Predictors of Alcohol Use Among Rural Drug Users After Disclosure of Hepatitis C Virus Status

DUSTIN B. STEPHENS, B.S.,[a] AND JENNIFER R. HAVENS, PH.D., M.P.H.[a,*]

[a]*Center on Drug and Alcohol Research, Department of Behavioral Science, University of Kentucky College of Medicine, Lexington, Kentucky*

ABSTRACT. Objective: Alcohol consumption dramatically increases the risk of liver damage among those with hepatitis C virus (HCV) infection, yet the impact of HCV status disclosure and standard informational counseling on alcohol use among rural drug users remains poorly understood. **Method:** In this prospective study, 503 rural Appalachian drug users were recruited using respondent-driven sampling. Participants were tested for HCV antibodies, and data on sociodemographic characteristics, lifetime and past-30-day drug and alcohol use, and psychiatric disorders were collected by interviewer-administered questionnaires. A total of 470 participants returned after 6 months for follow-up; however, 4 of those had no history of alcohol use, thus leaving a final sample size of 466. Multivariate negative binomial regression was used to determine the effect of disclosure of HCV status and posttest counseling on alcohol consumption at follow-up. **Results:** Despite an overall decrease in drinking frequency in the cohort, those who were HCV-positive were drinking at a frequency similar to their HCV-negative counterparts at follow-up, despite posttest counseling informing them of the risks of alcohol use with an HCV diagnosis (adjusted incidence rate ratio = 1.07, 95% CI [0.72, 1.61]). Significant predictors of increased days of alcohol use after 6 months included baseline alcohol use, baseline marijuana use, and meeting the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* criteria for antisocial personality disorder. Those using OxyContin at baseline had significantly fewer days of alcohol use at follow-up. **Conclusions:** HCV status disclosure and standard informational counseling alone do not curtail drinking among HCV-positive drug users in the rural setting. Targeted interventions with regard to alcohol use are warranted in order to mitigate the damage of the HCV epidemic. (*J. Stud. Alcohol Drugs, 74,* 386–395, 2013)

THE CONTINUED SPREAD OF HEPATITIS C VIRUS (HCV) poses a major global health problem, with approximately 180 million individuals chronically infected worldwide (Shepard et al., 2005). More than 3 million individuals are infected with HCV in the United States (Armstrong et al., 2006), where the virus is the most common cause of liver transplantations in cases of end-stage cirrhosis and hepatocellular carcinoma (HCC; National Institutes of Health [NIH], 2002). In part because the virus lacks direct cytopathic effects, 60%–85% of acute infections with HCV progress to chronic disease, and of these chronic cases up to 20% will develop cirrhosis over a 20-year period, conferring a greatly increased risk of HCC (NIH, 2002). It has been estimated that 27% of cirrhosis cases and 25% of HCC cases worldwide can be attributed to HCV (Alter, 2007).

HCV infection is especially common among injection drug users (IDUs), with prevalence rates greater than 50% found in 49 countries (Aceijas and Rhodes, 2007). Meta-analysis of 1,125 studies revealed an estimated 10 million (range: 6 million–15.2 million) IDUs infected worldwide, with China, the United States, and Russia hosting the three largest populations of HCV-positive drug injectors (Nelson et al., 2011). Furthermore, injection drug use is not uncommon in certain rural areas, and self-reported HCV prevalence among rural IDUs in eastern Kentucky was found to be elevated relative to non-IDUs, just as it is in urban centers (Havens et al., 2007). In fact, a recent study among rural drug users found the prevalence of HCV antibodies in 392 rural IDUs to be 54.6% (Havens et al., 2013), strikingly higher than the estimated prevalence of 1.6% for the U.S. population as a whole (Armstrong et al., 2006). Among the HCV-seropositive participants, only 31.2% were aware of their status (Havens et al., 2013). Although the presence of antibodies does not always imply ongoing infection, several studies have found the risk of developing chronic disease following exposure to HCV to be substantially elevated in both injecting and noninjecting drug users relative to nonusers (Grebely et al., 2007; Page et al., 2009; Poustchi et al., 2011). Moreover, as a single-stranded RNA virus characterized by error-prone replication, HCV fails to generate an effective memory-cell response (NIH, 2002). Thus, an effective vaccine remains elusive, and re-infection among high-risk groups such as IDUs has been found to be significantly elevated in several studies (Aitken et al., 2008; Micallef et al., 2007; van de Laar et al., 2009).

A broad consensus implicates alcohol consumption as a major contributor to hepatic fibrosis, accelerated cirrhosis, and increased incidence of HCC among HCV-positive individuals. In two independent studies, greater than 37% of

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*Correspondence may be sent to Jennifer R. Havens, Associate Professor, Center on Drug and Alcohol Research, 333 Waller Avenue, Suite 480, Lexington, KY 40504, or via email at: Jennifer.havens@uky.edu.

young IDUs engaged in heavy or problem drinking (Campbell et al., 2006; Hahn et al., 2008), a troubling association given that alcohol increases the risk of initial HCV exposure progressing to chronic disease (Piasecki et al., 2004; Thomas et al., 2000). This is especially pertinent among IDUs, who already face elevated risk of chronic HCV infection. Alcohol exerts synergistic effects on HCV replication (McCartney and Beard, 2010; Seronello et al., 2010), with clear multiplication of liver disease risk at moderate (<80 g of ethanol/day) to heavy (>80 g/day) levels of drinking (Donato et al., 1997; Wiley et al., 1998). This notion was reiterated by Tagger and colleagues (1999) in a case–control study of risk factors for HCC among those infected with hepatitis B virus and HCV, with a dose-dependent increase in risk of HCC associated with increasing levels of alcohol intake. Although the risks of light drinking among those chronically infected with HCV remain somewhat controversial (Khan et al., 1998; Monto et al., 2004; Sachithanandan et al., 1997), some researchers report significant interactive effects with regard to viremia and progression of hepatic fibrosis, even at light to moderate levels of alcohol intake (Pessione et al., 1998; Westin et al., 2002).

Unfortunately, conventional pharmacological treatment is only marginally effective for HCV genotype 1, the most common subtype in the United States including rural Appalachian Kentucky (Young et al., 2012), with a sustained virological response rate less than 51% after 48 weeks of conventional pegylated interferon/ribavirin treatment (Craxi and Licata, 2003) and considerable risk for severe hematological and neuropsychiatric adverse effects (NIH, 2002). Recently developed direct-acting antivirals such as telaprevir and boceprevir have demonstrated greatly improved outcomes among individuals infected with genotype 1 (Dore et al., 2011). However, like ribavirin and pegylated interferon, these drugs are costly and likely to be inaccessible to a substantial portion of IDUs. Perhaps most importantly, chronic infection with HCV genotype 1 has also been shown to confer a heightened risk of cirrhosis and HCC (Ripoli and Pazienza, 2011). In economically depressed rural areas such as Appalachia, these issues are likely to be compounded further because access to screening for blood-borne infections such as HCV, medical care for HCV, drug dependence treatment, and IDU harm-reduction programs are typically limited (Edeh and Spalding, 2008; Reif et al., 2005; Zhang et al., 2008). Clearly, the need remains for an effective and pragmatic means to prevent liver damage, cirrhosis, and potential HCC among people who are HCV-seropositive, particularly with regard to IDUs living in medically underserved areas.

