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Hepatitis C Viremia and Genotype Distribution among a sample of HCV-exposed Nonmedical Prescription Drug Users in Rural Appalachia

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Abstract

Research has demonstrated that hepatitis C (HCV) genotype distribution varies geographically and demographically. This exploratory study examines HCV viremia, viral concentration, and genotype distribution among anti-HCV positive, rural Appalachian nonmedical prescription drug users. The study population was randomly selected from a pool of 200 anti-HCV positive participants in a longitudinal study. Those randomly chosen were representative of the overall pool in terms of demographics, drug use, and other risk behaviors. Participants were tested serologically for HCV RNA, viral concentration, and genotype, and interview-administered questionnaires examined behavioral and demographic characteristics. Of the 81 participants, 69% tested RNA positive, 59% of which had viral loads exceeding 800,000 IU/mL. Approximately 66% of the RNA positive sample had genotype 1a; types 2b (16%) and 3a (13%) were less common. RNA positive participants were not significantly different than RNA negative participants demographically or behaviorally. Likewise, with the exception of education, genotype 1 participants were not significantly different than those with genotype 2 or 3. The prevalence of active HCV infection highlights a need for prevention and treatment in this population. However, the predominance of genotype 1 may present challenges due to its association with decreased responsiveness to drug treatment, although the novel class of direct-acting antivirals such as telaprevir and boceprevir offer new hope in this regard. The prevalence of genotype 1 may also foreshadow heightened burden of hepatocellular carcinoma and elevated healthcare expenditures. More research is needed to characterize HCV infection and genotype in this population.

Keywords

genotype; hepatitis C virus; injection drug use; rural

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Declaration of Competing Interests
The authors declare that they have no competing interests

Introduction

An estimated 3.2 million people in the US have chronic hepatitis C (HCV) infection, making the pathogen the most common chronic blood-borne infection nationwide [Armstrong et al., 2006]. Chronic HCV infection is a strong risk factor for the development of hepatocellular carcinoma (HCC) [Colombo, 1999; Di Bisceglie, 1997; El-Serag and Mason, 2000; Thomas and Seeff, 2005; Tsai et al., 1994] and cirrhosis of the liver [Thomas and Seeff, 2005]. The progression of chronic HCV infection to serious liver disease is associated with age at infection, male gender, immunosuppression, coinfection with HIV and hepatitis B virus (HBV), and heavy alcohol intake [Thomas and Seeff, 2005].

There has been considerable debate regarding differences in pathogenicity and hepatocarcinogenic potential of the various genotypes of HCV [e.g., Brechot, 1997; Bruno et al., 1997; Bruno et al., 2007; Fattovich et al., 2004; Romeo et al., 1996; Sangiovanni & Iavarone, 2008]. A recent meta-analysis of 21 age-corrected studies by Raimondi and colleagues (2009) found increased risk of HCC in patients infected with genotype 1b, with or without the presence of cirrhosis. Unfortunately, many of the studies included are from geographical regions where genotype 1b predominates [Zein, 2000], and there are few studies from HCV genotype 1a-predominant areas for comparison. Other studies have found similar associations with HCC risk for both 1a and 1b subtypes within genotype 1 [Lee et al., 2010; Tanaka & Hirohata, 1998; Zein et al., 1996; Zekri et al., 2000;], and even within genotypes 2a [Han et al., 1997], 3a [Khan et al., 2009], and 4, with no difference between subtypes [Ryu et al., 2009]. However, differences in relative risk reported in some studies may be due to regional differences in genotype prevalence [Haydon et al., 1997; Mangia, 1997; Reid, 1999; Widell, 2000] and/or a cohort effect reflecting confounding age-related and disease-progression variables [Di Tomasso et al., 2003; Lopez-Labrador et al., 1997; Sartori et al., 2006]. Thus while the association between HCV genotype and the severity of hepatic disease remains controversial, a majority of studies have found both subtypes within genotype 1 to confer heightened risk of histopathological damage, concomitant progression to HCC, and to a lesser extent, persistence of infection [Lehmann et al., 2004; Mehta et al., 2002; Strasfeld et al., 2003a; Thomas et al., 2000; Villano et al., 1999].

In addition, those infected with HCV genotype 1 have also shown a diminished sustained virologic response (SVR) to treatment with pegylated interferon-alpha (IFN-α) and ribavirin, and these patients typically require a longer duration and a greater dosage of combination therapy than do genotypes 2 and 3 [Manns et al., 2001; National Digestive Diseases Information Clearinghouse (NDDIC), 2006; Poynard et al., 1998; Scott and Perry, 2002; Shepherd et al., 2004; Zein et al., 1996]. However, the new class of direct-acting antivirals (DAAs) such as telaprevir and boceprevir have enabled a new “triple-therapy” standard-of-care combining the new agents with standard IFN-α and ribavirin therapy[Pawlotsky, 2011; Nelson, 2011]. Several studies have demonstrated improved outcomes and shortened treatment regimes amongst individuals infected with genotype 1 in both previously treated [Bacon et al., 2001; McHutchison, 2010] and untreated [Poordad et al., 2011] cases, with an increase in SVR from 50% up to 70% [Asselah et al., 2010] and even raising the possibility of interferon-free treatment options in the future [Dore et al., 2011]. However, as with ribavirin and IFN-α, DAA therapy is not without its own threat of adverse effects and resistance mutations [Fonseca-Coronado et al., 2011; Fried, 2011; Khalid & Bacon, 2011], and the high cost could present a barrier to uninsured and underinsured patients such as injection drug users (IDUs), who already tend to have significant barriers to HCV treatment [Grebely et al., 2008; Swan et al., 2010].

Despite earlier recommendations to avoid treating only former and recovering IDUs infected with HCV [National Institutes of Health (NIH), 1997], recent evidence suggests that

standard HCV treatment can be successful among active IDUs [e.g. Dore et al., 2010; Hellard et al., 2009; Manolakopoulos et al., 2010; Papadopoulos et al., 2010; Schulte et al., 2010;]. However, in addition to HCV genotype, HCV viral concentration can also impact treatment success. For example, previous evidence has suggested that patients with high HCV RNA concentrations are less responsive to pegylated interferon-alpha (IFN-α) and ribavirin combination therapy [Lam, 1999] and to IFN-α and ribavirin combination therapy [Munir et al., 2010]. Other studies have indicated that patients with high RNA levels, particularly those who are non-responders to other treatment regimens, may be more responsive to consensus interferon [Alberti, 1999; Witthöft, 2008; Witthöft et al., 2007], though there does appear to be some variability in cost effectiveness depending on the intensity of treatment [Sjogren et al., 2007]. The NDDIC suggests that a HCV viral concentration of less than 800,000 IU/mL can determine a better response to IFN-α and ribavirin treatments [NDDIC, 2006].

In addition to the clinical and epidemiological implications, HCV is associated with great economic burden in terms of increased absence from job-related activities and productivity, as well as increased healthcare service utilization and healthcare costs [Davis et al., 2011; DiBonaventura et al., 2010; Su et al., 2010]. In fact, Su and colleagues (2010) found that healthcare-related costs for HCV-infected individuals can be over $8000 per year more than that for non-infected individuals. A study by Grant and colleagues (2005) examining trends in healthcare service utilization for HCV infection in the US found that costs increase considerably with the aging of the HCV-infected population and with HCV disease progression. At this juncture, the authors note that, “as patients continue to age and disease burden progresses, suboptimal decisions regarding HCV treatments will bring increasing opportunity costs for the health care system and society” [Grant et al., 2005, p. 1406]. Moreover, a growing body of evidence suggests that decision-making regarding HCV treatment and its cost-effectiveness will be influenced by HCV RNA concentration and genotype. Higher HCV viral load and infection with genotype 1 have negative impacts on the cost-effectiveness of various treatments regimens [Hartwell et al., 2011; Salomon et al., 2003; Shepherd et al., 2004; Sullivan et al., 2004; Wong et al., 1998; Yeh et al., 2007] and of early intervention strategies [Shepherd et al., 2007]. The issue is complicated further in the active IDU population, in which reinfection following treatment is a serious concern, although the frequency of reinfection in IDUs following SVR to drug therapy is low [Grebely et al., 2010]. Furthermore, using mathematical modeling, Martin and colleagues (2011) have shown that treating active IDUs is more cost-effective than leaving them untreated, provided the prevalence of chronic HCV infection is under 60%.

Substantial geographic and demographic variation can exist in the distribution of HCV genotypes [Blatt et al., 2000; Zein and Rakela, 1996]. HCV genotypes 1a/1b, and to a lesser degree 2b and 3a, are predominant in the US population [Nainan et al., 2006; Zein, 2000; Zein and Rakela, 1996], and HCV genotypes and subtypes within the country vary according to ethnicity and age. In a nationally representative sample, increased age and non-Hispanic black race/ethnicity were associated with an increased likelihood of infection with HCV genotype 1b [Nainan et al., 2006]. Research examining HCV genotype distribution has been used for various purposes, including the identification of populations’ origin of HCV infection [Panduro et al., 2010; Spada et al., 2008], examination of historical trends in characteristics of HCV infection [Magiorkinis et al., 2009], and making inferences regarding routes of HCV transmission [van den Berg et al., 2009; Zein, 2000; Zhou et al., 2009]. In a review of the HCV literature on drug users published between 1989 and 2006, Stern et al. (2008) identified 123 studies which reported genotype distribution [Stern et al., 2008], and in the past two to three years, there has been growing recognition of the value of descriptive studies examining HCV genotype distribution in drug using populations [e.g. Lee et al.; Liao et al., 2011; Micalessi et al., 2008; Sereno et al., 2009; Viazov et al., 2010; Zhou et al.,

2009]. However, nearly all of the existing studies to date have been conducted either outside of the U.S. or in urban populations.

