would likely deem as having a higher likelihood of HCV treatment eligibility, need, or success. Substance abuse treatment systems should prioritize prevalent treatable diseases such as HIV/HCV coinfection and facilitate medical care to improve the quality of care for individuals with substance use disorders. Shared care models that give explicit attention to the coordination of addictions, primary care, and specialty care, while providing ongoing support to effectively engage these patients with complex health needs in appropriate care, need to be implemented and evaluated.

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Table 1

Characteristics and access to liver specialty care at baseline of participants with HIV and HCV coinfection

Baseline characteristics	Access to liver specialty care		*P*
	With access, *n* = 50	Without access, *n* = 181	
Age, *M* (*SD*)	45.0 (6.3)	43.5 (7.0)	.14
Female gender, *n* (%)	14 (28)	52 (29)	.92
Race or ethnicity, *n* (%)			.33
Black	17 (34)	70 (39)	
White	21 (42)	56 (31)	
Other	12 (24)	55 (30)	
Substance abuse treatment, *n* (%)	29 (58)	87 (48)	.21
Current ART receipt[a], *n* (%)	40 (80)	102 (56)	.002
Baseline CD4 cell count (cells/mm^3), *M* (*SD*)	423 (253)	408 (260)	.86
Liver disease complications[b,c], *n* (%)	9 (18)	6 (3)	.0002
Elevated ALT (>40 IU/L), *n* (%)	36 (75)	120 (68)	.39
Depressive symptoms[d], *n* (%)	29 (58)	110 (61)	.72
Ever had psychiatric treatment, *n* (%)	35 (70)	119 (66)	.57
Injection drug use[b], *n* (%)	7 (14)	45 (25)	.10
30-day alcohol abstinence, *n* (%)	38 (76)	107 (59)	.03
Alcohol dependence[b,e], *n* (%)	2 (4)	21 (12)	.11

[a] Highly active antiretroviral therapy.

[b] In the past 6 months.

[c] Any liver complications refer to jaundice, ascites, hepatic encephalopathy, esophageal varices, or gastrointestinal bleeding.

[d] Using the CES-D, where ≥21 denotes depressive symptoms in chronic diseases.

[e] Alcohol dependence as defined by the CIDI short form.

Table 2

Multivariable logistic regression model for factors associated with accessing liver specialty care (using generalized estimating equations)

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Substance abuse treatment	1.42 (0.99–2.03)	1.38 (0.90–2.11)
Female gender	0.95 (0.53–1.7)	0.87 (0.44–1.70)
Age (per 10-year increase)	1.37 (0.95–1.97)	1.22 (0.80–1.86)
Race or ethnicity[a]		
Black vs. White	0.77 (0.43–1.39)	0.70 (0.36–1.36)
Other vs. White	0.82 (0.44–1.52)	0.73 (0.38–1.41)
Current ART receipt[b]	2.50 (1.58–3.93)	2.18 (1.33–3.59)
CD4 (per 100 cells/mm^3 increase)	1.12 (1.03–1.21)	1.11 (1.02–1.20)
Liver disease complications[c,d]	2.09 (1.18–3.72)	2.15 (1.02–4.54)
ALT (per 40 IU/L)	1.15 (0.98–1.35)	1.10 (0.90–1.33)
Depressive symptoms[e]	0.87 (0.59–1.28)	0.81 (0.51–1.27)
Ever had psychiatric treatment	1.42 (0.82–2.45)	1.21 (0.65–2.25)
Injection drug use[c]	0.78 (0.49–1.24)	0.84 (0.48–1.45)
30-day alcohol abstinence	1.67 (1.17–2.38)	1.55 (1.04–2.32)
Alcohol dependence[c,f]	0.62 (0.35–1.08)	0.72 (0.35–1.49)

Note. The number of observations is 620.

[a] The reference group is White.

[b] Highly active antiretroviral therapy.

[c] In the past 6 months.

[d] Any liver complications refer to jaundice, ascites, hepatic encephalopathy, esophageal varices, or gastrointestinal bleeding.

[e] Using the CES-D, where ≥21 denotes depressive symptoms in chronic diseases.

[f] Alcohol dependence as defined by the CIDI short form.