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PRIMARY AND SECONDARY PREVENTION OF HEPATITIS C VIRUS AMONG RURAL APPALACHIAN PEOPLE WHO USE DRUGS

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PRIMARY AND SECONDARY PREVENTION OF HEPATITIS C VIRUS AMONG RURAL APPALACHIAN PEOPLE WHO USE DRUGS

DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Medicine at the University of Kentucky

By

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ABSTRACT OF DISSERTATION

PRIMARY AND SECONDARY PREVENTION OF HEPATITIS C VIRUS AMONG RURAL APPALACHIAN PEOPLE WHO USE DRUGS

Hepatitis C virus (HCV) remains a major cause of morbidity and mortality worldwide, with 3% of the global population chronically infected. Clinical impacts in the United States are projected to increase for two decades, and mortality attributed to HCV now exceeds HIV. Injection drug use (IDU) is the most common route of transmission in the developed world. Advances in treatment offer hope of mitigating HCV impacts, but substantial barriers obstruct people who inject drugs (PWID) from receiving care, particularly in medically underserved regions including Central Appalachia. This study assessed IDU paraphernalia sharing longitudinally over 24 months in a sample of 283 rural PWID recruited by respondent-driven sampling. Medical follow-up among 254 seropositive participants was also assessed using discrete-time survival analysis.

HCV-positive screening was associated with reduced IDU sharing frequency 18 months after testing compared to seronegative participants (adjusted OR [aOR]=1.4, 95% confidence interval [CI]: 1.0-1.9), but this effect was not sustained. HCV-positive participants were less likely to cease IDU 6 months after testing (aOR=0.4, 95% CI: 0.2-0.7). Predictors negatively associated with decreased IDU sharing included recent unprotected sex, sedative use, and frequency of prescription opioid IDU; protective associations included female gender and religious affiliation. IDU cessation was negatively associated with ever being incarcerated, recent unprotected sex with PWID, heavy alcohol use, lifetime use of OxyContin®, and baseline frequency of prescription opioid IDU; protective associations included number of dependents, receiving disability payments, and substance abuse treatment. Drug-specific associations decreasing IDU cessation included recent illicit use of OxyContin®, other oxycodone, and cocaine.

150 of 254 (59%) seropositive participants saw a clinician after HCV-positive screening and counseling, 35 (14%) sought treatment, and 21 (8%) received treatment. Positive predictors of following up with a clinician following testing and counseling included health insurance, internet access, past substance abuse treatment, generalized anxiety disorder, and recent marijuana use. Factors decreasing odds of follow-up included major depression, lifetime illicit methadone use, and recent legal methadone. These analyses shed valuable light on determinants of behavior impacting primary and secondary HCV prevention. Integrated, multidisciplinary approaches are recommended to meaningfully impact epidemic levels of HCV among rural PWID in Eastern Kentucky.

KEYWORDS: Hepatitis C, injection drug use, prevention, treatment uptake, rural Appalachia

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1.1 Introduction

Since its discovery in 1989 (Alter 1999; Houghton 2009; Houghton 2009), hepatitis C virus (HCV) has emerged as a major global health problem. The virus is prevalent worldwide, with nearly 200 million individuals now HCV antibody-positive (Mohd Hanafiah, Groeger et al. 2013), approximately 3% of the human population. Moreover, HCV is the most common blood-borne pathogen in the United States (Prevention 2014), where mortality stemming from the pathological impacts of chronic infection now exceed that of human immunodeficiency virus (HIV) (Ly, Xing et al. 2012). More ominously, despite declining incidence, the public health impacts of HCV are projected to worsen for at least the next two decades (Davis, Alter et al. 2010), adding substantially to the already crippling healthcare costs of HCV and demand for liver transplantation, for which HCV is the number one indication in most developed countries worldwide, including the United States (Brown and Gaglio 2003; Wiesner, Sorrell et al. 2003). The estimated incremental cost of HCV infection is over $23,000 annually per individual, and infection is associated with significantly higher risk of hospitalization, depression, cirrhosis, liver cancer and transplantation (McCombs, Yuan et al. 2011). The estimated economic impact of HCV in the United States between 2010 and 2019 is projected at over 190,000 deaths and $10.7 billion in direct medical costs (Wong, McQuillan et al. 2000), while the total global burden of HCV is now estimated at over 483,000 deaths per year (Lim, Vos et al. 2012) and over 16,000 per year in the United States (Centers for Disease Control and Prevention 2011), and growing (Wong, McQuillan et al. 2000). For these reasons, HCV is a major biomedical and public health challenge on multiple levels: individual, healthcare system, and society as a whole. Thus, vigorous public health outreach efforts fueled by epidemiological research of high-risk populations along with clinical management driven by evidence-based guidelines are crucial and ideally, complementary components in the battle to control HCV. With the goal of informing public health intervention efforts, the data presented in later chapters of this dissertation address issues specifically related to primary (transmission) and secondary (disease

manifestations) prevention of HCV in a infrequently studied medically underserved population in the rural Appalachian region of Eastern Kentucky.

1.2 Virology and taxonomy

(HCV) is a single-stranded, positive-sense RNA virus in the genus *Hepacivirus* of the family *Flaviviridae*. HCV's 9.6-kilobase viral genome encodes a polyprotein precursor of approximately 3000 amino acids (Moradpour, Penin et al. 2007) that is subsequently cleaved into three structural (core, envelope glycoproteins 1 and 2), six non-structural (NS2, NS3, NS4A, NS4B, NS5a, NS5b), and several other proteins serving a variety of catalytic and other molecular functions (Moradpour, Penin et al. 2007; Houghton 2009; Chevaliez and Pawlotsky 2012). In its infectious form, HCV primarily circulates in serum bound to low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL), although it can also circulate as free virions or bound to serum antibodies (Andre, Perlemuter et al. 2005). Upon cellular entry, the viral protein capsid releases its RNA genome into host cytoplasm, which then serves as messenger RNA to code for the HCV polyprotein (Chevaliez and Pawlotsky 2012). This protein precursor is targeted to the host endoplasmic reticulum, were it is processed by an assortment of host and viral proteins. Among the final protein products is NS5B, a viral RNA-dependent RNA polymerase that lacks a nucleotide "proofreading" function (Moradpour and Penin 2013). A critical component of HCV replication, NS5B generates frequent uncorrected errors such as point mutations and inversions in carrying out its molecular function. In fact, the genetic diversity of HCV is over ten-fold greater than that of HIV (Simmonds 2004; Moradpour, Penin et al. 2007) and chronically infected individuals typically generate and clear upwards of 10^{12} virions per day with a mean half-life of 2.7 hours (Neumann, Lam et al. 1998), warranting multi-drug treatment regimens to treat HCV and hindering of research towards a preventive vaccine

This error-prone replication and rapid mutation result in a highly unstable and heterogeneous viral genome, even within individuals in the form of multi-strain superinfection, or multiple viral genotypes coexisting within an infected individual (Farci, Shimoda et al. 2000; Moradpour, Penin et al. 2007). Moreover, HCV reinfection among individuals who have cleared the virus occurs at a rate of 2.4 cases per 100 person-years among people who use drugs and 6.4 cases per 100 person-years among people who inject drugs (PWID) (Aspinall, Corson et al. 2013; Grady, Schinkel et al. 2013), implying that at best there is only partial immunity induced following viral clearance. HCV's ability to evade immune recognition have hindered efforts to

synthesize an effective vaccine against HCV (Randal 1999; NIH 2002), although a few potential compounds are in phase 2 clinical trials (Shi and Ploss 2013; Swadling, Klenerman et al. 2013).