In light of the epidemiologic, clinical, and economic implications of HCV genotypes and their uneven dispersion within certain populations, more research is needed to elucidate the genotype distribution and prevalence of HCV viremia in high-risk, HCV-exposed groups from under-resourced settings in the US. As of 2007, Kentucky had the 7th highest HCV incidence rate in the nation [Daniels et al., 2009], yet the HCV burden has been largely uncharacterized. Given the implications of HCV viremia and genotype on treatment cost-effectiveness, this gap in knowledge can present a major barrier to the planning of HCV intervention strategies in the state's economically distressed region of Appalachia [Appalachian Regional Commission (ARC), 2011], where cost-effectiveness is a paramount consideration in healthcare system decision-making. Efforts to understand the HCV burden in Appalachia are made more relevant by the region's distinguishing burden of drug use. Unlike other populations that have been the focus of other HCV-related studies on drug users, Appalachia drug users are predominantly abusing prescription drugs [Drug Enforcement Agency, 2002; Havens et al., 2007; Young et al., in press], and have distinctive profiles of HCV-related drug risk behavior [Havens et al., 2007; Young and Havens, 2011; Young et al., 2010].

There is emerging evidence that demonstrates that IDUs in Appalachia are indeed much different than IDUs in other populations in terms of their risk behaviors and drug use characteristics. In fact, studies have demonstrated that drug users in Appalachia have substantially different trajectories of drug use than residents of urban areas in Kentucky, with significantly earlier ages of onset for use of oxycodone, hydrocodone, benzodiazepines, cocaine, and crack. Adjusting for age, gender, and race, the rural drug users had higher odds of lifetime and recent nonmedical prescription opioid use (specifically methadone, OxyContin®, and oxycodone) and had higher odds of lifetime cocaine and crack use [Young et al., in press]; the latter of which have been identified to be associated with HCV RNA concentration [Operskalski et al., 2008]. Evidence also demonstrates that compared an urban sample of drug users in the state, rural Appalachian drug users are more likely to use alternative routes of administration (e.g. snorting and injecting) for many drugs. In fact, among the Appalachian participants in one study, snorting was the most frequent route of administration for hydrocodone, methadone, OxyContin®, and oxycodone, and injection was most common for hydromorphone and morphine [Young et al., 2010]. These findings were corroborated by another study which demonstrated that prescription opiate misuse and injection drug use was higher among rural Appalachian probationers compared to their urban counterparts [Havens et al., 2007]. The prevalence of use of alternative routes of administration by drug users in the Appalachian region increases their risk for acquiring HCV and underscores the importance of examining HCV in the population.

A study based on recent retrospective survival analyses of drug users in Appalachia found that this population differs drastically from those involved in other studies of IDUs, and that nonmedical prescription opioid use may be the differentiating factor. OxyContin® was involved in nearly as many initiations to injection (48%) as were stimulants, other prescription opioids, and heroin combined. The rate from which users transitioned from first OxyContin® use to initiation of injection with OxyContin® was extremely fast, just 3 years on average. The sample's nonmedical prescription drug use played a significant role in their hazard for initiating injection, with five prescription drugs (benzodiazepines, illicit methadone, oxycodone, OxyContin® and other opiates) associated with an increased hazard for transitioning, adjusting for demographics characteristics [Young and Havens, in press].

Historically and culturally, there are also reasons to believe that the epidemiological characteristics of HCV in Appalachia could differ from that of other regions in the US. For example, molecular evidence has demonstrated that HCV type 1 was likely first introduced into the US in approximately 1909 and more widely disseminated throughout the US population in the 1960's [Mizokami et al., 2006; Tanaka et al., 2002]. During the diffusion of HCV in the 1960's, the Appalachian region was becoming increasingly recognized as being heavily isolated and distinct from other populations in the US, though efforts were underway to "integrate" and "modernize" its residents [Photiadis and Schwarzweller, 1970; Whisnant, 1980]. The degree to which Appalachian residents were isolated from larger society has been debated [Lewis and Billings, 1997], and the extent to which the isolation continues is not well-established and likely highly variable across communities. Nevertheless, there continues to be sociological and demographic evidence that suggests the region experiences extensive out-migration, but little in-migration of new residents [ARC, 2011; Bell, 2009]. The role that Appalachia's regional isolation and its unique patterns of drug use play in influencing the profile of HCV are speculative, but certainly cause for further investigation. Thus, the purpose of this exploratory study was to (1) assess the prevalence of HCV viremia (i.e. HCV RNA positivity), (2) examine quantitatively the HCV RNA viral concentration, and (3) determine the HCV genotype distribution among a random sample of anti-HCV positive drug users in a rural Appalachian region of Kentucky. Behavioral and demographic correlates to HCV RNA status and genotype were also assessed.

Materials and methods

Study sample

The study sample was randomly-selected from a larger cohort of anti-HCV positive rural Appalachian prescription opioid users involved in the Social Networks among Appalachian People (SNAP) study (N=436). The SNAP study is a longitudinal cohort study seeking to determine the prevalence and incidence of HCV, HIV and herpes simplex-2 virus in the context of rural drug and sex social networks in order to determine the potential for disease transmission in this largely understudied population of illicit prescription drug users. A storefront location in a rural Appalachian town of approximately 5000 residents was used for the SNAP study's participant recruitment and interviews. Participants were recruited using respondent-driven sampling, which is often the most appropriate sampling technique for hidden populations such as drug users [Heckathorn, 1997; Heckathorn, 2002; Wang et al., 2007]. Study recruitment began in November, 2008 and was completed in August, 2010. Eligibility criteria for the study included those who were at least 18 years of age, were residents of an Appalachian county and had used at least one of the following drugs to get high in the prior 30 day period: prescription opioids, heroin, crack/cocaine or methamphetamine. Probing participants to respond only about drugs they used 'to get high' is a lay-language, and more specific adaptation of the language used by the Substance Abuse and Mental Health Services Administration (SAMHSA) in the National Survey of Drug Use and Health, who defines nonmedical prescription drug use as "use of at least one [prescription-type psychotherapeutic] without a prescription belonging to the respondent, or use that occurred simply for the experience or feeling the drug caused [Substance Abuse and Mental Health Services Administration (SAMHSA), 2008]." It should be noted that while the eligibility criteria stated they could have used one of the four aforementioned substances, 100% of those screened and enrolled indicated they had used prescription opioids to get high in the 30 days prior to the screening. An interviewer-administered questionnaire was utilized to determine self-reported behaviors. Data were entered by the interviewers directly onto a touch screen laptop loaded with computer-assisted personal interviewing software. Participants were compensated $50 the baseline and follow-up interviews and $25 to

participate in the genotyping study. The Institutional Review Board at the University of Kentucky approved the protocol and informed consent was obtained from all participants.

At the baseline visit, all participants consented to antibody testing for hepatitis C using the Home Access test for HCV antibody, which uses a third-generation enzyme immunoassay on dried blood spot specimens collected by finger-stick (sensitivity: 98.2%; specificity 99.6%) and has demonstrated accuracy [O'Brien et al., 2001]. The baseline prevalence of anti-HCV was 45.9% (n=200). Tests for HIV and HSV-2 were conducted and currently, no participants were HIV-positive and the baseline seroprevalence for HSV-2 is low (11.5%). Prior to undergoing testing for anti-HCV, HIV and HSV-2, participants were provided with pre-test counseling that included a description of the test, risk factors for HCV, HIV and HSV-2 and the potential test results. After the sample was provided for HCV testing, the test was sent to the reference laboratory for testing using an anonymous PIN number so that only study staff was aware of the results. Results were returned via PIN number within approximately 2 weeks. Participants were asked to return at that time for their test results and were provided with post-test counseling that was tailored to their study result. For example, for those who were anti-HCV positive, counseling was given on how to prevent transmission to others and information was provided on treatment referrals in the area. Rapid testing was conducted for HIV and HSV-2 and results were provided during the baseline visit.

The following procedures were undertaken to ascertain the final sample of 81 participants included in this analysis. First, all participants who were anti-HCV positive at baseline (n=200) were added to a SPSS database. In an attempt to meet the participation goal of at least 100 participants submitting samples, the random selection procedure in SPSS was used to select 160 individuals for recruitment. Recruitment was conducted through phone calls and mailed letters. Of those randomly selected, 23 were unable to participate either due to incarceration out of the area, having moved out of the area, hospitalization, or traveling for work. Of the remaining 137, 84 (61.3%) participated in the study. Non-participants (n=53) included 36 who were unable to be contacted in the short time frame provided to complete the study, one who lacked transportation to the study site, one whose occupation conflicted with the study schedule, seven who confirmed but did not show, and seven for whom a reason was not specified. Participants who presented at the study site completed informed consent and the blood draw and were compensated $25 for their time. From June to July of 2010, 76 individuals presented at the study site to participate and 8 participated while incarcerated in the local jail.

Serological tests for detection of HCV RNA and HCV genotype

Phlebotomists were unable to acquire samples from 3 of the 84 participants, resulting in an overall sample size of 81. Approximately 17mL of blood was drawn from each participant and, following a standard protocol, plasma was separated for HCV RNA testing. Plasma was frozen immediately after centrifugation and was shipped frozen within 48 hours of collection to the performing laboratory (Quest Diagnostics Nichols Institute – Chantilly, VA).