Despite these issues, few studies have addressed changes in alcohol consumption following HCV diagnosis and standard posttest counseling, especially in rural populations. Of the few studies that do exist, most reveal mixed responses following HCV diagnosis. One study found a range of outcomes from complete abstinence to continued heavy drinking, with no significant trend toward reduction overall (Ompad et al., 2002). By contrast, HCV-positive opiate users in treatment were found to significantly decrease their alcohol intake relative to their HCV-negative counterparts, but this study looked specifically at a targeted intervention focused on harm-reduction behaviors rather than diagnosis and informational counseling alone (McCusker, 2001). Scognamiglio and colleagues (2007) reported that 74.5% of drinkers reduced or eliminated alcohol intake upon diagnosis of hepatitis C infection. However, this sample was drawn from three outpatient urban centers and was not specific to drug users or rural residents with limited access to medical care. Another study demonstrated only short-term reductions in drinking following diagnosis and informational counseling, with levels returning to near baseline by 6 and 12 months, and this short-term decline was shown to be independent of HCV serostatus (Tsui et al., 2009).

More recently, Drumright and colleagues (2011) compared two biweekly postdiagnostic interventions conducted over 3 weeks in a study of young HCV-positive IDUs in an urban setting. Although no additional benefit was found in "facilitated" educational sessions focused on HCV and liver health compared with "standard" postdiagnostic counseling, these interventions resulted in an overall 22.7% reduction in drinking after 6 months, but there are no data available beyond this time point (Drumright et al., 2011). Other studies of HCV-positive IDUs reflect the uncertainty of lasting declines in drinking following diagnosis (Stein et al., 2002; Watson et al., 2007), whereas Campbell and colleagues (2006) found high levels of problem drinking despite 84% of their sample reporting awareness of the increased risk of liver disease among HCV-positive individuals who continue to drink. Despite much research, however, the question has yet to be examined outside the context of major urban centers. Thus, the purpose of this study was to prospectively determine significant predictors of alcohol use 6 months following HCV testing and counseling among 466 rural Appalachian drug users with and without antibodies to HCV.

Method

Study population

Data were collected as part of a longitudinal study of social networks among drug users in rural Appalachia. Among the 503 baseline study participants recruited, all resided in rural Appalachian Kentucky, were at least 18 years of age, and had used one or more of the following drugs in the 30 days preceding baseline interview for the purposes of getting high: cocaine, heroin, methamphetamines, or prescription opioids. All study participants received and signed informed consent and were compensated $50 for their time. The Uni-

versity of Kentucky Institutional Review Board reviewed and approved the research protocol.

Study sample

To examine predictors of alcohol use, data from the baseline and 6-month follow-up interviews were used. Of the 503 baseline participants, 470 (93.4%) returned after 6 months to complete the questionnaire. A further 4 participants had no lifetime history of alcohol use and were excluded, leaving a final sample size of 466 for analysis. To recruit the baseline sample, we used respondent-driven sampling. Respondent-driven sampling is often used to expand access to hidden populations such as illicit drug users, which remain largely unsampled with standard sampling frame techniques (Broadhead et al., 2002; Frost et al., 2006; Heckathorn, 1997, 2002). Respondent-driven sampling has been shown to be effective in recruiting drug users from rural populations, where networks of drug users can be especially difficult to access (Borders and Booth, 2011; Wang et al., 2007). To collect the data analyzed here, study "seeds" were recruited with flyers seeking IDUs posted in public areas around a storefront location in rural eastern Kentucky. These initial respondents were screened for eligibility, and if they consented to participate, they were asked to recruit three of their drug-using peers, regardless of injection status. Respondents to this second round of sampling were screened for eligibility, enrolled in the longitudinal SNAP (Social Networks among Appalachian People) study if appropriate, and given three coupons to distribute to their respective peers for further recruitment, and so on. Study participants were compensated $10 for each resultant coupon redeemed and participant enrolled.

Measures

All study participants were tested for antibodies to HCV using the Home Access® test for HCV antibody. This test uses a third-generation enzyme immunoassay on a dried blood spot obtained via finger stick and has been shown to have excellent sensitivity and specificity (98.2% and 99.6%, respectively; O'Brien et al., 2001). Standard pretest counseling given to all participants included a description of the test, risk factors for HCV infection, and the potential test results. Participants were asked to return within approximately 2 weeks for test results and underwent posttest counseling specific to their results. Participants testing positive for HCV antibodies were given information on preventing the spread of infection by eliminating high-risk behaviors—such as sharing needles and preparation equipment—and were offered contact information for local health clinics for further testing and, if appropriate, treatment. With regard to alcohol use specifically, participants were informed that, to slow or prevent onset of serious liver disease, they should not drink alcohol. Those testing negative were counseled only on avoiding engagement in behaviors that would put them at increased risk for HCV acquisition.

Alcohol use was measured at both baseline and follow-up via the Addiction Severity Index (McLellan et al., 1990). Participants were asked if they had ever used alcohol and, if so, the number of days using in the prior 30 days. The dependent variable of interest was number of days using alcohol in the past 30 days at the 6-month follow-up visit. Demographic indicators and other drug use were also measured via the Addiction Severity Index. To assess for the presence of psychiatric disorders (based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [DSM-IV]; American Psychiatric Association, 1994), the Mini-International Neuropsychiatric Interview (Version 5.0) modules were administered for major depressive disorder, generalized anxiety disorder, posttraumatic stress disorder, and antisocial personality disorder (ASPD; Sheehan et al., 1998).

Statistical analysis

Demographic, drug use, and psychiatric characteristics were first compared between those with and without antibodies to HCV. Contingency tables and the chi-square statistic were used to examine differences in dichotomous/categorical variables, and the Wilcoxon rank-sum test was used to analyze the continuous variables. Differences in days using alcohol between baseline and follow-up visits were computed using the Mann–Whitney *U* test. Because the dependent variable had a count distribution (number of days using alcohol in the past 30 days) and was overdispersed, negative binomial regression was used to determine the independent predictors of alcohol use at follow-up. Therefore, a series of unadjusted models was constructed to determine which predictors would be considered for inclusion in the multivariable negative binomial model. Apart from HCV status, only those variables significant at the $p < .05$ level were tested in the model. The incidence rate ratios (IRRs), 95% confidence intervals (CIs), and *p* values are presented for each individual model in Table 2, adjusted for frequency of alcohol use at baseline. Finally, the multivariable model was constructed using a manual, forward elimination process until the most parsimonious model was achieved. IRRs in the multivariable model have been adjusted for all other variables in the model. The likelihood ratio test for the final model indicated a significantly better fit than the Poisson model ($p < .001$), further justifying the use of negative binomial regression. Stata® Version 12.0 (StataCorp LP, College Station, TX) was used for all analyses.