Due to this high genetic variability, HCV is often referred to as a "quasispecies." The virus has been formally delineated into seven major genotypes "1" through "7", which vary in sequence between one another by at least 30%, as well as 67 subtypes delineated by single lower case letters: *a, b,…k* and so on (Smith, Bukh et al. 2013). Genotypes vary in prevalence between geographic regions and have major impact on disease progression, long-term prognosis, and efficacy of treatment (Gottwein, Scheel et al. 2009). Genotype 1 is most prevalent in the United States (Mahaney, Tedeschi et al. 1994), accounting for 73% of a sample of 6807 chronic HCV (CHC) patients, with the remainder composed primarily of genotypes 2 and 3 (Blatt, Mutchnick et al. 2000). Genotype 3a is common among PWID in Europe and in individuals infected prior to July 1992 by non-sterile blood, tissue, and organ donation (Lavanchy 2011; Klevens, Hu et al. 2012). Egypt primarily features genotype 4 and also the highest prevalence of HCV of any country worldwide, with overall prevalence between 15-20% (el-Sayed, Gomatos et al. 1996; Lavanchy 2011). This is largely due to a long-term public campaign to parenterally treat endemic schistosomiasis along the Nile River Valley, which utilized inadequate sterilization procedures until halted in the 1980s (Frank, Mohamed et al. 2000). Overall, Central Africa has primarily genotypes 4 and 5, whereas West African features primarily genotypes 1 & 2 (Lavanchy 2011). In much of Asia and Southeast Asia in particular, genotype 6 is most prevalent (Li, Chan et al. 2009) along with genotypes 1 and 3, which are widely distributed worldwide (McOmish, Yap et al. 1994; Lavanchy 2011).

HCV genotype can also have major impact in terms of hepatic disease progression and long-term prognosis. Patients chronically infected with genotype 1 are more likely to experience a more aggressive disease course and poor response to treatment (Nainan, Alter et al. 2006; Klevens, Hu et al. 2012). Treatment success is defined in terms of sustained virologic response (SVR), which is the absence of HCV RNA (under detectable limits of 10-15 international units [IU] per mL) for at least 6 months following cessation of treatment (Thomas 2013). Regarding genotype 1, the original interferon-only treatment protocols featured an SVR rate of less than 15% (Hoofnagle and di Bisceglie 1997). Probability of SVR for genotype 1 patients increased with the addition of ribavirin to the 48-week treatment protocol in 1998 (McHutchison, Gordon et al. 1998) and then again in 2001 with the addition of polyethylene glycol to interferon-α to create the current form of the drug, peginterferon-α (Manns, McHutchison et al. 2001). Nonetheless,

SVR rates for patients with genotype 1 still lagged behind those with genotypes 2 and 3, and significant problems with toxicity remained (Manns, McHutchison et al. 2001). In recent years , the relatively novel class of direct-acting antiviral (DAA) drugs such as boceprevir and telaprevir, specifically targeted to HCV genotype 1, have made great strides in improving probability of SVR and reducing treatment time in these patients (Casey and Lee 2013). The second generation of DAAs such as sofosbuvir and ledipasvir will likely enable interferon-free treatment protocols with a more benign adverse effect profile in the near future (EASL 2013), as detailed in the *Screening and Disease Management* section below. There is significant potential that the continued advances in HCV drug treatment will enable substantial improvements in treatment uptake levels and reduced HCV prevalence in the years to come.

1.3 Epidemiology

Upwards of 3% of the world's population has antibodies to HCV (Shepard, Finelli et al. 2005), a total exceeding 185 million individuals (Mohd Hanafiah, Groeger et al. 2013; Thomas 2013). Although HCV incidence has been stable in the United States since 2004 following a peak in the mid-1980s (Armstrong, Alter et al. 2000; Ward 2013), the estimated total with CHC now exceeds 3 million individuals (1.3% CHC prevalence; 1.6% HCV seroprevalence) (Armstrong, Wasley et al. 2006). Due to the exclusion of certain high-risk groups, this figure may underestimate the total number of individuals with CHC in the United States by up to 2 million, bringing the number of Americans with chronic infection to over 5.2 million (Chak, Talal et al. 2011). In one study, CHC prevalence in the United States was estimated to have peaked in 2001 with a total of 3.57 million chronically infected individuals (Davis, Alter et al. 2010). As depicted in Figure 1.1, however, number of reported cases of acute HCV in the United States has increase since 2009 (Centers for Disease Control and Prevention 2011). Moreover, there remains a major public health problem with regard to the "baby boomer" cohort born between 1940 and 1965, which accounts for more than 75% of the population chronically infected with HCV, with the highest prevalence consistently found among this cohort as they age (Armstrong, Wasley et al. 2006; Rustgi 2007; Davis, Alter et al. 2010; Thomas 2013). Because of this, recommendations have been amended to promote screening of all individuals born between 1945 and 1965, regardless of behavioral risk history, in order to address the growing burden of severe liver disease in the United States (Smith, Morgan et al. 2012; Moyer 2013).

Among particular high-risk groups, HCV prevalence is considerably higher. While many economically developing nations remain plagued by high rates of HCV infection resulting primarily from non-sterile medical procedures, in the United States and most other post-industrial countries the primary route of HCV transmission is now injection drug use (IDU). IDU readily provides the ideal vehicle for efficient transmission of the virus, percutaneous exposure to infected blood (Amon, Garfein et al. 2008; Thomas 2013). Hyperendemic HCV has been reported in all previously studied populations of people who inject drugs (PWID), among whom prevalence is significantly elevated relative to the general population; a global review of findings published between 1998 and 2005 reported HCV prevalence among PWID exceeding 50% in 49 countries and territories (Aceijas and Rhodes 2007). Another systematic review incorporating 77 nations reported that 60-80% of PWID were HCV seropositive in 25 countries, and 80% or higher were seropositive in 12 countries, with a midpoint seroprevalence of 73.4% among PWID worldwide (Nelson, Mathers et al. 2011).