The presence and quantitation of HCV RNA was determined through COBAS® Ampliprep/ COBAS® TaqMan® HCV test kit (Roche Molecular Systems, Inc) using real-time polymerase chain reaction (PCR), transcription-mediated amplification (TMA), and multi-probe reverse hybridization of the 5′ untranslated region (5′ UTR) of the HCV genome. Results were reported in international units per milliliter (IU/mL). HCV RNA-positive specimens (RNA concentration > 5 IU/mL) then underwent testing for HCV genotype and subtype using HCV RNA Genotype, LiPA™ through reverse transcription and PCR (RT-PCR) and reverse hybridization (Line Probe) of the 5′ UTR and core region of the HCV

genome. Genotypes and subtypes detectable by this test include 1, 1a, 1b, 2, 2a/2c, 2b, 3, 3a, 3b, 3c, 4, 4a, 4b, 4c/4d, 4e, 4f, 4h, 5a, and 6a.

Nearly all specimens were of adequate quality and quantity for testing; however, the laboratory was unable to conduct genotyping on one sample due to a low RNA concentration and unable to differentiate HCV subtypes for one other. Thus, the total sample sizes were as follows: HCV RNA (n=81) and HCV genotype (n=80). Participants whose specimen was inadequate for testing were invited to return for re-testing, though none did. An IRB-approved post-test counseling protocol was administered to participants for their HCV RNA and HCV genotype results.

Assessment of demographic and behavioral correlates

At participants' baseline assessment, two true/false items were included to examine respondents' knowledge of the transmissibility of HCV through the sharing of needles and syringes and other injection equipment. Participants' HCV transmission knowledge and their demographic characteristics (see Table 1) were based on their baseline assessment in the study, while behavioral characteristics were extracted from their most recently completed interview (i.e. baseline, 6-month, 12-month, or 18-month interview). The average time which had elapsed between participants' most recent interview date and the date of their blood draw was 51.7 days (SD 41.1; range: 18 – 140).

Statistical Analysis

The randomly selected sample's representativeness of the pool of anti-HCV positive participants was assessed through a series of chi-square tests and independent samples t-tests. Demographic and behavioral correlates to HCV RNA positivity and for infection with HCV genotype 1 versus genotypes 2 and 3 were examined through chi-square tests and independent samples t-tests. Significance on all tests was defined as $p<.05$.

Results

Sample characteristics

Table 1 provides a demographic description of study participants (n=81). The sample was representative of the overall anti-HCV positive pool of individuals (n=200) from which they were drawn. The eighty-one participants did not significantly differ ($p<.05$) from those who did not participate or who were not randomly selected to the study in terms of demographic characteristics (gender, age, education, insurance status), health (self-reported health status, lifetime number of hospitalizations), lifetime number of incarcerations, or HCV risk behaviors (ever having injected drugs, ever having shared equipment for snorting drugs, and ever having received a blood transfusion). The mean age of participants was 35 years (SD 8.3; range 21–53), the vast majority were white (95%) and nearly 60% were male. Factors which could inhibit ability to seek care were common; 38% lacked access to transportation, 36% were unemployed, and 63% were uninsured. Nearly all participants were aware that HCV was transmitted by sharing works (99%) and by sharing needles and syringes (100%). The majority (86%) had a lifetime history of incarceration and 12% had been incarcerated within the last 30 days. Only 56% had a history of drug abuse treatment.

Table 2 describes behavioral characteristics of the sample. Most participants had a history of injection drug use (95%) and of sharing equipment to snort drugs (96%). Over half had engaged in injection drug use within the last 30 days (51%). Between 11–20% of the sample had been involved in some form of recent (<6 months) receptive and/or distributive syringe sharing. Just less than 28% had used alcohol to intoxication within the last 30 days.

Serologic Results

Sixty-nine percent (n = 56) of the sample (which is anti-HCV positive) were positive for HCV RNA. Figure 1 shows the distribution of HCV RNA concentrations for those testing positive for HCV RNA. The HCV RNA concentration ranged from 23 IU/mL to 1.95×10^7 IU/mL, with a median of 9.93×10^5 IU/mL. The viral load for 33 (59%) of the HCV RNA positive participants exceeded what is commonly considered a "low level" of HCV RNA (< 800,000 IU/mL) [NDDIC, 2006].

As shown in Table 1, HCV RNA positive participants were no different than their HCV RNA negative counterparts in terms of demographic characteristics, HCV knowledge, self-reported health status, lifetime hospitalizations, drug abuse treatment history, or lifetime and recent incarceration. Table 2 provides a description of lifetime and recent behavioral characteristics of the overall sample and of those who tested positive for HCV RNA. HCV RNA positive participants were not significantly different than HCV RNA negative participants in regard to their history of blood transfusion, lifetime and recent injection drug use, or needle- and equipment-sharing behaviors. However, an association between RNA positivity and injection drug use in the past 6 months neared significance (OR: 2.40, 95% CI: 0.89 – 6.48; p=.086).

Figure 2 displays the genotype distribution for the sample. Among the 56 people who tested positive for HCV RNA, HCV genotype 1a was most common (n=36, 65.5%), followed by 2b (n=9, 16.4%), and 3a (n=7, 12.7%). Two participants had dual infection with heterologous HCV genotypes (1a/2b and 2b/3a), another had genotype 2 but subtype was unable to be specified, and one participant had a RNA concentration too low to allow genotyping. The HCV RNA concentration for participants with HCV genotype 1 did not differ significantly from participants with genotypes 2 or 3 (p=.366). Participants with HCV genotype 1 (which included hybridized type 1a/2b) were compared to those infected by types 2 and 3 in terms of the demographic or lifetime behavioral characteristics listed in Table 2. Participants who had graduated from high school were more likely to have HCV genotype 1 than were participants who were not high school graduates (OR: 3.41, 95% CI: 1.01 – 11.55, p = .04). None of the other correlates examined had a statistically significant association with genotype (data not shown).

Discussion

Among a random sample of anti-HCV positive prescription drug users drawn from a longitudinal cohort study in Appalachia, the majority (69%) had active HCV infection. HCV RNA positive participants were more likely to have a history of blood transfusion and more likely to have injected drugs in the past 6 months and past 30 days. Significantly more participants who were HCV RNA positive were white and uninsured than those who were HCV RNA negative. HCV genotype 1a was detected in 66% of the HCV RNA positive sample, while types 2b (16%) and 3a (13%) were less common.

The sample's genotype distribution and RNA status have clinical implications. The most prevalent HCV genotype in the sample, type 1, is less responsive to treatment, requires a longer duration and higher dosage of combination therapy [Manns et al., 2001; NDDIC, 2006; Poynard et al., 1998; Scott and Perry, 2002; Zein and Rakela, 1996], and has potential association with higher RNA levels and decreased likelihood of spontaneous clearance of the virus [Berger et al., 1996; Kobayashi et al., 1996]. Also, in the majority of studies HCV genotypes 1a and 1b seem to be more strongly associated with HCC than genotypes 2 and 3 [Raimondi et al., 2009; Tanaka & Hirohata, 1998; Zein et al., 1996;]. The proportion of HCV-positive individuals who would require a long duration of treatment could present an especially difficult situation in rural Appalachia, given marked health and economic

disparities and barriers in access to care. The sample's high RNA concentration may also have implications for treatment [NDDIC, 2006] and prognosis [Hisada et al., 2005]. Ability to extrapolate from the RNA concentration data is limited by the study's cross-sectional design, but it warrants mention that the RNA concentration for 59% of the sample exceeded the range which usually determines a better response to peginterferon and ribavirin treatments (< 800,000 IU/mL) [NDDIC, 2006]. However, new direct acting antivirals boceprevir and telaprevir may mitigate some of the efficacy lost due to heightened viral load in genotype 1-infected individuals [Asselah, 2010; Dore et al., 2011; Nelson, 2011].

The median viral concentration in this sample is nearly double that found other recent studies of injection and non-IDUs [Schulte et al., 2010; Strasfeld et al., 2003a], similar to that found in others [Boodram et al., 2011; Hisada et al., 2005], and lower than that found in HIV co-infected cohorts [Obermeier et al., 2011]. Given the prevalence of high risk behavior in this sample, the findings regarding elevated RNA concentration are not unexpected; previous research has found that HCV viral concentration is positively associated with risky drug use behaviors, including lifetime cocaine, marijuana, amphetamine, or heroin use [Operskalski et al., 2008] and frequency of sharing unclean syringes [Boodram et al., 2011]. The high viral concentration is concerning not only given participants' continued syringe sharing, but also given the prevalence of straw sharing (96%). There is limited evidence to suggest that drug users with high HCV viral loads can have detectable levels of HCV RNA in nasal secretions, which could have consequences for HCV transmissibility through the sharing of straws [McMahon et al., 2004] and other drug preparation equipment [Hagan et al., 2001].