Results

The study sample ($N = 466$) was predominantly male (56.6%) and White (94.0%), and the median age was 31

TABLE 1. Demographic and behavioral characteristics of sample (N = 466)

Characteristic	HCV-positive (n = 203)		HCV-negative (n = 263)		
	n or M (IQR)	%	n or M (IQR)	%	p
Male	123	60.6	141	53.6	.132
Age, in years	32 (27, 38)		31 (25, 38)		.324
White race	195	96.1	243	92.4	.099
Married	**38**	**18.7**	**79**	**30.0**	**.005**
Education, in years	12 (9, 12)		12 (10, 12)		.079
Unemployed	**64**	**31.5**	**58**	**22.0**	**.021**
Uninsured	**146**	**71.9**	**163**	**61.3**	**.024**
Receiving disability benefits	27	13.3	29	11.0	.454
DSM-IV psychiatric disorders					
Major depressive disorder	60	29.6	63	23.9	.174
Generalized anxiety disorder	61	30.0	78	29.7	.927
Posttraumatic stress disorder	26	12.8	43	16.3	.286
Antisocial personality disorder	59	29.1	89	33.8	.272
Past-30-day drug use at baseline					
Alcohol	111	54.7	143	53.4	.947
Alcohol to intoxication	86	42.4	108	41.1	.778
OxyContin	**160**	**78.8**	**166**	**62.1**	**<.001**
Hydrocodone	163	80.7	218	82.9	.542
Other oxycodone	146	71.9	193	73.4	.725
Illicit methadone	**108**	**53.2**	**172**	**65.4**	**.008**
Heroin	8	3.9	12	4.5	.753
Benzodiazepines	174	85.7	221	84.0	.616
Cocaine	**57**	**28.1**	**49**	**18.6**	**.016**
Crack cocaine	27	13.3	27	10.3	.310
Marijuana	117	57.6	168	63.9	.170
Methamphetamine	8	3.9	7	2.7	.438
Injection drug use					
Past 30 days	**143**	**70.4**	**81**	**30.8**	**<.001**
Lifetime	**196**	**96.5**	**164**	**62.4**	**<.001**

Notes: **Bold** indicates statistical significance. HCV = hepatitis C virus; IQR = interquartile range; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.*

years (interquartile range: 26, 38). The overall prevalence of HCV at baseline was 43.6%. Those who were HCV-seropositive were more likely to be unemployed and uninsured and were less likely to be married (Table 1). HCV-seropositive participants were also significantly more likely to be using OxyContin® and cocaine and less likely to be using illicit methadone in the 30 days before the baseline interview. HCV-seropositive participants were more than twice as likely to have a history of injecting drugs ($p < .001$).

The majority of participants used alcohol—254 (54.0%) reported alcohol consumption in the 30 days preceding baseline. The mean number of days using alcohol in the past 30 days at baseline was 3.64 (SE = 0.33). At baseline, there was no difference in mean days of drinking in the 30 days preceding interviewing in the HCV-seropositive participants (3.90 days) versus HCV-seronegative participants (3.45 days; $p = .50$). Although there was a significant drop in alcohol consumption between the baseline and 6-month interviews, it did not differ between subjects testing HCV seropositive and those testing HCV seronegative (2.28 days vs. 2.71 days, $p = .33$).

Table 2 depicts negative binomial regression models predicting alcohol use at follow-up, adjusted for baseline alcohol use. Although those who were HCV-seropositive were less likely to be using alcohol at follow-up (IRR = 0.87, 95% CI [0.59, 1.30]), this did not differ significantly from the HCV-seronegative participants. Those who met the DSM-IV criteria for ASPD were more likely to be using alcohol at follow-up, as were those who indicated marijuana use at baseline. A 36% reduction in the number of days using alcohol was noted at follow-up among those who were using OxyContin at baseline. Not surprisingly, the strongest predictors of alcohol use at follow-up were any alcohol use at baseline and alcohol use to intoxication at baseline (both $p < .001$).

As depicted in Table 3, when adjusted for other variables in the model, including baseline alcohol use, those who were HCV-seropositive and received standard counseling against continued alcohol use upon diagnosis were no less likely than those who were HCV-seronegative to be using alcohol at 6-month follow-up interviews (adjusted IRR = 1.07, 95% CI [0.72, 1.61]). Independent predictors of days using alcohol at follow-up included baseline marijuana use (adjusted IRR = 1.91, 95% CI [1.25, 2.91]) and ASPD (adjusted IRR = 1.88, 95% CI [1.24, 2.84]). Even after adjustment for other drug use variables, HCV status, and ASPD, those using OxyContin were 39% less likely to be drinking more often

TABLE 2. Bivariate negative binomial regression models predicting number of days drinking alcohol at 6 months following HCV serostatus disclosure, adjusted for alcohol use at baseline ($N = 466$)

Variable	IRR	[95% CI]	*p*
HCV-positive status	0.87	[0.59, 1.30]	.504
Male	1.36	[0.91, 2.06]	.132
Age	1.01	[0.99, 1.03]	.473
White race	1.09	[0.47, 2.51]	.827
Married	0.83	[0.52, 1.30]	.414
Years of Education	1.00	[0.99, 1.00]	.328
Unemployed	0.72	[0.46, 1.14]	.168
Uninsured	1.50	[0.99, 2.28]	.056
Receiving disability benefits	0.56	[0.30, 1.05]	.072
DSM-IV psychiatric disorders			
Major depressive disorder	0.82	[0.52, 1.28]	.383
Generalized anxiety disorder	1.09	[0.71, 1.69]	.669
Posttraumatic stress disorder	0.93	[0.53, 1.63]	.813
Antisocial personality disorder	**1.66**	**[1.09, 2.49]**	**.018**
Past-30-day drug use at baseline			
Alcohol	**3.90**	**[2.52, 6.04]**	**<.001**
Alcohol to intoxication	**2.34**	**[1.52, 3.61]**	**<.001**
OxyContin	**0.64**	**[0.42, 0.98]**	**.038**
Hydrocodone	0.84	[0.50, 1.41]	.514
Other oxycodone	0.79	[0.51, 1.23]	.295
Illicit methadone	1.35	[0.91, 2.03]	.137
Heroin	1.60	[0.62, 4.12]	.328
Benzodiazepines	0.70	[0.41, 1.20]	.193
Cocaine	1.02	[0.63, 1.63]	.925
Crack cocaine	0.63	[0.33, 1.20]	.159
Marijuana	**1.96**	**[1.31, 2.95]**	**.001**
Methamphetamine	0.36	[0.10, 1.25]	.107
Received substance treatment after baseline	0.99	[0.53, 1.85]	.988
Injection drug use			
Past 30 days	0.72	[0.49, 1.08]	.113
Lifetime	0.97	[0.61, 1.56]	.906