In the United States, HCV seroprevalence among PWID varies but is consistently elevated from that of the general population (Alter 2011). Seroprevalences between 35% and 65% were reported in four large cohorts drawn from urban PWID in Baltimore, Chicago, Los Angeles, and New York City, although prevalence declined among PWID in Los Angeles and Baltimore between 1994 and 2004 (Amon, Garfein et al. 2008). Nonetheless, sporadic outbreaks and high regional HCV prevalences have been reported recently in the United States , especially in suburban and rural areas (Centers for Disease Control and Prevention 2008; 2011; 2012). HCV seroprevalence in a sample of PWID in Central Appalachian region of eastern Kentucky was reported to be 54.6% (Havens, Lofwall et al. 2013), and Kentucky has led the nation in cases of acute HCV in reported annually since 2008 (Centers for Disease Control and Prevention 2011). For these reasons, Central Appalachia is in need of expanded public health intervention efforts and focused research to inform such efforts; more detail concerning the Central Appalachian region and HCV among people who use and inject drugs can be found in the latter sections of this chapter.

1.4 Clinical course and public health impact

HCV infection is characterized by an insidious clinical course, typically with an asymptomatic acute phase and a protracted trajectory of chronic infection stretching over two or three decades before symptoms manifest. Indeed, it has been hypothesized that a foremost

selective advantage of HCV is its ability to thrive unnoticed within host hepatocytes, replicating productively without causing clinical consequences for many years through sophisticated viral mechanisms to evade or dampen host immune responses (Foy, Li et al. 2005) and induce long-term tolerance of CHC until hepatic damage reaches an advanced stage (Thomas 2013). Acute HCV is defined as occurring within 6 months of viral exposure and is symptomatic in less than one-third of individuals (Hoofnagle 1997; NIH 2002), substantially limiting awareness of HCV status among infected individuals. When symptomatic, acute HCV includes a range of clinical effects including jaundice, and up to ten-fold elevation of hepatic aminotransferase enzymes (Hoofnagle 1997; Alberti, Chemello et al. 1999). Acute HCV spontaneously resolves in 10-40% of individuals, resulting in detectable serum antibodies but no long-term clinical consequences (Hoofnagle 1997; Lee, Yang et al. 2012).

The majority of serious clinical complications resulting from HCV occur over a 30-year period among individuals with chronic infection, which develops in approximately 70-80% of those infected with the virus (NIH 2002; Lavanchy 2011; Lee, Yang et al. 2012). Among individuals chronically infected, approximately 20% progress to serious liver disease including advanced hepatic fibrosis and cirrhosis, which can eventually progress to decompensated cirrhosis, particularly among individuals with other risk factors such as moderate to heavy drinking, comorbid HIV and/or hepatitis B, smoking, obesity and insulin resistance, schistosomiasis, and iron overload. Modifiable lifestyle factors are crucial determinants of CHC progression (Missiha, Ostrowski et al. 2008). Patients with decompensated cirrhosis suffer substantially increased mortality and a constellation of signs and symptoms related to end-stage liver failure, including bleeding esophageal and rectal varices, splenomegaly, ascites, hepatic encephalopathy, asterixis, jaundice, hypoalbumenia, respiratory alkalosis, coagulopathy and easy bruising. Among these individuals, liver transplantation (LT) is the only remaining treatment option (NIH 2002; U.S. Department of Veteran's Affairs: National Hepatitis C Program Office 2007). In addition, an array of extrahepatic manifestations of CHC cause significant morbidity as well, including mixed cryoglobulinemia vasculitis, membranoproliferative glomerulonephritis, porphyria cutanea tarda, thyroid disorders, lichen planus, depression and other psychiatric disorders, and a potential link to type 2 diabetes (Mehta, Brancati et al. 2000; NIH 2002; Thomas 2013).

Globally, HCV is responsible for an estimated 583,000 deaths per year (Lim, Vos et al. 2012). The majority of CHC-related mortality is caused by decompensated cirrhosis rather than

hepatocellular carcinoma (NIH 2002), and the vast majority of individuals with HCC are also clinically cirrhotic (El-Serag 2012). Ultimately, up to 5% of cirrhotic individuals with CHC develop hepatocellular carcinoma (HCC), the most common form of liver cancer worldwide (Hoofnagle 2002). HCC has among the worst prognoses of all cancers, with 5-year survival rates under 18% and relatively poor treatment options, particularly in later stages of disease (Altekruse, McGlynn et al. 2012; Padhya, Marrero et al. 2013). Although 85% of the cases of liver cancer occur in the developing world and are caused by hepatitis B virus, in North America HCV is the most common cause of HCC, which is now among the fastest-growing of all cancer types (El-Serag 2012). In the United States, morbidity and mortality due to CHC are projected to increase over the next two decades, as the cohort infected between 25 to 45 years old ages (Davis, Alter et al. 2010). This group accounts for over 75% of CHC in the U.S., and the severe hepatic complications of CHC most often develop in individuals over 60 years of age (Thomas 2013). For this reason, even conservative projections indicate the brunt of the HCV-related healthcare burden in the United State is yet to come. In 2002, CHC caused an estimated 10,000 to 12,000 deaths in the United States based on death certificate information (NIH 2002), although this is a moderate estimate. More recent estimates put the number of deaths in the United States annually due to CHC at over 15,000 per year (Ly, Xing et al. 2012), with incidence of both decompensated cirrhosis and HCC predicted to continue increasing for 10 more years. Given current levels of screening, treatment, and drug efficacy, CHC-related mortality is projected to peak in the United States in 2022, and 283,378 deaths are estimated between 2020 and 2029 due to serious liver disease (Davis, Alter et al. 2010). In light of these projections, it is clear that demand for LT will significantly increase in the decades to come. In the United States, HCV is the most common cause of LT (NIH 2002), with CHC-related cirrhosis and/or HCC being the primary indication in over 30% of individuals on the waiting list for LT procedures (Berg, Steffick et al. 2009). HCV is the most common cause of LT in many other developed countries as well, along with hepatitis B virus-induced cirrhosis and HCC (Perz, Armstrong et al. 2006), which predominates in most Asian countries (El-Serag 2012; Liao, Yang et al. 2012).

With regard to mitigating disease progression, several host factors accelerate disease progression due to CHC. Foremost among these are older age at time of infection, male gender, alcohol use (particular at levels above 30g/day for men and 20g/day for women), concurrent HIV, concurrent HBV, and miscellaneous other factors, including iron overload conditions such as hemochromatosis, non-alcoholic fatty liver disease, insulin resistance/obesity,

schistosomiasis, hepatotoxic drugs, and various environmental toxins (NIH 2002; Missiha, Ostrowski et al. 2008). As a modifiable behavioral target with robust potential to improve the long-term prognosis, alcohol use among individuals with CHC is of particular interest as a form of secondary disease prevention (Tagger, Donato et al. 1999; Siu, Foont et al. 2009; Drumright, Hagan et al. 2011). Reducing or eliminating alcohol consumption is included in standard post-test counseling materials to be provided to individuals testing HCV-positive, along with messages to reduce the likelihood of spreading the virus to others by common routes of transmission (Ghany, Strader et al. 2009), which are detailed in chapter 2. However, HCV-seropositive status disclosure and standard counseling has not been found to reduce alcohol consumption in most drug-using samples, and the same held true among HCV-seropositive individuals relative to their seronegative counterparts in a rural Appalachian sample of people who use drugs (Stephens and Havens 2013).