The serological profile of this sample of Appalachian drug users, in some respects, mirrors that of the US general population, and in other ways, is unique. The proportion of anti-HCV positive individuals who tested positive for HCV RNA in our study (69%) was less than that found in a nationally-representative sample (78%) [Nainan et al., 2006]. However, the samples were similar in terms of HCV genotype. Among white, non-Hispanic individuals in the national study, the weighted percentage of HCV RNA positive individuals infected with genotype 1 was 70%, comparable to the prevalence of 66% reported in this study [Nainan et al., 2006]. Similarly, the prevalence of genotypes 1, 2, and 3 in this study were comparable to that found in samples from a large cohort of chronic HCV patients [Blatt et al., 2000]. In terms of subtype, the present study found a higher percentage of individuals infected with type 1a than did the national study or large clinic-based study (66% versus 52% and 39%, respectively) and a lower percentage infected with type 1b (0% versus 27% and 30%, respectively) [Blatt et al., 2000; Nainan et al., 2006]. In the present study, participants with HCV genotype 1 were more likely to have graduated from high school than participants with genotypes 2 and 3, though the difference was marginally significant (p=.04) and the confidence interval was wide. This association between education and genotype remained statistically significant even after controlling for age. The study's finding that HCV genotype 1 was associated with higher educational status is curious. To explore explanations for the association of education and genotype, demographic and behavioral correlates to education were examined. Educational status was positively associated with age (p=.018), but not associated with any other demographic or behavioral variables (data not shown). When analysis of the association between education and genotype was adjusted for age, the association between education and genotype remained statistically significant (OR: 3.87, 95% CI: 1.03 – 14.53). To our knowledge, no other study to date has reported an association between education and genotype, thus further research is necessary to verify and explore this potential association.

The disparity in the subtype findings may be attributed to differences in racial composition of the samples, as type 1b is more common among non-Hispanic blacks. The differences

may also be attributable to the likely infection route for the source populations. Genotypes 1a and 3a are more common among those with a history of injection drug use [Serra et al., 2003; Zein, 2000; Zeuzem et al., 1996], a behavior which characterizes 95% of our sample. Some research has suggested that genotype may be correlated with year of infection [Chlabicz et al., 2008; Pybus et al., 2001; Zeuzem et al., 1996; Zhou et al., 2009], or correspondingly, with the year of the genotype's introduction into the population [Gérard et al., 2005; Katsoulidou et al., 2006]. The vast majority of participants began injecting drugs within the last 15 years, over half between 1995 and 2005, and over a quarter since 2005 (data not shown). The exploratory nature of this study precludes our ability to make inference regarding the mechanisms that produced the identified genotype distribution. However, further research could explore whether the relatively recent initiation of drug-related risk behavior within the sample corresponds with the national, temporal shift in prevalence from genotype 1b to 1a [Nainan et al., 2006].

This study not only contributes to epidemiologic knowledge about HCV in rural Appalachia, but also offers insight for intervention. An alarming proportion of individuals with active HCV infection were engaging in risk behaviors which could promulgate the infection through the study population. Among those with active infection, one in seven had engaged in recent distributive needle sharing (i.e. had sold, returned, or given away a needle after using it). On the flipside, among individuals without active infection (i.e. HCV RNA negative), nearly one in eight had engaged in recent *receptive* needle sharing. This population's involvement in risk behavior is likely not attributable to inadequate knowledge about HCV transmission. In fact, 100% of the sample was aware that HCV could be transmitted through sharing needles and syringes and 99% was aware HCV could be transmitted through sharing other injection equipment.

These findings demonstrate a need for behavioral, clinical, and structural interventions to prevent secondary transmission and increase access to treatment. Intervention may be particularly difficult in rural Appalachia due to a lack of resources. Previous research has shown that syringe exchange programs (SEPs) can substantially decrease risk behavior [Des Jarlais et al., 2005; NIH, 1997, 2002], HCV prevalence [van den Berg et al., 2007], and HCV incidence when coupled with drug treatment [Des Jarlais et al., 2009]. SEPs also provide a strategy for providing drug users with condoms, referrals to substance abuse treatment, and HCV testing and counseling [NIH, 1997, 2002]. Nationally, the implementation of SEPs is difficult due to legal and regulatory restrictions; Kentucky is no exception. While Kentucky does not directly prohibit the establishment of SEPs, statutes regulate the sale and disposal of hypodermic syringes and needles and criminalize the possession of drug paraphernalia [Kentucky Legislative Research Commission (KLRC), 1992; KLRC, 2005]. In addition to regulatory barriers, economic circumstances may impede the implementation of a SEP in the region. According to the Centers for Disease Control and Prevention (CDC), 28% of existing SEPs operate on a budget of less than $25,000, 37% operate on a budget between $25,000 and $100,000, and 35% on budgets greater than $100,000 [Centers for Disease Control and Prevention (CDC), 2005]. Given the impact of chronic HCV infection on quality of life [Bernstein et al., 2002; Foster et al., 1998] and healthcare costs [Davis et al., 2011; DiBonaventura et al., 2010; Su et al., 2010], the cost-effectiveness of a SEP in the region is worth consideration. In lieu of SEPs, behavioral and clinical interventions may be applicable. Peer-driven and other behavioral interventions could also be considered as a way to reduce HCV risk behavior in this population [Garfein et al., 2007; Latka et al., 2008; Sacks-Davis et al., 2011]. Programs and funding to improve residents' access to health care and to drug treatment also could help to prevent and/or mitigate the long-term consequences of HCV infection. Clinical interventions, however, must be coupled with strategies which address structural barriers, such as lack of transportation.

While the study provides foresight into possibilities for intervention in this population, it is not without limitations. The study's reliance on self-report subjects the data to potential information bias, which if present, would likely bias the results toward the null hypothesis and would make the reported findings more conservative than if no bias existed. Like other recent descriptive studies regarding HCV genotype distribution [e.g. Lee et al., 2010; Liao et al., 2011; Micalessi et al., 2008; Sereno et al., 2009; Viazov et al., 2010; Zhou et al., 2009], the study's sample size and cross-sectional design present limitations. Though the sample was drawn randomly from and was representative of a larger pool of HCV antibody positive drug users, the sample's size and homogeny in terms of behavioral and demographic characteristics limits the power to distinguish correlates to HCV RNA positivity and genotype. The cross-sectional design also precludes the ability to make causal inferences and to draw conclusions about dynamics of fluctuation in viral concentration, as well as reinfection, coinfection, and superinfection. The inability of the study to provide more detailed phylogenetic analysis also limits inference about the dynamics of transmission.

Conclusion

Despite limitations, this study provides important insights into a high-risk, under-studied, rural population. The prevalence of active HCV infection and distribution of certain genotypes in this sample of HCV-exposed drug users highlight a need for primary and secondary prevention strategies as well as interventions aimed at increasing access to appropriate treatment. Though more research is needed to determine the underpinning factors associated with HCV infection and subtype distribution within this population, it is clear that a combination of structural, behavioral, and clinical intervention is necessary to mitigate the consequences of HCV in this region with marked health disparities.

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References

Alberti A. Interferon Alfacon-1: a novel interferon for the treatment of chronic hepatitis C. Biodrugs. 1999; 12:343–357. [PubMed: 18031187]

Appalachian Regional Commission. Economic overview of Appalachia 2010. Regional Planning and Research Division; 2011.

Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med. 2006; 144:705–714. [PubMed: 16702586]

Asselah T, Estrabaud E, Bieche I, Lapalus M, De Muynck S, Vidaud M, Saadoun D, Soumelis V, Marcellin P. Hepatitis C: viral and host factors associated with non-response to pegylated interferon plus ribavirin. Liver Int. 2010; 30:1259–1269. [PubMed: 20633102]

Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzum S, Poordad F, Goodman ZD, Sings HL, Boparai N, Burroughs M, Brass CA, Albrecht JK, Esteban R. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011; 364:1207–1217. [PubMed: 21449784]

Beld M, Penning M, Lukashov V, McMorrow M, Roos M, Pakker N, van den Hoek A, Goudsmit J. Evidence that both HIV and HIV-induced immunodeficiency enhance HCV replication among HCV seroconverters. Virology. 1998; 244:504–512. [PubMed: 9601518]

Bell SE. There ain't no bond in town like there used to be": the destruction of social capital in the West Virginia coalfields. Sociol Forum. 2009; 24:631–657.

Berger A, von Depka Prondzinski M, Doerr H, Rabenau H, Weber B. Hepatitis C plasma viral load is associated with HCV genotype but not with HIV coinfection. J Med Virol. 1996; 48:339–343. [PubMed: 8699166]

Bernstein D, Kleinman N, Barker C, Revicki D, Green J. Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients. Hepatology. 2002; 35:704–708. [PubMed: 11870387]

Blatt LM, Mutchnick MG, Tong MJ, Klion FM, Lebovics E, Freilich B, Bach N, Smith C, Herrera J, Tobias H, Conrad A, Schmid P, McHutchison JG. Assessment of hepatitis C virus RNA and genotype from 6807 patients with chronic hepatitis C in the United States. J Viral Hepat. 2000; 7:196–202. [PubMed: 10849261]

Boodram B, Herschow R, Cotler S, Ouellet L. Chronic hepatitis C virus infection and increases in viral load in a prospective cohort of young, HIV-uninfected injection drug users. Drug Alcohol Depend. 2011; 119:166–171. [PubMed: 21724339]

Brechot C. Hepatitis C virus 1b, cirrhosis, and hepatocellular carcinoma. Hepatology. 1997; 25:772–774. [PubMed: 9049234]

Bruno S, Crosignani A, Maisonneuve P, Rossi S, Silini E, Mondelli MU. Hepatitis C virus genotype 1b as a major risk factor associated with hepatocellular carcinoma in patients with cirrhosis: a seventeen-year prospective cohort study. Hepatology. 2007; 46:1350–1356. [PubMed: 17680653]

Bruno S, Silini E, Crosignani A, Borzio F, Leandro G, Bono F, Asti M, Rossi S, Larghi A, Cerino A, Podda M, Mondelli MU. Hepatitis C virus genotypes and risk of hepatocellular carcinoma in cirrhosis: a prospective study. Hepatology. 1997; 25:754–758. [PubMed: 9049231]

Centers for Disease Control and Prevention. Update: syringe exchange programs -- United States, 2002. MMWR. 2005:54.