Notes: **Bold** indicates statistical significance. HCV = hepatitis C virus; IRR = incidence rate ratio; 95% CI = 95% confidence interval; IQR = interquartile range; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.*

TABLE 3. Predictors of number of days of drinking at 6 months following HCV serostatus disclosure and posttest counseling ($N = 466$)

Variable	aIRR	[95% CI]	*p*
HCV-positive status	1.07	[0.72, 1.61]	.718
Alcohol use at baseline	6.80	[4.51, 10.2]	<.001
Marijuana use at baseline	1.91	[1.25, 2.91]	.003
OxyContin use at baseline	0.61	[0.40, 0.94]	.024
Antisocial personality disorder	1.88	[1.24, 2.84]	.003

Notes: HCV = hepatitis C virus; aIRR = adjusted incidence rate ratio; 95% CI = 95% confidence interval.

at follow-up (adjusted IRR = 0.61, 95% CI [0.40, 0.94]). Baseline alcohol users were also significantly more likely to report more days of drinking at follow-up (adjusted IRR = 6.80, 95% CI [4.51, 10.2]) after controlling for all other variables in the model.

Discussion

Overall, this sample of rural drug users reported drinking less frequently at 6-month follow-up interviews relative to baseline. However, stratification by baseline HCV status revealed that disclosure of HCV-seropositive status and posttest informational counseling were not associated with a significantly differential change in frequency of alcohol use relative to HCV-seronegative participants. Distinction between the two groups was further diminished upon adjustment for significant covariates in the multivariate model. Postdiagnostic counseling was tailored to the results of the HCV test. For HCV-seropositive individuals, this consisted of standardized information with printed materials covering the significance of HCV infection, recommendations for proper medical treatment and the restriction of risk behaviors such as sharing needles and drug preparation equipment, as well as regional clinic information, specific statements regarding the greatly increased risk of liver damage among individuals with HCV who drink, with emphasis on the importance of abstaining from alcohol use following diagnosis. HCV-seronegative participants were counseled only to avoid engaging in behaviors that put them at increased risk for HCV infection. This distinction in posttest counseling, combined with disclosure of individual serostatus, seemed to lack significant efficacy in reducing drinking among participants infected with HCV in this sample.

The long-term sequelae of chronic HCV are well documented, including dramatically increased risks of cirrhosis

and HCC (Alter and Seeff, 2000; Amarapurkar, 2000; Caselmann and Alt, 1996; NIH, 2002; Simonetti et al., 1992; Tagger et al., 1999). The odds of developing HCC have been estimated to be 69 times greater among HCV-positive individuals in a case-control analysis (Simonetti et al., 1992), and the prognosis is among the worst of all neoplasms, with a median survival time in the United States of 10 months (Stuart et al., 1996). These risks have been shown to be even greater among HCV-positive individuals who continue to consume alcohol at moderate to high levels (Bhattacharya and Shuhart, 2003; NIH, 2002; Stroffolini et al., 2010; Tagger et al., 1999), particularly among untreated individuals (Westin et al., 2002).

Synergistic effects of alcohol on HCV replication via altered lipid metabolism and elevated concentrations of intracellular nicotinamide adenine dinucleotide (Seronello et al., 2010), as well as a general increase in oxidative stress (McCartney and Beard, 2010), have been proposed and demonstrated in vitro. In addition, alcohol consumption has been implicated in decreased response to HCV pharmacotherapy, particularly with regard to pegylated interferon-alpha combined with ribavirin (McCartney and Beard, 2010). Other investigators have suggested that this apparent decline in efficacy resulted from poor compliance and advised additional support for patients with a history of alcohol use (Anand et al., 2006), particularly at heavy levels (Russell et al., 2012).

The null effect of HCV-positive serostatus disclosure and subsequent informational counseling on drinking frequency relative to HCV-negative study participants complements some previous studies while contradicting others. Tsui and colleagues (2009) found past-month alcohol intake to decrease in young IDUs upon HCV seroconversion and posttest counseling, although this effect was not sustained over 6-month and, especially, 12-month time points. Moreover, the decline in drinking was independent of HCV serostatus disclosure and counseling (Tsui et al., 2009), as was the case in this study. Similarly, despite a wide range of individual behavioral changes, Ompad and collaborators (2002) found no significant trend in alcohol consumption in their cohort following HCV status disclosure and standard counseling. By contrast, a cross-sectional study by Scognamiglio and colleagues (2007) found that HCV-seropositive outpatients recruited from three Italian clinical centers significantly reduced their alcohol intake upon diagnosis. In contrast to the sample analyzed here, their study consisted primarily of an older population (mean age of 46 years at HCV diagnosis) receiving individualized medical attention in an outpatient clinical setting. Similarly, modest reductions in alcohol intake were found in self-identified HCV-positive individuals undergoing treatment for opiate dependence (McCusker, 2001), whereas Kwiatkowski and colleagues (2002) found no significant difference in alcohol intake among IDUs in Denver when stratified by HCV status.

In each setting, the data suggest that an intensive and targeted approach to reducing alcohol use among HCV-infected individuals who drink is more likely to be effective than diagnosis and standard posttest counseling alone. A survey of urban HCV-seropositive IDUs found a high prevalence (37%) of problem drinking, despite 84% of the sample understanding the increased risk of drinking following diagnosis of HCV (Campbell et al., 2006). This suggests that more intensive interventional counseling focused on curtailing alcohol consumption may be justified following HCV diagnosis in rural drug users as well. Further bolstering this notion, a French study found the specific medical recommendations in a brief intervention from a primary care physician to considerably reduce drinking in HCV-seropositive patients (Nalpas et al., 2001), although this study was not specific to drug users or HCV-seropositive individuals in the rural setting. Similarly, a study by Watson and colleagues (2007) reported a decrease in alcohol intake of 3.1 g per day following a targeted intervention in a small sample of HCV-positive individuals undergoing methadone maintenance treatment. However, neither study reported levels of alcohol intake among HCV-negative or HCV-positive participants not undergoing the targeted intervention for control purposes.