1.5 HCV screening and management

Clinical management of HCV requires individual-level awareness of HCV infection. Screening and identifying individuals infected with HCV remains a primary challenge to mitigating the impact of CHC worldwide. Population-based studies in the U.S. indicate that less than 50% of HCV-positive individuals are aware of their status, and of this subgroup only 3.7% were tested by a doctor because of their HCV risk profile (Denniston, Klevens et al. 2012). Other researchers have reported that HCV risk advising (Shehab, Orrego et al. 2003), assessment, and screening procedures are suboptimal among primary care physicians in the U.S., with screening rates of only 8% among high-risk individuals (Almario, Vega et al. 2012), despite long-standing national guidelines that individuals with known risk factors for HCV be serotested (Centers for Disease Control and Prevention 1998; Ghany, Strader et al. 2009). Furthermore, as previously mentioned, CDC recommendations now formally advise the screening of all individuals born in the United States between 1945 and 1965, as this birth cohort is likely to experience the majority of CHC-related clinical impacts in the decades to come (Davis, Alter et al. 2010; Thomas 2013). The amended guidelines indicating an individual should be screened for HCV antibodies are summarized below in Table 1.

Table 1.1
Recommended guidelines indicating individuals should be screened for HCV

- Persons who have ever injected illegal drugs
- Persons who are human immunodeficiency virus (HIV)-positive
- Persons who have received clotting factor concentrates before 1987
- Persons who received blood from a donor who later tested HCV-positive
- Persons who received blood or blood component transfusion before July 1992
- Persons who received an organ transplant before July 1992
- Healthcare, emergency medical, and public safety workers following needle stick, sharps, or mucosal exposure to HCV-positive blood
- Persons who have ever been on long-term hemodialysis
- Persons with persistently elevated alanine aminotransferase levels (ALT)
- Children born to HCV-positive women
- Current sexual partners of HCV-infected individuals
- *Individuals born between 1945 and 1965*

Medical assessment and indications for treatment

At the point of receiving medical evaluation after a positive HCV serotest, important decisions face the patient and physician. Given the substantial cost, time and personal commitment requirements, and potential adverse effects of HCV pharmacotherapy, determining patient eligibility for treatment is vital, and approaches vary between medical cultures and individual clinicians. The initial management step of an HCV antibody-positive patient is to assess for active infection via quantification of serum HCV RNA level, typically by real-time polymerase chain reaction (RT-PCR). A genotyping assay should also be performed on all patients for whom antiviral treatment is being considered, as genotype dictates the therapy protocols outlined in the following section. Liver biopsy or non-invasive tests such as FibroSure® that assess serum biomarkers to determine hepatic fibrosis staging may also be considered for the purposes of prognostic and treatment determination, at the discretion of the physician and patient (Ghany, Strader et al. 2009).

Because of the adverse effect profile of many HCV drugs (Casey and Lee 2013) and the high prevalence (50-80%) of illicit drug use and IDU among individuals with HCV infection (Shepard, Finelli et al. 2005; Aceijas and Rhodes 2007), decisions regarding treatment eligibility can be complex for healthcare providers. There are many potential adverse effects of ribavirin and pegylated interferon, including anemia and other hematologic disorders (leukopenia, neutropenia, thrombocytopenia), myalgias, fever, pruritis, rash/dermatitis, flu-like symptoms, nausea, weight loss, thyroid disorders, headache, insomnia, anxiety, and depression (NIH 2002;

Casey and Lee 2013). Moreover, with the addition of the first-generation direct-acting antivirals (DAA) drugs boceprevir and telaprevir to treatment regimens, the degree of hematologic (particular with boceprevir), dermatologic (including Steven-Johnson syndrome with telaprevir), gastrointestinal adverse effects, and drug interactions are substantially increased (Gaetano and Reau 2013). The second generation of DAAs such as sofosbuvir and ledipasvir featured significantly increased efficacy and lower toxicity relative to older drugs, although adverse effects and drug interactions remain an issue, and the cost of HCV treatment has substantially increased (Thomas 2013; Hoofnagle and Sherker 2014). The formal guidelines for U.S. physicians emphasize the highly patient- and situation-specific nature of determining treatment eligibility among CHC patients, summarized by the American Association for the Study of Liver Diseases (AASLD) as follows (Ghany, Strader et al. 2009):

> Treatment decisions should be *individualized* based on the severity of liver disease, the potential for serious side effects, the likelihood of treatment response, the presence of comorbid conditions, and the patient's readiness for treatment

With this in mind, specific guidelines with regard to whom treatment is "widely accepted" from the American Association for the Study of Liver Diseases (AASLD) are summarized below in Table 2.

AASLD guidelines also give individualized recommendations for making the decision to treat five specific CHC patient subgroups: children and individuals with renal disease, major depressive disorder, active substance abuse, or HIV coinfection. With regard to patients who are actively using and/or injecting illicit drugs, the original NIH consensus statement advised withholding treatment from patients with a history of drug injection until a period of IDU cessation lasting at least 6 months had occurred (NIH 1997). NIH amended its consensus statement in 2002, advising individualized assessment of patients currently injecting drugs, along with an advisory to couple HCV therapy with addiction treatment and opioid substitution therapy (OST) (NIH 2002). Current AASLD guidelines for HCV management continue to emphasize a highly individualized approach, reiterating that it remains "important to consider the individual issues that may affect the risks and benefits of treatment of HCV infection in

Table 1.2
Characteristics of individuals for whom HCV drug treatment is widely accepted

- 18 years of age or older
- HCV RNA detectable in serum
- Liver biopsy showing chronic hepatitis with "bridging" grade fibrosis or higher
- Compensated liver disease (total serum bilirubin <1.5g/dL; INR 1.5; serum albumin >3.4; platelet count ≥75,000/mm^3) without evidence of decompensation (hepatic encephalopathy or ascites)
- Hemoglobin ≥13g/dL for men or ≥12g/dL for women; neutrophil count ≥155mm^3; creatinine <1.5mg/dL
- Symptomatic cryoglobulinemia
- Willing to be treated and adhere to treatment requirements
- No absolute contraindications (see Table 3)

persons who use illicit drugs, rather than to make categorical recommendations" (Ghany, Strader et al. 2009). This conservative approach is supported by some studies of HCV treatment failure among active PWID (Alvarez-Uria, Day et al. 2009) and to some extent by intuition, with regard to the unstable lifestyle and inadequate social support resources typical of many people actively using and/or injecting drugs. Nonetheless, it has been noted that some early recommendations were not necessarily evidence-based (Edlin, Seal et al. 2001), and some researchers consider withholding treatment from people who are actively using drugs to be a form of clinician bias and considerable barrier to mitigating impact of the HCV epidemic (Grebely and Dore 2014). Many researchers, particularly those outside of the United States, have reported that active drug injectors can be equally adherent to treatment regimens and achieve SVR rates similar to that of other HCV patient groups if treated in a controlled setting in conjunction with appropriate peer support and addiction services (Robaeys, Van Vlierberghe et al. 2006; Grebely, Raffa et al. 2007; Bruggmann, Falcato et al. 2008; Melin, Chousterman et al. 2010; Aspinall, Corson et al. 2013; Robaeys, Grebely et al. 2013). Thus, there is some indication that clinical consensus may be shifting towards specific evidence-based guidelines with regard to HCV treatment eligibility among people who use and inject drugs. This shift in medical culture has considerable implications public health and future cost burdens on healthcare in the United States, given that PWID have accounted for the vast majority of HCV incidence since safe blood transfusion procedures were instituted in 1992 (Armstrong, Wasley et al. 2006; Davis, Alter et al. 2010). Absolute contraindications to HCV treatment as published b the AASLD in 2014 are outlined below in Table 3.