Chlabicz S, Flisiak R, Kowalczuk O, Grzeszczuk A, Pytel-Krolczuk B, Prokopowicz D, Chyczewski L. Changing HCV genotypes distribution in Poland—relation to source and time of infection. J Clin Virol. 2008; 42:156–159. [PubMed: 18353714]

Colombo M. Hepatitis C virus and hepatocellular carcinoma. Best Pract Res Clin Gastroenterol. 1999; 13:519–528.

Daniels D, Grytdal S, Wasley A. Surveillance for acute viral hepatitis -- United States, 2007. MMWR Surveillance Summaries. 2009; 58:1–27.

Davis K, Mitra D, Medjedovic J, Beam C, Rustgi VK. Direct economic burden of chronic hepatitis C virus in a United States managed care population. J Clin Gastroenterol. 2011; 45:17–24.

Des Jarlais DC, McKnight C, Goldblatt C, Purchase D. Doing harm reduction better: syringe exchange in the United States. Addiction. 2009; 104:1441–1446. [PubMed: 19215605]

Des Jarlais DC, Perlis T, Arasteh K, Torian LV, Hagan H, Beatrice S, Smith L, Wethers J, Milliken J, Mildvan D, Yancovitz S, Friedman SR. Reductions in hepatitis C virus and HIV infections among injecting drug users in New York City, 1990–2001. AIDS. 2005; 19(Suppl 3):S20–S25. [PubMed: 16251819]

Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. Hepatology. 1997; 26:34S–38S. [PubMed: 9305661]

DiBonaventura M, Wagner J, Yuan Y, L'Italien G, Langley P, Ray Kim W. Humanistic and economic impacts of hepatitis C infection in the United States. J Med Econ. 2010; 13:709–718. [PubMed: 21091098]

Di Tommaso L, Macchia S, Morandi L, Leoncini S, Pession A, Dal Monte PR, Foschini MP. Correlation between histologic staging, hepatitis C virus genotypes and clinical features in HCV chronic hepatitis: evidence of a new pattern. Int J Surg Pathol. 2003; 11:197–204. [PubMed: 12894351]

Dore GJ, Matthews GV, Rockstroh J. Future of hepatitis C therapy: development of direct-acting antivirals. Curr Opin HIV AIDS. 2011; 6:508–513. [PubMed: 21897228]

Dore GJ, Hellard M, Matthews GV, Grebely J, Haber PS, Petoumenos K, Yeung B, Marks P, van Beek I, McCaughan G, White P, French R, Rawlinson W, Lloyd AR, Kaldor JM. Australian Trial

In Acute Hepatitis C Study Group. Effective treatment of injecting drug users with recently acquired hepatitis C virus infection. Gastroenterology. 2010; 138:123–135. [PubMed: 19782085]

Drug Enforcement Administration. OxyContin: Pharmaceutical Diversion. Mar. 2002 Drug Intelligence Brief.

El-Serag HB, Mason AC. Risk factors for the rising rates of primary liver cancer in the United States. Arch Intern Med. 2000; 160:3227–3230. [PubMed: 11088082]

Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology. 2004; 127:S35–50. [PubMed: 15508101]

Ferenci P, Reddy KR. Impact of HCV protease-inhibitor-based triple therapy for chronic HCV genotype 1 infection. Antivir Ther. 2011; 16:1187–1201. [PubMed: 22155901]

Fonseca-Coronado S, Escobar-Gutierrez A, Ruiz-Tovar K, Cruz-Rivera MY, Rivera-Osorio P, Vazquez-Pichardo M, Carpio-Pedroza JC, Ruiz-Pacheco JA, Cazares F, Vaughan G. Specific Detection of Naturally Occurring Telaprevir and Boceprevir (Protease Inhibitors) HCV Resistant Mutants among Treatment Naive Infected Individuals. J Clin Microbiol. 2011 [Epub ahead of print; Nov 23, 2011].

Foster G, Goldin R, Thomas H. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. Hepatology. 1998; 27:209–212. [PubMed: 9425939]

Fried MW. The role of triple therapy in HCV genotype 1-experienced patients. Liv Int. 2011; 31(Suppl 1):58–61.

Garfein RS, Golub ET, Greenberg AE, Hagan H, Hanson DL, Hudson SM, Kapadia F, Latka MH, Ouellet LJ, Purcell DW, Strathdee SA, Thiede H. A peer-education intervention to reduce injection risk behaviors for HIV and hepatitis C virus infection in young injection drug users. AIDS. 2007; 21:1923–1932. [PubMed: 17721100]

Gérard C, Delwaide J, Vaira D, Bastens B, Servais Bt, Wain E, Bataille C, Daenen G, Belaïche J. Evolution over a 10 year period of the epidemiological profile of 1,726 newly diagnosed HCV patients in Belgium. J Med Virol. 2005; 76:503–510. [PubMed: 15977247]

Grant WC, Jhaveri RR, McHutchison JG, Schulman KA, Kauf TL. Trends in health care resource use for hepatitis C virus infection in the United States. Hepatology. 2005; 42:1406–1413. [PubMed: 16317670]

Grebely J, Conway B, Raffa JD, Lai C, Krajden M, Tyndall MW. Hepatitis C virus reinfection in injection drug users. Hepatology. 2006; 44:1139–1145. [PubMed: 17058216]

Grebely J, Genoway KA, Raffa JD, Dhadwal G, Rajan T, Showler G, Kalousek K, Duncan F, Tyndall MW, Fraser C, Conway B, Fischer B. Barriers associated with the treatment of hepatitis C virus infection among illicit drug users. Drug Alcohol Depend. 2008; 93:141–147. [PubMed: 17997050]

Grebely J, Knight E, Ngai T, Genoway KA, Raffa JD, Storms M, Gallagher L, Krajden M, Dore GJ, Duncan F, Conway B. Reinfection with hepatitis C virus following sustained virological response in injection drug users. J Gastroenterol Hepatol. 2010; 25:1281–1284. [PubMed: 20594256]

Hagan H, Thiede H, Weiss NS, Hopkins SG, Duchin JS, Alexander ER. Sharing of drug preparation equipment as a risk factor for hepatitis C. Am J Public Health. 2001; 91:42–46. [PubMed: 11189822]

Han CJ, Lee HS, Kim HS, Choe JH, Kim CY. Hepatitis C virus genotypes in Korea and their relationship to clinical outcome in type C chronic liver diseases. Korean J Intern Med. 1997; 12:21–27. [PubMed: 9159033]

Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. Health Technol Assess. 2011; 15:1–210.

Havens JR, Oser CB, Leukefeld CG, Webster J, Martin S, O'Connell D, Surratt H, Inciardi J. Differences in prevalence of prescription opiate misuse among rural and urban probationers. Am J Drug Alcohol Abuse. 2007; 33:309–317. [PubMed: 17497554]

Haydon GH, Jarvis LM, Simmonds P, Harrison DJ, Garden OJ, Hayes PC. Association between chronic hepatitis C infection and hepatocellular carcinoma in a Scottish population. Gut. 1997; 40:128–132. [PubMed: 9155590]

Heckathorn D. Respondent-driven sampling: A new approach to the study of hidden populations. Soc Probl. 1997; 44:174–179.

Heckathorn D. Respondent-driven sampling II: Deriving valid population estimates from chain-referral samples of hidden populations. Soc Probl. 2002; 49:11–34.

Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clin Infect Dis. 2009; 49:561–573. [PubMed: 19589081]

Hisada M, Chatterjee N, Kalaylioglu Z, Battjes RJ, Goedert JJ. Hepatitis C virus load and survival among injection drug users in the United States. Hepatology. 2005; 42:1446–1452. [PubMed: 16317675]

Katsoulidou A, Sypsa V, Tassopoulos NC, Boletis J, Karafoulidou A, Ketikoglou I, Tsantoulas D, Vafiadi I, Hatzis G, Skoutelis A, Akriviadis E, Vasiliadis T, Kitis G, Magiorkinis G, Hatzakis A. Molecular epidemiology of hepatitis C virus (HCV) in Greece: temporal trends in HCV genotype-specific incidence and molecular characterization of genotype 4 isolates. J Viral Hepat. 2006; 13:19–27. [PubMed: 16364078]

Kentucky Legislative Research Commission. [Accessed on February 6, 2011] Definitions for KRS 218A.500 and 218A.510 -- unlawful practices--penalties, KRS 218A.500(1992). 1992. at http://www.lrc.ky.gov/krs/218a00/500.PDF

Kentucky Legislative Research Commission. [Accessed on February 6, 2011] Sale and disposal of hypodermic syringes or needles, KRS 217.177(2005). 2005. at http://law.justia.com/kentucky/codes/2009/217-00/pdf/177.pdf

Khalid O, Bacon BR. Management of the treatment-experienced patient infected with hepatitis C virus genotype 1: options and considerations. Clin Liver Dis. 2011; 15:573–583. [PubMed: 21867937]

Khan A, Tanaka Y, Azam Z, Abbas Z, Kurbanov F, Saleem U, Hamid S, Jafri W, Mizokami M. Epidemic spread of hepatitis C virus genotype 3a and relation to high incidence of hepatocellular carcinoma in Pakistan. J Med Virol. 2009; 81:1189–1197. [PubMed: 19475617]