Given the null effect of HCV-positive diagnosis and informational counseling on frequency of alcohol consumption in this cohort, the distinction between standard posttest counseling and focused intervention may represent a critical opportunity to preserve the long-term liver function among recently diagnosed HCV-seropositive drug users in the rural setting. Somewhat surprisingly, a study by Drumright and colleagues (2011) comparing two interventions among young HCV-seropositive IDUs from three U.S. cities found no significant effect on drinking in study participants undergoing an expanded intervention focusing specifically on HCV management, liver health, and the heightened risks of alcohol consumption accompanying HCV infection when compared with standard postdiagnostic interventional counseling. Study participants had been diagnosed previously as HCV-seropositive, and 75% recalled receiving standard counseling at the time of diagnosis on the risks of drinking while infected with HCV. Nonetheless, more than 72% of the sample reported alcohol use at baseline randomization, with 48% scoring 8 or more on the Alcohol Use Disorders Identification Test scale (Drumright et al., 2011), implying poor compliance following standard postdiagnosis informational counseling with regard to the risks of continued drinking. Moreover, the significant decrease in drinking in both the expanded and standard interventions in this study suggests that alcohol-focused intervention, in either form, is likely to considerably benefit HCV-seropositive drug users who drink. This concept is further supported by the work of Zule and collaborators (2009), who found a significant reduction in alcohol consumption in a focused motivational intervention

compared with a more standard educational one of the same length.

As noted previously, a spectrum of sociobiological issues exacerbate the problem of widespread chronic HCV in low-income rural areas such as Appalachia, including poor access to care and scarce availability of disease screening, substance misuse treatment, and harm-reduction programs relative to urban areas (Day et al., 2006; Edeh and Spalding, 2006; Reif et al., 2005); lack of health care providers; and in general, a variety of health care indicators generally well below average values for the United States as a whole (Stensland et al., 2002; Zhang et al., 2008). Compounding these challenges, genotype 1 is the predominant form of HCV in the United States (Nainan et al., 2006), and in a random subsample of 81 from this study population, with 2 of 3 participants sequenced with genotype 1a (Young et al., 2012). Although direct-acting antiviral drugs—such as telaprevir and boceprevir in combination with pegylated interferon-alpha and ribavirin—have demonstrated substantially improved outcomes and shortened treatment regimens among individuals infected with genotype 1 (Dore et al., 2011), obtaining these expensive pharmacotherapies is likely to be difficult for IDUs, who typically have poor access to medical care (Grebely et al., 2008; Swan et al., 2010). In addition, 66% of participants had no health insurance in this rural cohort, a significantly higher proportion of which came from the HCV-seropositive group.

In contrast with HCV status, several other variables were associated with significant change in frequency of alcohol intake between baseline and 6-month follow-up. Unsurprisingly, baseline alcohol use was a highly significant predictor of increased drinking 6 months after baseline HCV testing, and there was a greater than two-fold higher incidence of increased drinking for those participants who reported drinking to intoxication in the 30 days preceding baseline. Similarly, diagnosis of ASPD conferred a significantly increased incidence of alcohol consumption; an abundance of previous studies corroborate the association of ASPD with elevated drinking (Compton et al., 2005; Goldstein et al., 2007).

Less expected was the nearly two-fold higher incidence of increased alcohol consumption among those using marijuana at baseline, a finding not entirely predicated by previous studies. Other researchers have suggested a trend toward adult alcohol use among teenagers who use cannabis (Patton et al., 2007), as well as considerable shared genetic factors and an overlapping incidence of alcohol and marijuana use disorders and ASPD (Fu et al., 2002; True et al., 1999), which could help explain the high incidence of increased drinking among participants reporting baseline use of marijuana and/or diagnosed with ASPD. By contrast, OxyContin use at baseline was associated with a significant decrease in drinking frequency at 6 months. This finding is also somewhat surprising and worth noting because 100% of the sample had a lifetime history of using prescription opioids nonmedically. In addition, OxyContin was among the most frequently misused prescription opioids among the study participants at baseline, along with hydrocodone and other oxycodone-containing drugs.

Because this emerging drug epidemic is just beginning to be explored, the significance of the ostensibly "protective" effect of nonmedical OxyContin use at baseline merits careful scrutiny. Recent social network analysis of Appalachian drug users has revealed a strong association of daily OxyContin misuse with increased odds of elevated "social capital," or effective network size, in stark contrast with other drugs commonly used on a daily basis, including alcohol (heavy use), hydrocodone, and marijuana (Jonas et al., 2012). This implies that a novel social dynamic exists with regard to recreational users of OxyContin in the rural setting, and individuals with daily access to the popular prescription opioid attain higher status within their networks relative to users of other drugs. Furthermore, the daily use of marijuana was associated with the opposite effect in regard to social capital—diminishing users' effective network size (Jonas et al., 2012)—which is analogous to the opposing associations exhibited by baseline use of marijuana and OxyContin regarding drinking frequency in the present analysis. Thus, given the strong tendency of OxyContin users to transition quickly to injection relative to other commonly used drugs (Young and Havens, 2012), there appears to be a unique sociobiological phenomenon underpinning the widespread nonmedical use of OxyContin in rural Appalachia. Indeed, the counterintuitive "protective" effect of OxyContin use with regard to drinking suggests an inverse relationship between social capital and alcohol consumption among rural drug users in this region. Nonetheless, regardless of specific substance use history, decreasing or eliminating alcohol intake remains a highly pragmatic strategy to improve the clinical prognosis of all individuals infected with HCV.

A few limitations should be addressed when considering findings of this study. First, the dependent variable used to evaluate alcohol intake does not address actual volume of alcohol consumed during individual days or the frequency of drinking during the first 5 months between baseline interview and 6-month follow-up. However, because the posttest counseling materials advised participants to completely abstain from drinking, a question as to whether they were drinking at follow-up addresses our research question and hypothesis, albeit not as specifically as we could. Second, many of the data in this study were self-reported by research participants, which could affect the accuracy of the findings. However, many studies have determined self-reported drug use data to be valid indicators of actual levels of use (Darke, 1998; Kokkevi et al., 1997). Lastly, HCV seropositivity does not always imply chronic infection, as approximately 15%–40% of individuals will spontaneously clear the virus while retaining antibodies in the serum (NIH, 2002). However, polymerase chain reaction analysis of 81 randomly

selected anti–HCV-positive individuals from this cohort confirmed that 56 (69%) had detectable HCV RNA (Young et al., 2012), indicative of active infection and congruent with typical prevalence rates for chronic disease among HCV-antibody-positive individuals.

Despite these limitations, the data presented here mark an important step into largely uncharted terrain. Often hidden from public awareness relative to their urban counterparts, rural drug users are a rarely studied group at high risk for blood-borne infections such as HCV. From the standpoint of public health policy, clinical care, and long-term cost control, it is crucially important to better understand this undertreated population, especially in low-income rural areas where access to disease screening and health care is often limited geographically and economically. The mortality resulting from HCV in the United States has now surpassed that of HIV (Ly et al., 2012), thus presenting one of the more daunting public health crises the nation has faced in recent decades. To that end, research facilitating interventions among socially marginalized HCV-infected populations is vital to improve long-term clinical outcomes and ease the social burden of this disease.