Table 1.3
Absolute contraindications to drug treatment for HCV

- Major uncontrolled depression
- Solid organ transplant
- Autoimmune hepatitis or other autoimmune condition exacerbated by peginterferon and ribavirin
- Untreated thyroid disease
- Pregnant women or women unwilling to comply with contraceptive requirements
- Severe hypertension, heart failure, poorly controlled diabetes, or chronic obstructive pulmonary disease
- Less than 2 years of age
- Hypersensitivity to HCV drugs

Understandably, there is concern regarding the risk of reinfection among active PWID (Aitken, Lewis et al. 2008; Grebely, Knight et al. 2010). However, reinfection among PWID have been shown to be rare in some studies, provided access to OST or sterile syringes is available (Edlin, Seal et al. 2001; Grady, Vanhommerig et al. 2012; Grady, Schinkel et al. 2013; Robaeys, Grebely et al. 2013). However, with regard to the setting of the present study, state law in Kentucky prohibit the services of syringe-exchange programs (Kentucky Legislative Research Commission 2010), perhaps fueling provider concerns of HCV reinfection among active drug injectors in the Central Appalachian region.

In sum, current treatment eligibility guidelines in the United States dictate that individual clinician judgment remains the most important arbiter of the decision whether to treat PWID who are diagnosed and seek medical care. Therefore, individual physician preferences, biases, and variability in medical culture on the regional level factor heavily into treatment decisions in the frequently stigmatized patient population of drug users and injectors (Nicklin, Schultz et al. 1999; Treloar, Newland et al. 2010; Cox, Graves et al. 2011; Harris and Rhodes 2013). One AASLD recommendation for treatment eligibility bears particular relevance to PWID: "*Willing to be treated and adhere to treatment requirements*." Despite rapid improvements in drug options (Afdhal, Zeuzem et al. 2013) and suggestions of the long-term cost-effectiveness (Martin, Vickerman et al. 2013), HCV treatment remains expensive, demanding, and relatively lengthy in nature, requiring parenteral administration of interferon, with a daunting adverse effect profile and total cost of nearly $100,000 in the United States (Thomas 2013). Therefore, this recommendation is particularly relevant to CHC patients and their physicians whether or not to undertake treatment of the virus. Of course, individuals with HCV are screened, diagnosed, and visit a physician for medical evaluation if testing positive,

although high willingness to be treated has been reported among HCV-seropositive PWID (Stein, Maksad et al. 2001), despite low levels of eligibility and treatment initiation (Hagan, Latka et al. 2006). The complex web of patient, provider, and social issues surrounding access to HCV medical care following a positive serotest are explored in detail in chapter 4.

Treatment guidelines

In the rapidly evolving field of HCV clinical care, new viral targets, novel drugs, and updated treatment guidelines are emerging on a continual basis. The American Association for the Study of Liver Diseases (AASLD) regularly updates the treatment guidelines intended to be used by all specialist physicians currently treating CHC patients in the United States. These guidelines are genotype-specific and continually updated as research advanced to reflect the rapidly changing arsenal of HCV drug agents, including the relatively new direct-acting antiviral protease inhibitors specifically targeted to improve the SVR among genotype 1 patients. In clinical practice, however, the adverse effects of the first-generated DAAs were often more severe than anticipated given their promise in clinical trials (Afdhal, Zeuzem et al. 2013; Pollack 2013). Moreover, given the likelihood that all-oral, interferon-free and even ribavirin-free treatment options are likely to be available in the near future (Everson, Sims et al. 2013; Martel-Laferriere, Bichoupan et al. 2013), so many specialists treating HCV are opting to delay treatment of eligible patients until superior pharmaceutical agents receive FDA approval (Pollack 2013). In short, the field of medical treatment for CHC is in considerable flux. Nonetheless, at this stage there is reason enough for optimism: recent interferon-free phase III clinical trials of sofosbuvir and ledipasvir given effecting SVR in 98-99% genotype 1 patients, with or without ribavirin, among both previously untreated individuals receiving 12 weeks of treatment (Afdhal, Zeuzem et al. 2014) and previously treated patients given 24 weeks of treatment (Afdhal, Reddy et al. 2014), with no patients in either group discontinuing use of either DAA agent due to adverse events. Formal practice guidelines are still in the process of being revised at the time of this publication.

Lastly, it is worth nothing that considerable progress was made with regard to older treatment protocols using a “personalized medicine” approach predicting treatment outcomes using genetic sequencing of the promoter site of the cytokine IL-28B, which has been shown a robust predictor of HCV treatment success (Estrabaud, Vidaud et al. 2012). This finding has been consistently reproducible and is often cited as an example of the successful application of

genome-wide association scan (GWAS) research techniques to clinical practice (Venegas, Brahm et al. 2012). However, genotyping the IL-28B locus is currently recommended in the clinical management of CHC only if the physician or patient desires additional information regarding disease progression and probability of achieving SVR (Ghany, Strader et al. 2009; Ghany, Nelson et al. 2011), and it is likely that variation at the IL-28B locus will be less important in determining treatment outcomes in the era of newer anti-HCV drug agents.

1.6 Injection drug use in rural Appalachia

Non-medical prescription opioid use (NMPOU) has surged dramatically upwards in the United States over the last 15 years (Cicero, Surratt et al. 2007; Manchikanti, Helm et al. 2012; CDC 2013), fueled largely by increases in rural and suburban areas (Havens, Walker et al. 2007; Okie 2010; Young, Havens et al. 2010; Estep 2011). This trend has been accompanied by a commensurate rise in IDU, with reports that potent extended-release painkillers such as OxyContin® and roxicodone confer high risk of transition to IDU in multiple settings (Hays 2004; Grau, Dasgupta et al. 2007; Kirsh, Peppin et al. 2012), including rural eastern Kentucky (Young and Havens 2012). Moreover, the incidence of drug overdose (OD) has increased nearly ten-fold since 1999 nationwide, up to a total of 38,329 in 2010 (CDC 2013), a trend that is strongly associated with per capita sales of prescription opioids (Paulozzi and Ryan 2006). Prescription drugs account for more than 60% of OD deaths, with three-quarters of these being due to prescription opioids (CDC 2013). Moreover, the Central Appalachian region in particular suffers from among the highest rates drug overdose nationwide (Hall, Logan et al. 2008).