Kobayashi M, Tanaka E, Sodeyama T, Urushihara A, Matsumoto A, Kiyosawa K. The natural course of chronic hepatitis C: a comparison between patients with genotypes 1 and 2 hepatitis C viruses. Hepatology. 1996; 23:695–699. [PubMed: 8666319]

Lam N. Clinical review. Hepatitis C: natural history, diagnosis, and management. Am J Health Syst Pharm. 1999; 56:961–976. [PubMed: 10365720]

Latka MH, Hagan H, Kapadia F, Golub ET, Bonner S, Campbell J, Coady M, Garfein RS, Pu M, Thomas DL, Thiel T, Strathdee SA. A randomized intervention trial to reduce the lending of used injection equipment among injection drug users infected with hepatitis C. Am J Public Health. 2008; 98:853–861. [PubMed: 18382005]

Lee MH, Yang HI, Lu SN, Jen CL, Yeh SH, Liu CJ, Chen PJ, You SL, Wang LY, Chen WJ, Chen CJ. Hepatitis C virus seromarkers and subsequent risk of hepatocellular carcinoma: long-term predictors from a community-based cohort study. J Clin Oncol. 2010; 28:4587–4593. [PubMed: 20855826]

Lee Y-M, Lin H-J, Chen Y-J, Lee C-M, Wang S-F, Chang K-Y, Chen T-L, Liu H-F, Chen Y-MA. Molecular epidemiology of HCV genotypes among injection drug users in Taiwan: Full-length sequences of two new subtype 6w strains and a recombinant form_2b6w. J Med Virol. 2010; 82:57–68. [PubMed: 19950240]

Lehmann M, Meyer MF, Monazahian M, Tillmann HL, Manns MP, Wedemeyer H. High rate of spontaneous clearance of acute hepatitis C virus genotype 3 infection. J Med Virol. 2004; 73:387–391. [PubMed: 15170633]

Lewis R, Billings D. Appalachian culture and economic development: A retrospective view on the theory and literature. Journal of Appalachian Culture. 1997; 3:3–42.

Liao K-F, Lai S-W, Lin C-Y, Huang C-H, Lin Y-Y. Diversity of hepatitis C virus genotypes among intravenous heroin users in Taiwan. Am J Med Sci. 2011; 341:110–112. [PubMed: 20924285]

Lopez-Labrador FX, Ampurdanes S, Forns X, Castells A, Saiz JC, Costa J, Bruix J, Sanchez Tapias JM, Jimenez de Anta MT, Rodes J. Hepatitis C virus (HCV) genotypes in Spanish patients with HCV infection: relationship between HCV genotype 1b, cirrhosis and hepatocellular carcinoma. J Hepatol. 1997; 27:959–965. [PubMed: 9453419]

Magiorkinis G, Magiorkinis E, Paraskevis D, Ho SYW, Shapiro B, Pybus OG, Allain J-P, Hatzakis A. The global spread of hepatitis C virus 1a and 1b: a phylodynamic and phylogeographic analysis. PLoS Med. 2009; 6:1–12.

Mangia A, Cascavilla I, Lezzi G, Spirito F, Maertens G, Parlatore L, Saracco G, Rizzeto M, Andriulli A. HCV genotypes in patients with liver disease of different stages and severity. J Hepatol. 1997; 26:1173–1178. [PubMed: 9210601]

Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Mei-Hsiu L, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001; 358:958–965. [PubMed: 11583749]

Manolakopoulos S, Deutsch M, Anagnostou O, Karatapanis S, Tiniakou E, Papatheodoridis G, Georgiou E, Manesis E, Tzourmakliotis D, Archimandritis A. Substitution treatment or active intravenous drug use should not be contraindications for antiviral treatment in drug users with chronic hepatitis C. Liver Int. 2010; 2010:10.

Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. Hepatology. 2011 [Epub ahead of print; Sep 2, 2011].

McHutchison JG, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhal NH, Heathcote EJ, Zeuzem S, Reesink HW, Garg J, Bsharat M, George S, Kauffman RS, Adda N, Di Bisceglie AM. Telaprevir for previously treated chronic HCV infection. N Engl J Med. 2010; 362:1292–1303. [PubMed: 20375406]

McMahon JM, Simm M, Milano D, Clatts M. Detection of hepatitis C virus in the nasal secretions of an intranasal drug-user. Ann Clin Microbiol Antimicrob. 2004; 3:6. [PubMed: 15132748]

Mehta SH, Cox A, Hoover DR, Xiao-Hong W, Qing M, Ray S, Strathdee SA, Vlahov D, Thomas DL. Protection against persistence of hepatitis C. Lancet. 2002; 359:1478. [PubMed: 11988247]

Micalessi MI, Gérard C, Ameye L, Plasschaert S, Brochier B, Vranckx R. Distribution of hepatitis C virus genotypes among injecting drug users in contact with treatment centers in Belgium, 2004–2005. J Med Virol. 2008; 80:640–645. [PubMed: 18297717]

Mizokami M, Tanaka Y, Miyakawa Y. Spread times of hepatitis C virus estimated by the molecular clock differ among Japan, the United States, and Egypt in reflections of their distinct socioeconomic backgrounds. Intervirology. 2006; 49:28–36. [PubMed: 16166786]

Munir S, Saleem S, Idrees M, Tariq A, Butt S, Rauff B, Hussain A, Badar S, Naudhani M, Fatima Z, Ali M, Ali L, Akram M, Aftab M, Khubaib B, Awan Z. Hepatitis C treatment: current and future perspectives. Virol J. 2010; 7:296. [PubMed: 21040548]

Nainan OV, Alter MJ, Kruszon-Moran D, Gao F-X, Xia G, McQuillan G, Margolis HS. Hepatitis C virus genotypes and viral concentrations in participants of a general population survey in the United States. Gastroenterology. 2006; 131:478–484. [PubMed: 16890602]

National Digestive Diseases Information Clearinghouse (NDDIC). NIH Publication No 07-4230. 2006. Chronic hepatitis C: Current disease management.

National Institutes of Health. Management of Hepatitis C. NIH Consens Statement. 1997; 15:1–41.

National Institutes of Health. NIH Consensus Statement on Management of Hepatitis C: 2002. NIH Consens State Sci Statements. 2002; 19:1–46.

Nelson DR. The role of triple therapy with protease inhibitors in hepatitis C virus genotype 1 naive patients. Liver Int. 2011; 31(Suppl 1):53–7. [PubMed: 21205138]

O'Brien J, Kruzel K, Wandell M, Vinogradov I, Sheagren J, Frank A. Detection of Hepatitis C antibody with at-home collection kits using an innovative laboratory algorithm. Infect Dis Clin Pract. 2001; 10:474–480.

Obermeier M, Inqiliz P, Weitner L, Cordes C, Moll A, Hinsche B, Schlote F, Koeppe S, Christensen S, Mayr C, Baumgarten A. Acute hepatitis C in persons infected with the human immunodeficiency virus (HIV): the 'real-life setting' proves the concept. Eur J Med Res. 2011; 16:237–242. [PubMed: 21719398]

Operskalski EA, Mack WJ, Strickler HD, French AL, Augenbraun M, Tien PC, Villacres MC, Spencer LY, Degiacomo M, Kovacs A. Factors associated with hepatitis C viremia in a large cohort of HIV-infected and -uninfected women. J Clin Virol. 2008; 41:255–263. [PubMed: 18243785]

Panduro A, Roman S, Khan A, Tanaka Y, Kurbanov F, Martinez-Lopez E, Campollo O, Hernandez-Nazara Z, Mizokami M. Molecular epidemiology of hepatitis C virus genotypes in West Mexico. Virus Res. 2010; 151:19–25. [PubMed: 20347896]

Papadopoulos V, Gogou A, Mylopoulou T, Mimidis K. Should active injection drug users receive treatment for chronic hepatitis C? Arq Gastroenterol. 2010; 47:238–241. [PubMed: 21140082]

Pawlotsky JM. The results of Phase III clinical trials with telaprevir and boceprevir presented at the Liver Meeting 2010: a new standard of care for hepatitis C virus genotype 1 infection, but with issues still pending. Gastroenterology. 2011; 140:746–754. [PubMed: 21255572]

Photiadis, J.; Schwarzweller, H., editors. Change in Rural Appalachia: implications for action programs. Philadelphia: University of Pennsylvania Press; 1970.

Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011; 364:1195–1206. [PubMed: 21449783]

Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, Bain V, Heathcote J, Zeuzem S, Trepo C, Albrecht J. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet. 1998; 352:1426–1432. [PubMed: 9807989]

Pybus OG, Charleston MA, Gupta S, Rambaut A, Holmes EC, Harvey PH. The epidemic behavior of the hepatitis C virus. Science. 2001; 292:2323–2325. [PubMed: 11423661]

Raimondi S, Bruno S, Mondelli MU, Maisonneuve P. Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: A meta-analysis. J Hepatol. 2009; 50:1142–1154. [PubMed: 19395111]

Reid AE, Koziel MJ, Aiza I, Jeffers L, Reddy R, Schiff E, Lau JY, Dienstag JL, Liang TJ. Hepatitis C virus genotypes and viremia and hepatocellular carcinoma in the United States. Am J Gastroenterol. 1999; 94:1619–1626. [PubMed: 10364034]

Romeo R, Colombo M, Rumi M, Soffredini R, Del Ninno E, Donato MF, Russo A, Simmonds P. Lack of association between type of hepatitis C virus, serum load and severity of liver disease. J Viral Hepat. 1996; 3:183–190. [PubMed: 8871879]

Ryu SH, Fan X, Xu Y, Elbaz T, Zekri AR, Abdelazziz AO, Di Bisceglie AM. Lack of association between genotypes and subtypes of HCV and occurrence of hepatocellular carcinoma in Egypt. J Med Virol. 2009; 81:844–847. [PubMed: 19319951]

Sacks-Davis R, Horyniak D, Grebely J, Hellard M. Behavioural interventions for preventing hepatitis C infection in people who inject drugs: A global systematic review. Int J Drug Policy. 2011 [Epub ahead of print; Oct 12, 2011].