Alcohol consumption is a modifiable behavioral factor with robust potential for limiting hepatic injury and progression to cirrhosis and HCC among HCV-positive individuals. Although a crucial step in the management of HCV, disclosure of seropositivity and informational counseling alone were not sufficient to achieve a meaningful decrease in alcohol consumption in this sample of rural drug users. Targeted interventions such as motivational alcohol-cessation counseling—ideally coupled with individualized care from a physician, substance use disorder treatment, and HCV pharmacotherapy—hold great promise to achieve a significant decrease in the risk of cirrhosis and HCC. This may be especially true among HCV-infected marijuana users, those who drink to intoxication, and individuals with ASPD in the rural setting, all of whom appear to be at highest risk for the alcohol-enhanced liver damage typically accompanying chronic infection with HCV. Further study evaluating the impact of targeted interventions versus simple diagnosis and standard counseling in the setting of a randomized trial among rural HCV-positive drug users would impart critical insight into the most pragmatic strategies to manage this smoldering public health crisis.

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References

Aceijas, C., & Rhodes, T. (2007). Global estimates of prevalence of HCV infection among injecting drug users. *International Journal on Drug Policy, 18,* 352–358.

Aitken, C. K., Lewis, J., Tracy, S. L., Spelman, T., Bowden, D. S., Bharadwaj, M., . . . Hellard, M. (2008). High incidence of hepatitis C virus reinfection in a cohort of injecting drug users. *Hepatology, 48,* 1746–1752.

Alter, H. J., & Seeff, L. B. (2000). Recovery, persistence, and sequelae in hepatitis C virus infection: A perspective on long-term outcome. *Seminars in Liver Disease, 20,* 17–36.

Alter, M. J. (2007, May 7). Epidemiology of hepatitis C virus infection. *World Journal of Gastroenterology, 13*(17), 2436–2441.

Amarapurkar, D. (2000). Natural history of hepatitis C virus infection. *Journal of Gastroenterology and Hepatology, 15, Supplement s2,* E105–E110.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Anand, B. S., Currie, S., Dieperink, E., Bini, E. J., Shen, H., Ho, S. B., & Wright, T., & the VA-HCV-001 Study Group. (2006). Alcohol use and treatment of hepatitis C virus: Results of a national multicenter study. *Gastroenterology, 130,* 1607–1616.

Armstrong, G. L., Wasley, A., Simard, E. P., McQuillan, G. M., Kuhnert, W. L., & Alter, M. J. (2006, May 16). The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Annals of Internal Medicine, 144,* 705–714.

Bhattacharya, R., & Shuhart, M. C. (2003). Hepatitis C and alcohol: Interactions, outcomes, and implications. *Journal of Clinical Gastroenterology, 36,* 242–252.

Borders, T. F., & Booth, B. M. (2012). Stimulant use trajectories and the longitudinal risk of heavy drinking: Findings from a rural population-based study. *Addictive Behaviors, 37,* 269–272.

Broadhead, R. S., Heckathorn, D. D., Altice, F. L., van Hulst, Y., Carbone, M., Friedland, G. H., . . . Selwyn, P. A. (2002). Increasing drug users' adherence to HIV treatment: Results of a peer-driven intervention feasibility study. *Social Science & Medicine, 55,* 235–246.

Campbell, J. V., Hagan, H., Latka, M. H., Garfein, R. S., Golub, E. T., Coady, M. H., . . . Strathdee, S. A., & the STRIVE Project. (2006). High prevalence of alcohol use among hepatitis C virus antibody positive injection drug users in three US cities. *Drug and Alcohol Dependence, 81,* 259–265.

Caselmann, W. H., & Alt, M. (1996). Hepatitis C virus infection as a major risk factor for hepatocellular carcinoma. *Journal of Hepatology, 24, Supplement 2,* 61–66.

Compton, W. M., Conway, K. P., Stinson, F. S., Colliver, J. D., & Grant, B. F. (2005). Prevalence, correlates, and comorbidity of DSM-IV antisocial personality syndromes and alcohol and specific drug use disorders in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry, 66,* 677–685.

Craxi, A., & Licata, A. (2003). Clinical trial results of peginterferons in combination with ribavirin. *Seminars in Liver Disease, 23, Supplement 1,* 35–46.

Darke, S. (1998). Self-report among injecting drug users: A review. *Drug and Alcohol Dependence, 51,* 253–263, discussion 267–268.

Day, C., Conroy, E., Lowe, J., Page, J., & Dolan, K. (2006). Patterns of drug use and associated harms among rural injecting drug users: Comparisons with metropolitan injecting drug users. *Australian Journal of Rural Health, 14,* 120–125.

Donato, F., Tagger, A., Chiesa, R., Ribero, M. L., Tomasoni, V., Fasola, M., . . . Nardi, G. (1997). Hepatitis B and C virus infection, alcohol drinking, and hepatocellular carcinoma: A case-control study in Italy. *Hepatology, 26,* 579–584.

Dore, G. J., Matthews, G. V., & Rockstroh, J. (2011). Future of hepatitis C therapy: Development of direct-acting antivirals. *Current Opinion in HIV and AIDS, 6,* 508–513.

Drumright, L. N., Hagan, H., Thomas, D. L., Latka, M. H., Golub, E. T., Garfein, R. S., . . . Strathdee, S. A. (2011). Predictors and effects of

alcohol use on liver function among young HCV-infected injection drug users in a behavioral intervention. *Journal of Hepatology, 55,* 45–52.

Edeh, J., & Spalding, P. (2000). Screening for HIV, HBV, and HCV markers among drug users in treatment in rural south-east England. *Journal of Public Health Medicine, 22,* 531–539.

Frost, S. D. W., Brouwer, K. C., Firestone Cruz, M. A., Ramos, R., Ramos, M. E., Lozada, R. M., . . . Strathdee, S. A. (2006). Respondent-driven sampling of injection drug users in two U.S.–Mexico border cities: Recruitment dynamics and impact on estimates of HIV and syphilis prevalence. *Journal of Urban Health, 83, Supplement,* 83–97.

Fu, Q., Heath, A. C., Bucholz, K. K., Nelson, E., Goldberg, J., Lyons, M. J., . . . Eisen, S. A. (2002). Shared genetic risk of major depression, alcohol dependence, and marijuana dependence: Contribution of antisocial personality disorder in men. *Archives of General Psychiatry, 59,* 1125–1132.

Goldstein, R. B., Dawson, D. A., Saha, T. D., Ruan, W. J., Compton, W. M., & Grant, B. F. (2007). Antisocial behavioral syndromes and DSM-IV alcohol use disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Alcoholism: Clinical and Experimental Research, 31,* 814–828.

Grebely, J., Genoway, K. A., Raffa, J. D., Dhadwal, G., Rajan, T., Showler, G., . . . Fischer, B. (2008). Barriers associated with the treatment of hepatitis C virus infection among illicit drug users. *Drug and Alcohol Dependence, 93,* 141–147.