Indeed, widespread NMPOU has been reported in the rural Appalachian area of eastern Kentucky, particularly with regard to OxyContin® and other prescription opioids containing oxycodone and hydrocodone (Havens, Walker et al. 2007; Havens, Oser et al. 2010). Rapid transition to IDU was reported in this population, with a median time of 3 years from first illicit use to first IDU reported in a sample of 503 PWUD living in the region (Young and Havens 2012). HCV seroprevalence of 54.6% was discovered among rural PWID in this region (Havens, Lofwall et al. 2013), affirming that high HCV prevalence among drug injectors in the United States extends to rural areas. Preliminary analysis from the same study sample reveals high incidence of HCV as well. Rural Central Appalachia is a largely low-income region characterized by considerable socioeconomic distress and generally poor access to hospitals, primary care, disease screening, and social support services (Stensland, Mueller et al. 2002; Reif, Golin et al.

2005; Zhang, Infante et al. 2008; ARC 2011), with vital health statistics often comparable to those of an economically developing country (Murray, Kulkarni et al. 2005; Murray, Kulkarni et al. 2006). Given that people who use and inject drugs are already subject to a wide variety of barriers to healthcare and disease screening services (Grebely, Genoway et al. 2008) and HCV-infected individuals typically report low rates of screening and treatment (Harris and Rhodes 2013; Thomas 2013), dismal levels of HCV status awareness, healthcare engagement, and treatment initiation might be expected among rural Appalachian individuals at risk of contracting HCV. In turn, it is logical to surmise that this combination of frequently undiagnosed HCV combined with widespread barriers to medical care for HCV will likely be followed by disastrous elevations in HCV-related morbidity and mortality in the decades to come, as with multiple projections for the United States overall (Wong, McQuillan et al. 2000; Davis, Alter et al. 2010)—a public health burden likely to be crippling for already financially distressed regional healthcare systems like that of Central Appalachia. A growing body of research indicates that scaling-up integrated social services to mitigate the impact of HCV, including education efforts, substance abuse treatment, opioid substitution treatment, harm reduction programs to reduce IDU and promote safer injection practices (primary prevention), peer-driven counseling, and HCV medical care, are successful in reducing HCV transmission risk (Latka, Hagan et al. 2008; Turner, Hutchinson et al. 2011). Moreover, treatment of PWID infected with HCV likely to be cost-effective in the long run (Martin, Vickerman et al. 2012). At present, however, there are few integrated programs of this nature for PWID in the United States, and unsurprisingly, none in Central Appalachia. Moreover, there is little research focused on HCV in rural America or on factors impacting HCV transmission risk and healthcare engagement in the context of rural Appalachia, an area where such research is most needed to inform public health intervention efforts in the years to come.

1.7 Rationale and aims of project

With less than 50% of HCV-infected individuals in the United States likely to be aware of their status (Denniston, Klevens et al. 2012), inadequate levels of screening have been reported as one of the most significant barriers to the control of hepatitis C (Clark and Muir 2012; Ward 2012). In rural populations at risk of acquiring HCV, this proportion is likely to be even lower. For this reason, assessing the impact of HCV screening among rural individuals who do receive screening is vital to optimizing this key window of opportunity for prevention in a population

with little access to other social, substance abuse, or harm reduction services. Understanding behavior following HCV-seropositive status disclosure and counseling is crucial to efforts aimed at reducing the risk of viral transmission, as well as to expanding insight into the convoluted process of disease management and potential treatment. Successful treatment of HCV can avert disease manifestations as well as further viral transmission, resulting in HCV prevention on multiple levels. This "treatment as prevention" benefit has been promoted by several researchers (Edlin 2011; Page, Morris et al. 2013; Grebely and Dore 2014; Hellard, Doyle et al. 2014) and is likely to substantially improve the cost-effectiveness of treating people who are actively using and/or injecting illicit drugs if delivered in a targeted manner in combination with substance abuse treatment and harm reduction services (Martin, Vickerman et al. 2012; Martin, Vickerman et al. 2013). Epidemiological research of individual-level factors affecting primary and particularly secondary prevention are vital in the era of rapidly improving HCV drug therapies outlined earlier in this chapters, as well as substantial healthcare changes in the United States occurring with implementation of the Affordable Care Act.

Because of the protracted clinical trajectory of HCV, the public health impact among chronically infected individuals in the United States is only beginning to be felt. At current treatment uptake levels, the impacts on the U.S. economy as well as morbidity and mortality of the aging population with CHC will be increasingly severe in the coming decades (Davis, Alter et al. 2010; Thomas 2013). Meanwhile, of course, incident cases of continue to occur, necessitating interventions that target multiple levels of prevention for meaningful reductions in prevalence in high-risk populations (Page, Morris et al. 2013). Thus, this purpose of this dissertation is to illuminate tractable and pragmatic behaviors related to prevention of HCV transmission and disease progression: sharing of IDU paraphernalia and following up with a healthcare provider after receipt of a positive HCV serotest. With the goal of informing public health efforts to control HCV among rural Appalachian people most at risk of acquiring and transmitting HCV, the results presented in subsequent chapters focus on the following research questions:

1. Does HCV screening and informational counseling impact behavior promoting primary prevention of HCV among rural PWID? Which sociodemographic and behavioral characteristics predict change in injection-related risk? Relevant prior studies and data from a cohort of rural Appalachian PWID are explored in the following chapter, *Routes of Transmission*.

2. What proportion of rural Appalachian people who use drugs follow up with a healthcare provider after receiving a positive HCV serotest and informational counseling? What characteristics predict healthcare engagement among these individuals? This topic and relevant findings among rural Appalachian people who use drugs are presented in chapter 4, *Barriers to Care*.

Routes of Transmission:
Risk factors for the spread of HCV

2.1 Overview

In the human body, HCV exists primarily in the bloodstream and is transmitted almost exclusively through percutaneous contact with blood and blood products (Seeff 2002). Thus, the most common modes of HCV transmission are injection-related: IDU with contaminated needles and other injection-related items being perhaps the most well-known, along with other percutaneous exposures such as contaminated blood and blood product transfusion. In parts of the developing world lacking adequate HCV screening protocols, healthcare-mediated transmission remains the most common means of HCV incidence (Hauri, Armstrong et al. 2004; Alter 2011; Thomas 2013). However, other less frequent means of percutaneous exposure to contaminated blood and have been documented by researchers, including needle-stick exposures among healthcare workers (Cainelli 2013; Thomas 2013), non-sterile tattooing (Ko, Ho et al. 1992) and piercing (Tohme and Holmberg 2012), organ transplantation (Seem, Lee et al. 2013), vertical transmission during childbirth (Zanetti, Tanzi et al. 1995; Mast, Hwang et al. 2005), sharing of personal hygiene items such as toothbrushes and razors (Cavalheiro Nde, De La Rosa et al. 2009), and lastly, invasive medical procedures such as digestive endoscopy (Karmochkine, Carrat et al. 2006), although other studies have contradicted this finding (Ciancio, Manzini et al. 2005).