Salomon J, Weinstein M, Hammitt J, Goldie S. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. JAMA. 2003; 290:228–237. [PubMed: 12851278]

Sangiovanni A, Iavarone M. Hepatitis C virus genotype 1b, cirrhosis, and risk of hepatocellular carcinoma. Hepatology. 2008; 47:357. [PubMed: 18161732]

Sartori M, Andorno S, Avogadro E, Ballare M, La Terra G, Leone F, Quaglia V, Fortina G, Aglietta M. High prevalence of hepatitis C virus (HCV) genotype 2 in Italian patients with chronic liver disease. Ital J Gastroenterol. 1996; 28:452–456. [PubMed: 9032588]

Schulte B, Schütt S, Brack J, Isernhagen K, Deibler P, Dilg C, Verthein U, Haasen C, Reimer J. Successful treatment of chronic hepatitis C virus infection in severely opioid-dependent patients under heroin maintenance. Drug Alcohol Depend. 2010; 109:248–251. [PubMed: 20167441]

Scott LJ, Perry CM. Interferon-alpha-2b plus ribavirin: a review of its use in the management of chronic hepatitis C. Drugs. 2002; 62:507–556. [PubMed: 11827565]

Sereno S, Perinelli P, Laghi V. Changes in the prevalence of hepatitis C virus genotype among Italian injection drug users: Relation to period of injection started. J Clin Virol. 2009; 45:354–357. [PubMed: 19497783]

Serra MA, Rodríguez F, del Olmo JA, Escudero A, Rodrigo JM. Influence of age and date of infection on distribution of hepatitis C virus genotypes and fibrosis stage. J Viral Hepat. 2003; 10:183–188. [PubMed: 12753336]

Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J. Pegylated interferon alpha-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation. Health Technol Assess. 2004; 8:1–125.

Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. Health Technol Assess. 2007; 11:1–205. [PubMed: 17346498]

Sjogren M, Sjogren RJ, Lyons M, Ryan M, Santoro J, Smith C, Reddy K, Bonkovsky H, Huntley B, Faris-Young S. Antiviral response of HCV genotype 1 to consensus interferon and ribavirin versus pegylated interferon and ribavirin. Dig Dis Sci. 2007; 52:1540–1547. [PubMed: 17406822]

Spada E, Abbate I, Sicurezza E, Mariano A, Parla V, Rinnone S, Cuccia M, Capobianchi MR, Mele A. Molecular epidemiology of a hepatitis C virus outbreak in a hemodialysis unit in Italy. J Med Virol. 2008; 80:261–267. [PubMed: 18098132]

Stern RK, Hagan H, Lelutiu-Weinberger C, Jarlais DD, Scheinmann R, Strauss S, Pouget ER, Flom P. The HCV Synthesis Project: scope, methodology, and preliminary results. BMC Med Res Methodol. 2008; 8:62. [PubMed: 18789163]

Strasfeld L, Lo Y, Netski D, Thomas DL, Klein RS. The association of hepatitis C prevalence, activity, and genotype with HIV infection in a cohort of New York City drug users. J Acquir Immune Defic Syndr. 2003a; 33:356–364. [PubMed: 12843747]

Su J, Brook R, Kleinman N, Corey-Lisle P. The impact of hepatitis C virus infection on work absence, productivity, and healthcare benefit costs. Hepatology. 2010; 52:436–442. [PubMed: 20683943]

Substance Abuse and Mental Health Administration. 2007 National Survey on Drug Use and Health: National results. Rockville, MD: Office of Applied Studies; 2008.

Sullivan S, Jensen D, Bernstein D, Hassanein T, Foster G, Lee S, Cheinquer H, Craxi A, Cooksley G, Klaskala W, Pettit K, Patel K, Green J. Cost-effectiveness of combination peginterferon alpha-2a and ribavirin compared with interferon alpha-2b and ribavirin in patients with chronic hepatitis C. Am J Gastroenterol. 2004; 99:1490–1496. [PubMed: 15307866]

Swan D, Long J, Carr O, Flanagan J, Irish H, Keating S, Keaveney M, Lambert J, McCormick PA, McKiernan S, Moloney J, Perry N, Cullen W. Barriers to and facilitators of hepatitis C testing, management, and treatment among current and former injecting drug users: a qualitative exploration. AIDS Patient Care STDs. 2010; 24:753–762. [PubMed: 21138381]

Tanaka K, Hirohata T. Relationship of hepatitis C virus genotypes and viremia levels with development of hepatocellular carcinoma among Japanese. Fukuoka Igaku Zasshi. 1998; 89:238–248. [PubMed: 9778916]

Tanaka Y, Hanada K, Mizokami M, Yeo A, Shih JW, Gojobori T, Alter HJ. A comparison of the molecular clock of hepatitis C virus in the United States and Japan predicts that hepatocellular carcinoma incidence in the United States will increase over the next two decades. Proceeds of the National Academy of Sciences. 2002; 99:15584–15589.

Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, Bolt K, Nelson KE, Strathdee SA, Johnson L, Laeyendecker O, Boitnott J, Wilson LE, Vlahov D. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA. 2000; 284:450–456. [PubMed: 10904508]

Thomas DL, Seeff LB. Natural history of hepatitis C. Clinics In Liver Disease. 2005; 9:383. [PubMed: 16023972]

Thomas DL, Shih JW, Alter HJ, Vlahov D, Cohn S, Hoover DR, Cheung L, Nelson KE. Effect of human immunodeficiency virus on hepatitis C virus infection among injecting drug users. J Infect Dis. 1996; 174:690–695. [PubMed: 8843204]

Toyoda H, Fukuda Y, Hayakawa T, Takayama T, Kumada T, Nakano S, Takamatsu J, Saito H. Characteristics of patients with chronic infection due to hepatitis c virus of mixed subtype: prevalence, viral RNA concentrations, and response to interferon therapy. Clin Infect Dis. 1998; 26:440–445. [PubMed: 9502468]

Tsai JF, Chang WY, Jeng JE, Ho MS, Lin ZY, Tsai JH. Effects of hepatitis C and B viruses infection on the development of hepatocellular carcinoma. J Med Virol. 1994; 44:92–95. [PubMed: 7528262]

van den Berg C, Smit C, van Brussel G, Coutinho R, Prins M. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C

virus: evidence from the Amsterdam Cohort Studies among drug users. Addiction. 2007; 102:1454–1462. [PubMed: 17697278]

van den Berg CH, van de Laar TJ, Kok A, Zuure FR, Coutinho RA, Prins M. Never injected, but hepatitis C virus-infected: a study among self-declared never-injecting drug users from the Amsterdam Cohort Studies. J Viral Hepat. 2009; 16:568–577. [PubMed: 19243497]

Viazov S, Ross SS, Kyuregyan KK, Timm J, Neumann-Haefelin C, Isaeva OV, Popova OE, Dmitriev PN, El Sharkawi F, Thimme R, Michailov MI, Roggendorf M. Hepatitis C virus recombinants are rare even among intravenous drug users. J Med Virol. 2010; 82:232–238. [PubMed: 20029799]

Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. Hepatology. 1999; 29:908–914. [PubMed: 10051497]

Wang J, Falk RS, Li L, Rahman A, Carlson RG. Respondent-driven sampling in the recruitment of illicit stimulant drug users in a rural setting: Findings and technical issues. Addict Behav. 2007; 32:924–937. [PubMed: 16901654]

Whisnant, D. Modernizing the mountaineer: people, power, and planning in Appalachia. Boone, NC: Appalachian Consortium Press; 1980.

Widell A, Verbaan H, Wejstal R, Kaczynski J, Kidd-Ljunggren K, Wallerstedt S. Hepatocellular carcinoma in Sweden: its association with viral hepatitis, especially with hepatitis C viral genotypes. Scand J Infect Dis. 2000; 32:147–152. [PubMed: 10826899]

Witthöft T. Review of consensus interferon in the treatment of chronic hepatitis C. Biologics. 2008; 2:635–643. [PubMed: 19707444]

Witthöft T, Fuchs M, Ludwig D. Recent i.v.-drug users with chronic hepatitis C can be efficiently treated with daily high dose induction therapy using consensus interferon: an open-label pilot study. World J Gastroenterol. 2007; 28:579–584.

Wong J, Bennett W, Koff R, Pauker S. Pretreatment evaluation of chronic hepatitis C: risks, benefits, and costs. JAMA. 1998; 280:2088–2093. [PubMed: 9875876]

Yeh W, Armstrong E, Skrepnek G, Malone D. Peginterferon alfa-2a versus peginterferon alfa-2b as initial treatment of hepatitis C virus infection: a cost-utility analysis from the perspective of the Veterans Affairs Health Care System. Pharmacotherapy. 2007; 27:813–824. [PubMed: 17542764]

Young AM, Havens JR. 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. 2011 [Epub ahead of print; Aug 28, 2011].