Grebely, J., Raffa, J. D., Lai, C., Krajden, M., Conway, B., & Tyndall, M. W. (2007). Factors associated with spontaneous clearance of hepatitis C virus among illicit drug users. *Canadian Journal of Gastroenterology, 21,* 447–451.

Hahn, J. A., Page-Shafer, K., Ford, J., Paciorek, A., & Lum, P. J. (2008). Traveling young injection drug users at high risk for acquisition and transmission of viral infections. *Drug and Alcohol Dependence, 93,* 43–50.

Havens, J. R., Lofwall, M. R., Frost, S. D. W., Oser, C. B., Leukefeld, C. G., & Crosby, R. A. (2013). Individual and network factors associated with prevalent hepatitis C infection among rural Appalachian injection drug users. *American Journal of Public Health, 103,* e44–e52.

Havens, J. R., Walker, R., & Leukefeld, C. G. (2007). Prevalence of opioid analgesic injection among rural nonmedical opioid analgesic users. *Drug and Alcohol Dependence, 87,* 98–102.

Heckathorn, D. D. (1997). Respondent-driven sampling: A new approach to the study of hidden populations. *Social Problems, 44,* 174–199.

Heckathorn, D. D. (2002). Respondent-driven sampling II: Deriving valid population estimates from chain-referral samples of hidden populations. *Social Problems, 49,* 11–34.

Jonas, A. B., Young, A. M., Oser, C. B., Leukefeld, C. G., & Havens, J. R. (2012). OxyContin® as currency: OxyContin® use and increased social capital among rural Appalachian drug users. *Social Science & Medicine, 74,* 1602–1609.

Khan, M. H., Thomas, L., Byth, K., Kench, J., Weltman, M., George, J., . . . Farrell, G. C. (1998). How much does alcohol contribute to the variability of hepatic fibrosis in chronic hepatitis C? *Journal of Gastroenterology and Hepatology, 13,* 419–426.

Kokkevi, A., Richardson, C., Palermou, B., & Leventakou, V. (1997). Reliability of drug dependents' self-reports. *Drug and Alcohol Dependence, 45,* 55–61.

Kwiatkowski, C. F., Fortuin Corsi, K., & Booth, R. E. (2002). The association between knowledge of hepatitis C virus status and risk behaviors in injection drug users. *Addiction, 97,* 1289–1294.

Ly, K. N., Xing, J., Klevens, R. M., Jiles, R. B., Ward, J. W., & Holmberg, S. D. (2012, February 21). The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Annals of Internal Medicine, 156,* 271–278.

McCartney, E. M., & Beard, M. R. (2010). Impact of alcohol on hepatitis C virus replication and interferon signaling. *World Journal of Gastroenterology, 16,* 1337–1343.

McCusker, M. (2001). Influence of hepatitis C status on alcohol consumption in opiate users in treatment. *Addiction, 96,* 1007–1014.

McLellan, A. T., Randall, M., Joseph, N., & Alterman, A. I. (1990). Categorizing substance abusers using the ASI: Implications for evaluation and treatment. *NIDA Research Monograph, 105,* 227–235.

Micallef, J. M., Macdonald, V., Jauncey, M., Amin, J., Rawlinson, W., Van Beek, I., . . . Dore, G. J. (2007). High incidence of hepatitis C virus reinfection within a cohort of injecting drug users. *Journal of Viral Hepatitis, 14,* 413–418.

Monto, A., Patel, K., Bostrom, A., Pianko, S., Pockros, P., McHutchison, J. G., & Wright, T. L. (2004). Risks of a range of alcohol intake on hepatitis C-related fibrosis. *Hepatology, 39,* 826–834.

Nainan, O. V., Alter, M. J., Kruszon-Moran, D., Gao, F. X., Xia, G., McQuillan, G., & Margolis, H. S. (2006). Hepatitis C virus genotypes and viral concentrations in participants of a general population survey in the United States. *Gastroenterology, 131,* 478–484.

Nalpas, B., Martin, S., Fontaine, H., Fabbro-Peray, P., Bréchot, C., & Pol, S. (2001). Impact of medical recommendations on alcohol consumption in HCV positive patients. *Journal of Hepatology, 35,* 312–313.

National Institutes of Health. (2002). NIH consensus statement on management of hepatitis C: 2002. *NIH Consensus and State-of-the-Art Science Statements, 19,* 1–46.

Nelson, P. K., Mathers, B. M., Cowie, B., Hagan, H., Des Jarlais, D., Horyniak, D., & Degenhardt, L. (2011). Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: Results of systematic reviews. *The Lancet, 378,* 571–583.

O'Brien, J. M., Kruzel, K. E., Wandell, M. G., Vinogradov, I. V., Sheagren, J. N., & Frank, A. P. (2001). Detection of hepatitis C antibody with at-home collection kits using an innovative laboratory algorithm. *Infectious Diseases in Clinical Practice, 10,* 474–480.

Ompad, D. C., Fuller, C. M., Vlahov, D., Thomas, D., & Strathdee, S. A. (2002). Lack of behavior change after disclosure of hepatitis C virus infection among young injection drug users in Baltimore, Maryland. *Clinical Infectious Diseases, 35,* 783–788.

Page, K., Hahn, J. A., Evans, J., Shiboski, S., Lum, P., Delwart, E., . . . Busch, M. P. (2009). Acute hepatitis C virus infection in young adult injection drug users: A prospective study of incident infection, resolution, and reinfection. *Journal of Infectious Diseases, 200,* 1216–1226.

Patton, G. C., Coffey, C., Lynskey, M. T., Reid, S., Hemphill, S., Carlin, J. B., & Hall, W. (2007). Trajectories of adolescent alcohol and cannabis use into young adulthood. *Addiction, 102,* 607–615.

Pessione, F., Degos, F., Marcellin, P., Duchatelle, V., Njapoum, C., Martinot-Peignoux, M., . . . Rueff, B. (1998). Effect of alcohol consumption on serum hepatitis C virus RNA and histological lesions in chronic hepatitis C. *Hepatology, 27,* 1717–1722.

Piasecki, B. A., Lewis, J. D., Reddy, K. R., Bellamy, S. L., Porter, S. B., Weinrieb, R. M., . . . Chang, K. M. (2004). Influence of alcohol use, race, and viral coinfections on spontaneous HCV clearance in a US veteran population. *Hepatology, 40,* 892–899.

Poustchi, H., Esmaili, S., Mohamadkhani, A., Nikmahzar, A., Pourshams, A., Sepanlou, S. G., . . . Malekzadeh, R. (2011). The impact of illicit drug use on spontaneous hepatitis C clearance: Experience from a large cohort population study. *PLoS ONE, 6*(8), e23830.

Reif, S., Golin, C. E., & Smith, S. R. (2005). Barriers to accessing HIV/AIDS care in North Carolina: Rural and urban differences. *AIDS Care, 17,* 558–565.

Ripoli, M., & Pazienza, V. (2011). Impact of HCV genetic differences on pathobiology of disease. *Expert Review of Anti-Infective Therapy, 9,* 747–759.