In addition, HCV transmission via permucosal routes has also been reported. As detailed below, several studies have found the sharing of straws used for intranasal administration ("snorting") of illicit drugs to be a risk factor, although this route may in fact represent a clandestine bloodborne exposure (Allison, Conry-Cantilena et al. 2012). Despite growing evidence against heterosexual transmission, sexual transmission of HCV remains somewhat controversial (Gross 2001; Cainelli and Vento 2002; Alter 2011) and is an occasional source of incident cases documented among mostly in cases of "rough" sex, men who have sex with men (MSM), particularly those coinfected with HIV, and in other situations with high risk of mucosal tearing during intercourse (Alter 2011; Lambers, Prins et al. 2011; Bradshaw, Matthews et al.

2013; Thomas 2013). Finally, sporadic permucosal transmission has also been reported via contaminated blood products being splashed into the conjunctiva of the eyes of healthcare worker (Sartori, La Terra et al. 1993). The primary well-established routes of HCV transmission are reviewed in greater detail in the following sections.

Injection drug use

Since the advent of safe screening precautions in the United States in July 1992, the sharing of syringes, needles, and other injection-related equipment among PWID has been the primary mechanism of incident HCV in the United States (Williams, Bell et al. 2011) and in most developed countries worldwide (Alter 2011; Thomas 2013). As outlined in Chapter 1, HCV prevalence is high among PWID worldwide, with 49 countries reporting prevalences of at least 50% (Aceijas and Rhodes 2007) and up to 10 million seropositive PWID worldwide (Nelson, Mathers et al. 2011). Nelson and colleagues (2011) also reported midpoint seroprevalence among PWID as 67.5% worldwide, with the highest numbers of HCV-seropositive individuals in China, Russia, and the United States. In one study, HCV seroprevalence among 5088 PWID aged 18 to 40 years living in 4 major U.S. cities ranged from 35% to 65%, and the odds of testing HCV-seropositive increased with years of injection (OR=1.9, 95% CI: 1.7-2.2) per year. Although HCV prevalence among PWID in Baltimore and Los Angeles declined between 1994 and 2004 (Amon, Garfein et al. 2008), there are recent indications that regional prevalences among high-risk groups may still be rising in parts of the United States, particularly in suburban and rural areas (Centers for Disease Control and Prevention 2008; 2011; 2012).

Incidence of HCV among PWID in the United States has been reported between 11.6 (Hagan, Thiede et al. 2004) up to 25.1 (Hahn, Page-Shafer et al. 2002) and 27.2 cases per 100 person-years of follow-up (Cox, Netski et al. 2005), with a median time to seroconversion of 2.1 years in a study of urban PWID (Hagan, Thiede et al. 2004). Importantly, HCV transmission risk via IDU is not limited to the sharing of contaminated needles and syringes. Several recent studies have documented an association between incident HCV and the sharing of contaminated cookers, cotton, and waters used during the preparation of drugs for injection (Thorpe, Ouellet et al. 2002; Hagan, Thiede et al. 2004; De, Roy et al. 2008), an often overlooked route of transmission that remains poorly understood in many populations of PWID. Finally, interventions using a combination of strategies including behavioral intervention, substance-use treatment, syringe access and distribution have been shown to be effective in preventing HCV

infection among PWID (Hagan, Pouget et al. 2011), and several studies have demonstrated the efficacy of syringe-exchange programs (SEP) and/or opioid substitution therapy (OST) in reducing injection-related HCV transmission (Des Jarlais, Perlis et al. 2005; Turner, Hutchinson et al. 2011; Iversen, Wand et al. 2013). Unsurprisingly, the prevalence of injection-related risk behaviors such as sharing syringes and injecting equipment has been reported to be higher in areas not offering SEP harm-reduction programs to reduce the spread of bloodborne infectious diseases such as HCV and HIV (Neaigus, Zhao et al. 2008), and PWID in New York City who utilized syringe-exchange were more likely to inject with a new syringe (Rudolph, Crawford et al. 2010). Kentucky, however—the state in which collection of data analyzed in this dissertation occurred—is one of 18 states not offering SEP of any kind (Foundation for AIDS Research 2013).

Intranasal drug use

Up to 20% of incident HCV is not explained by the major established modes of transmission (Centers for Disease Control and Prevention 2011), particularly among HCV-positive non-injection drug users (Tortu, Neaigus et al. 2001; Scheinmann, Hagan et al. 2007), who typically have higher HCV prevalence than the general population despite denial of past IDU history (Koblin, Factor et al. 2003). One explanation put forth by some researchers is that the sharing of straws used for drug snorting such as cocaine and heroin explains some of this discrepancy (Tortu, McMahon et al. 2004), as blood with HCV RNA has been detected in the nasal secretions and straws and other intranasal use implements of non-injecting drug users (Aaron, McMahon et al. 2008). Koblin and colleagues (2003) found an association of intranasal administration of heroin and heroin mixed with cocaine with prevalent HCV among non-injecting drug users, while Allison et al. (2012) found intranasal use of cocaine in particular to be a risk factor, conferring an odds ratio of 8.5 in a longitudinal study of 738 blood donors in one study. As mentioned previously, this heightened risk was suggested to be conferred by parenteral rather than permucosal transmission, due to frequent epistaxis (nosebleed) during shared intranasal cocaine use, facilitating blood-borne transmission (Allison, Conry-Cantilena et al. 2012). Macias and colleagues (2008) found a similar pattern (adjusted OR=3.6, 95% CI = 1.3-9.8) among non-injecting drug users who reported sharing straws for the inhalation of crack cocaine. Nonetheless, the association of intranasal transmission with HCV risk remains less robust relative to parenteral transmission. Some researchers have found no association with shared snorting implements (Hermanstyne, Bangsberg et al. 2012), while others have suggested

that intranasal drug use could in fact confer a protective effect as an alternative route of administration with regard to HCV transmission risk relative to IDU, conferring multivariate odds ratios near 0.50 or below for seroprevalent HCV among recent intranasal users of heroin and heroin-cocaine mixtures in a sample of prior drug injectors recruited from a detoxification program in New York City (Des Jarlais, Hagan et al. 2011).