Young AM, Havens JR, Leukefeld CG. Route of administration for illicit prescription opioids: a comparison of rural and urban drug users. Harm Reduct J. 2010; 7:24. [PubMed: 20950455]

Young AM, Havens JR, Leukefeld CG. A comparison of rural and urban nonmedical prescription opioid users' lifetime and recent drug use. Am J Drug Alcohol Abuse. (in press).

Zein NN. Clinical significance of hepatitis C virus genotypes. Clin Microbiol Rev. 2000; 13:223–235. [PubMed: 10755999]

Zein NN, Rakela J, Krawitt EL, Reddy KR, Tominaga T, Persing DH. Hepatitis C virus genotypes in the United States: epidemiology, pathogenicity, and response to interferon therapy. Collaborative Study Group. Ann Intern Med. 1996; 125:634–639. [PubMed: 8849147]

Zekri AR, Bahnassy AA, Shaarawy SM, Mansour OA, Maduar MA, Khaled HM, El-Ahmadi O. Hepatitis C virus genotyping in relation to neu-oncoprotein overexpression and the development of hepatocellular carcinoma. J Med Microbiol. 2000; 49:89–95. [PubMed: 10628830]

Zeuzem S, Teuber G, Lee JH, Rüster B, Roth WK. Risk factors for the transmission of hepatitis C. J Hepatol. 1996; 24:3–10. [PubMed: 8836883]

Zhou Y, Wang X, Mao Q, Fan Y, Zhu Y, Zhang X, Lan L, Jiang L, Tan W. Changes in modes of hepatitis C infection acquisition and genotypes in southwest China. J Clin Virol. 2009; 46:230–233. [PubMed: 19729342]

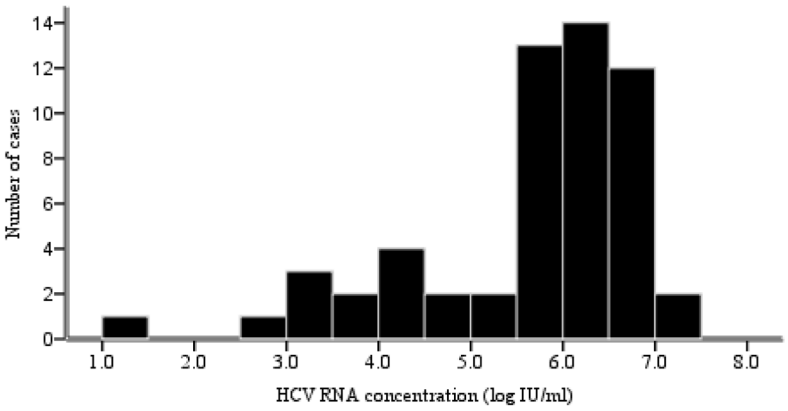

Figure 1.

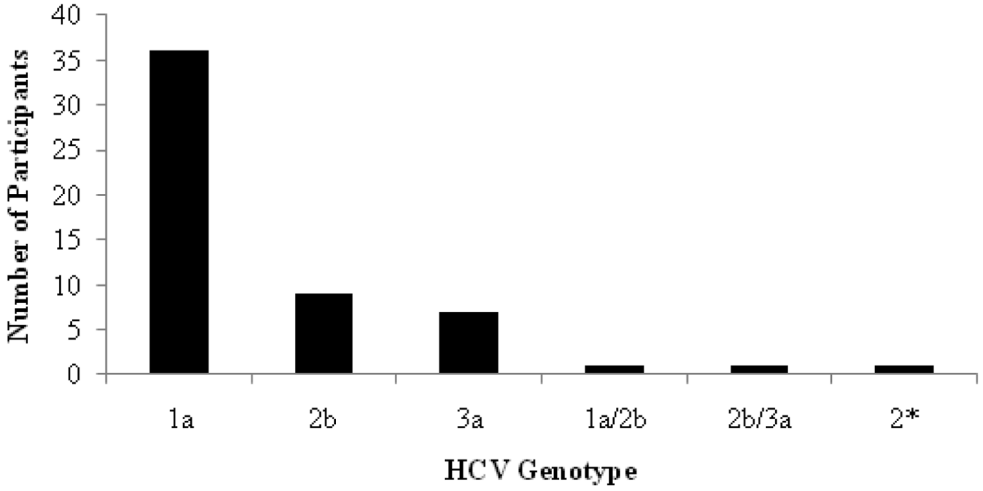

Figure 2.

Table 1

Demographic and behavioral characteristics of sample (n=81)

Characteristic	Total N (%)	HCV RNA+ (n=56) n(%)	HCV RNA− (n=25) n(%)	OR (95% CI)	p-value
Male	48 (59.3)	31 (55.4)	17 (68.0)	0.58 (0.22 – 1.57)	.287
Age (years) - mean (SD)	35.0 (8.2)	34.3 (8.1)	36.5 (8.8)	0.97 (0.92 – 1.03)	.265
Caucasian	77 (95.1)	55 (98.2)	22 (88.0)	0.13 (0.01 – 1.35)	.088
Married/remarried	17 (21.0)	11 (19.6)	6 (24.0)	0.77 (0.25 – 2.40)	.657
High school graduate	42 (50.0)	27 (48.2)	13 (52.0)	0.86 (0.34 – 2.21)	.753
Unemployed	29 (35.8)	20 (35.7)	9 (36.0)	0.99 (0.37 – 2.64)	.980
Access to transportation *	31 (38.3)	24 (42.9)	7 (28.0)	1.93 (0.70 – 5.35)	.207
Uninsured	51 (63.0)	39 (69.6)	12 (48.0)	2.49 (0.94 – 6.55)	.066
Self-reported health as ‘fair’ or ‘poor’	37 (45.7)	24 (42.9)	13 (52.0)	1.61 (0.62 – 4.19)	.328
HCV knowledge †					
HCV is transmitted by sharing works. ‡	80 (98.8) †	56 (100.0)	24 (96.0)	--	--
HCV is transmitted by sharing needles/syringes	81 (100.0) †	56 (100.0)	25 (100.0)	--	--
Lifetime number of hospitalizations - mean (SD)	7.3 (13.8)	7.3 (15.6)	7.3 (8.4)	1.00 (0.97 – 1.04)	.987
Lifetime history of drug abuse treatment	45 (56)	2.3 (3.7)	1.7 (2.6)	1.06 (0.91 – 1.25)	.461
Incarceration	70 (86.4)	50 (89.3)	20 (80.0)	2.08 (0.57 – 7.61)	.267
Lifetime number of incarcerations - mean (SD)	9.4 (22.0)	9.0 (24.1)	10.3 (16.9)	1.00 (0.98 – 1.02)	.809
Been in jail in the past 30 days	10 (12.3)	8 (14.3)	2 (8.0)	1.92 (0.38 – 9.76)	.430

* Defined as having a valid driver’s license and access to automobile

† Percentage who answered items correctly

‡ “Works” include cookers, cotton, or rinse water

Table 2

Description of lifetime and recent behavioral characteristics of sample (n=81)

	Total n (%)	HCV RNA^{+} n=56 n (%)	HCV RNA^{-} n=25 n (%)	OR (95% CI)	p-value
Lifetime behaviors					
History of blood transfusion	6 (7.4)	6 (10.7)	0 (0)	--	--
Ever injected any drug in lifetime	77 (95.1)	54 (96.4)	23 (92.0)	2.35 (0.31 – 17.70)	.408
Ever shared equipment to snort drugs	78 (96.3)	53 (94.6)	25 (100.0)	--	--
Recent behaviors					
Injected drugs in the past 6 months	45 (55.6)	35 (62.5)	10 (40.0)	2.40 (0.89 – 6.48)	.086
Injected drugs in the past 30 days	41 (50.6)	32 (57.1)	9 (36.0)	1.19 (0.11 – 12.82)	.889
Receptive equipment sharing					
Used dirty needle(s) in the past 6 months	10 (12.3)	7 (12.5)	3 (12.0)	0.58 (0.12 – 2.85)	.505
Used dirty needle(s) in the past 30 days	3 (3.7)	2 (3.6)	1 (4.2)	0.89 (0.08 – 10.25)	.922
Shared works[*] in the past 6 months	16 (19.8)	12 (21.4)	4 (16.0)	0.78 (0.19 – 3.32)	.740
Shared works[*] in the past 30 days	16 (19.8)	11 (19.6)	5 (20.0)	0.42 (0.09 – 1.89)	.257
Engaged in distributive needle sharing in the past 6 months[†]	9 (11.1)	8 (14.3)	1 (4.0)	4.00 (0.47 – 33.86)	.203
Cleaned needles with bleach at least once in the past 6 months	33 (73.3)	25 (71.4)	8 (80.0)	1.60 (0.29 – 8.88)	.591
Used alcohol in the past 30 days	28 (34.6)	19 (33.9)	9 (36.0)	0.91 (0.34 – 2.45)	.856
Used alcohol to intoxication in the past 30 days[‡]	22 (27.8)	15 (27.3)	7 (29.2)	0.94 (0.33 – 2.70)	.910
Consulted a healthcare provider after testing anti-HCV positive[¶]	29 (39.7)	19 (36.5)	10 (47.6)	0.63 (0.23 – 1.77)	.383
Received treatment for HCV in past 6 months[††]	8 (9.8)	5 (8.9)	3 (12.0)	0.72 (0.16 – 3.28)	.670

[*] "Works" include cookers, cotton, or rinse water

[†] Defined as selling, returning, or giving a needle to someone after use

[‡] Variable had missing value for 2 participants

[¶] Variable had missing value for 8 participants

[††] Includes interferon or pegylated interferon (n=4), 'alternative treatment' (n=1), and undefined other (n=3)