Russell, M., Pauly, M. P., Moore, C. D., Chia, C., Dorrell, J., Cunanan, R. J., . . . Martin, S. (2012). The impact of lifetime alcohol use on hepatitis C

treatment outcomes in privately insured members of an integrated health care plan. *Hepatology, 56,* 1223–1230.

Sachithanandan, S., Kay, E., Leader, M., & Fielding, J. F. (1997). The effect of light drinking on HCV liver disease: The jury is still out. *Biomedicine & Pharmacotherapy, 51,* 295–297.

Scognamiglio, P., Galati, V., Navarra, A., Longo, M. A., Aloisi, M. S., Antonini, M. G., . . . Girardi, E. (2007, May 21). Impact of hepatitis C virus infection on lifestyle. *World Journal of Gastroenterology, 13,* 2722–2726.

Seronello, S., Ito, C., Wakita, T., & Choi, J. (2010). Ethanol enhances hepatitis C virus replication through lipid metabolism and elevated NADH/NAD+. *Journal of Biological Chemistry, 285,* 845–854.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59, Supplement 20,* 22–33, quiz 34–57.

Shepard, C. W., Finelli, L., & Alter, M. J. (2005). Global epidemiology of hepatitis C virus infection. *The Lancet Infectious Diseases, 5,* 558–567.

Simonetti, R. G., Cammà, C., Fiorello, F., Cottone, M., Rapicetta, M., Marino, L., . . . Pagliaro, L. (1992, January 15). Hepatitis C virus infection as a risk factor for hepatocellular carcinoma in patients with cirrhosis: A case-control study. *Annals of Internal Medicine, 116,* 97–102.

Stein, M. D., Charuvastra, A., Maksad, J., & Anderson, B. J. (2002). A randomized trial of a brief alcohol intervention for needle exchangers (BRAINE). *Addiction, 97,* 691–700.

Stensland, J., Mueller, C., & Sutton, J. (2002). *An analysis of the financial conditions of health care institutions in the Appalachian region and their economic impacts.* Washington, DC: Appalachian Regional Commission. Retrieved from http://www.arc.gov/assets/research_reports/AnalysisoftheFinancialConditionsofHealthCareInstitutionsinAppalachianRegion.pdf

Stroffolini, T., Cotticelli, G., Medda, E., Niosi, M., Del Vecchio-Blanco, C., Addolorato, G., . . . Loguercio, C. (2010). Interaction of alcohol intake and cofactors on the risk of cirrhosis. *Liver International, 30,* 867–870.

Stuart, K. E., Anand, A. J., & Jenkins, R. L. (1996). Hepatocellular carcinoma in the United States. Prognostic features, treatment outcome, and survival. *Cancer, 77,* 2217–2222.

Swan, D., Long, J., Carr, O., Flanagan, J., Irish, H., Keating, S., . . . Cullen, W. (2010). Barriers to and facilitators of hepatitis C testing, management, and treatment among current and former injecting drug users: A qualitative exploration. *AIDS Patient Care and STDs, 24,* 753–762.

Tagger, A., Donato, F., Ribero, M. L., Chiesa, R., Portera, G., Gelatti, U., . . . Nardi, G. (1999). Case-control study on hepatitis C virus (HCV) as a risk factor for hepatocellular carcinoma: The role of HCV genotypes and the synergism with hepatitis B virus and alcohol. *International Journal of Cancer, 81,* 695–699.

Thomas, D. L., Astemborski, J., Rai, R. M., Anania, F. A., Schaeffer, M., Galai, N., . . . Vlahov, D. (2000). The natural history of hepatitis C virus infection: Host, viral, and environmental factors. *Journal of the American Medical Association, 284,* 450–456.

True, W. R., Heath, A. C., Scherrer, J. F., Xian, H., Lin, N., Eisen, S. A., . . . Tsuang, M. T. (1999). Interrelationship of genetic and environmental influences on conduct disorder and alcohol and marijuana dependence symptoms. *American Journal of Medical Genetics, 88,* 391–397.

Tsui, J. I., Vittinghoff, E., Hahn, J. A., Evans, J. L., Davidson, P. J., & Page, K. (2009). Risk behaviors after hepatitis C virus seroconversion in young injection drug users in San Francisco. *Drug and Alcohol Dependence, 105,* 160–163.

van de Laar, T. J. W., Molenkamp, R., van den Berg, C., Schinkel, J., Beld, M. G. H. M., Prins, M., . . . Bruisten, S. M. (2009). Frequent HCV reinfection and superinfection in a cohort of injecting drug users in Amsterdam. *Journal of Hepatology, 51,* 667–674.

Wang, J., Falck, R. S., Li, L., Rahman, A., & Carlson, R. G. (2007). Respondent-driven sampling in the recruitment of illicit stimulant drug users in a rural setting: Findings and technical issues. *Addictive Behaviors, 32,* 924–937.

Watson, B., Conigrave, K. M., Wallace, C., Whitfield, J. B., Wurst, F., & Haber, P. S. (2007). Hazardous alcohol consumption and other barriers to antiviral treatment among hepatitis C positive people receiving opioid maintenance treatment. *Drug and Alcohol Review, 26,* 231–239.

Westin, J., Lagging, L. M., Spak, F., Aires, N., Svensson, E., Lindh, M., . . . Wejstål, R. (2002). Moderate alcohol intake increases fibrosis progression in untreated patients with hepatitis C virus infection. *Journal of Viral Hepatitis, 9,* 235–241.

Wiley, T. E., McCarthy, M., Breidi, L., McCarthy, M., & Layden, T. J. (1998). Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology, 28,* 805–809.

Young, A. M., Crosby, R. A., Oser, C. B., Leukefeld, C. G., Stephens, D. B., & Havens, J. R. (2012). Hepatitis C viremia and genotype distribution among a sample of nonmedical prescription drug users exposed to HCV in rural Appalachia. *Journal of Medical Virology, 84,* 1376–1387.

Young, A. M., & Havens, J. R. (2012). Transition from first illicit drug use to first injection drug use among rural Appalachian drug users: A cross-sectional comparison and retrospective survival analysis. *Addiction, 107,* 587–596.

Zhang, Z., Infante, A., Meit, M., English, N., Dunn, M., & Harper Bowers, K. (2008). *An analysis of mental health and substance abuse disparities & access to treatment services in the Appalachian region.* Retrieved from http://www.arc.gov/assets/research_reports/AnalysisofMentalHealthandSubstanceAbuseDisparities.pdf

Zule, W. A., Costenbader, E. C., Coomes, C. M., & Wechsberg, W. M. (2009). Effects of a hepatitis C virus educational intervention or a motivational intervention on alcohol use, injection drug use, and sexual risk behaviors among injection drug users. *American Journal of Public Health, 99, Supplement 1,* S180–S186.