Blood transfusion, transplantation, and other iatrogenic exposures

Iatrogenic transmission of HCV, particularly via transfusion of contaminated blood products and reuse of non-sterile medical equipment, remains a serious global health problem and the most common mode of incident HCV in the developing world (Alter 2011; Thomas 2013). Safe antibody and RNA-based screening procedures for blood and blood product transfusion introduced in 1992 have all but eliminated HCV transmission by this route in economically developed countries (Schreiber, Busch et al. 1996; Busch, Glynn et al. 2005), although sporadic outbreaks of iatrogenic transmission via errors in tissue transplant testing have been reported recently in Kentucky and Massachusetts (Centers for Disease Control and Prevention 2011). Contaminated blood products remain a serious issue in parts of the world lacking in adequate blood supply and access to advanced HCV screening technology. Moreover, non-sterile therapeutic methods including the reuse of syringes for drug and vaccine administration likely contribute to a substantial portion of incident infections—an estimated 2 million cases worldwide in the year 2000, or 40% of new infections (Hauri, Armstrong et al. 2004). This phenomenon is epitomized by the tragic example of Egypt, where a public schistosomiasis eradication campaign spanning several decades resulted in the epidemic spread of HCV genotype 4 described in the chapter 1. However, sporadic outbreaks of HCV in the iatrogenic setting have also occurred via transfusion and injection in economically developed countries, resulting from patient-to-patient (Perz, Thompson et al. 2010) and transplant-related (Centers for Disease Control and Prevention 2011) transmission resulting from breakdowns in precautionary infection control safeguards. Finally, due to highly efficient rates of infection via percutaneous exposure , HCV transmission to healthcare professionals via needle-stick accidents among healthcare workers has long been observed as a transmission risk factor (Lanphear, Linnemann et al. 1994) and occurs in 0.9 to 2.2% of exposures to blood from HCV-infected patients, a proportion far exceeding the transmission efficiency of HIV (Cainelli 2013).

Vertical transmission

The risk of transmission from an HCV-infected mother to newborn falls between 2-8% (Syriopoulou, Nikolopoulou et al. 2005; Prasad and Honegger 2013), and this route remains a significant source of incident HCV in many regions with high prevalence. Unfortunately, unlike HIV, there is not yet an effective prophylactic treatment to reduce the risk of vertical HCV transmission, and conventional HCV drug therapy is contraindicated in pregnant women due to the teratogenic properties of ribavirin and pegylated interferon (Prasad and Honegger 2013). However, while the impact of newer DAA drugs on the therapeutic options available for HCV-infected mothers remains to be seen, there is considerable optimism for substantially reduced toxicity and amendment of treatment guidelines. Typical risk-enhancing factors for this mode of HCV transmission include maternal HIV coinfection, maternal IDU, HCV RNA level (Zanetti, Tanzi et al. 1995; Syriopoulou, Nikolopoulou et al. 2005), membrane rupture, and internal fetal monitoring (Mast, Hwang et al. 2005). Breastfeeding has not been found to significantly increase the risk of vertical HCV transmission, perhaps due to insufficient viral load or inactivation of HCV in the stomach. CDC recommendations (1998) refer to the data regarding breastfeeding with HCV as "limited," and both CDC and the American College of Obstetricians and Gynecologists advise HCV-positive mothers without HIV infection to abstain from breastfeeding if nipples are cracked or bleeding (ACOG 2007).

Tattooing, piercing, and folk medical practices

A few relatively minor but well-documented sources of incident cases HCV can be categorized together under various invasive non-medical procedures practiced without adequate sanitation precautions, including tattooing, body piercing, and Eastern medical practices such as acupuncture. Given the efficiency of parenteral transmission of HCV, each has potential for the viral spread via contaminated blood if needles and other equipment are reused without recommended sterilization procedures. While most researchers have found little evidence of transmission risk in establishments following professional sterilization standards, Howe and colleagues (2005) reported a significant association between HCV-seropositive status and receiving a non-professional tattoo (adjusted OR 3.6, 95% CI: 1.2-11.3). Similarly, in a meta-analysis by Tohme and Holmberg (2012), substantial risk of HCV infection (adjusted odds ratios ranging from 2.0 to 3.6) was found when tattoos or piercings were received under non-sterile conditions, such as in prisons or from friends. The role for piercing as a risk factor is less clear,

with 5 of 23 studies reporting significant odds ratios from 2.0 up to 7.3 (Tohme and Holmberg 2012). An earlier study found a similar relationship with regard to non-professional tattooing, albeit in a small sample of 213 non-PWID (OR=5.9, 95% CI 1.6-22.0) (Ko, Ho et al. 1992). Similarly, Macias and colleagues (2008) reported an OR of 3.5 (95% CI: 1.3-9.1) for seroprevalent HCV among 182 non-PWID undergoing addiction treatment with a history of tattooing, although other factors, such as a history of incarceration, were possible confounders. Finally, certain non-Western medical practices including non-sterile acupuncture and other procedures have been reported by some researchers as risk factors for HCV acquisition, particularly in Asian countries (Kiyosawa, Tanaka et al. 1994; Aikawa and Kojima 2004; Lim 2009).

Sexual transmission and other mucosal routes

The potential role of sexual contact in HCV transmission remains controversial. Data reported between molecular and epidemiological approaches to the question are conflicting (Gross 2001; Cainelli and Vento 2002; Alter 2011). Undoubtedly, this mode of transmission is inefficient relative to direct parenteral exposures such as equipment sharing during IDU and transfusion of contaminated blood products (Terrault 2002; Cainelli 2013). Several older studies and case reports have reported that transmission of HCV via sexual contact can occur, albeit very infrequently (Alter, Coleman et al. 1989; Capelli, Prati et al. 1997; Halfon, Riflet et al. 2001; Quer, Murillo et al. 2003). Moreover, analysis of 500 HCV-seropositive individuals who were not currently injecting drugs and their long-term heterosexual partners found extremely low incidence of HCV transmission by sexual contact, with maximum incidence of 0.07% per year (95% CI 0.01-0.13%), or one incident case of HCV per 190,000 sexual contacts, after 8,377 person-years of follow-up (Terrault, Dodge et al. 2013). Twenty (4%) of the study couples had evidence of mutual infection via serotesting, among which nine couples had the same genotype and only three (0.6%) had viral isolates determined to be highly related by genetic sequencing, indicating very low incidence of sexual transmission. Similarly, a longitudinal study followed a cohort of 895 monogamous heterosexual partners of HCV-infected partners for 10 years and found no evidence of intra-spousal transmission of HCV via sexual activity using viral sequencing techniques (Vandelli, Renzo et al. 2004). Researchers suggest that if HCV transmission does occur among heterosexual partners, it may occur percutaneously via vaginal mucosal tearing or anal intercourse (Cainelli 2013), shared history of IDU or other surreptitious HCV exposures (Stroffolini, Lorenzoni et al. 2001), or alternatively, potential permucosal transmission during the

early (acute) phase of HCV infection, which would explain why transmission among longer-term partners is so infrequent (Alter 2011; Thomas 2013).

Among MSM, however, the story of HCV sexual transmission is quite different. Rising incidence among homosexual men who are not injecting drugs has been documented over the last decade in many populations (Lambers, Prins et al. 2011; Bradshaw, Matthews et al. 2013). This trend was first reported in the UK (Browne, Asboe et al. 2004), followed by studies of similar dynamics in France (Ghosn, Pierre-Francois et al. 2004), the Netherlands (Gotz, van Doornum et al. 2005), United States (Luetkemeyer, Hare et al. 2006), and Australia (Matthews, Hellard et al. 2007). More recently, Witt and colleagues (2013) reported that sexual transmission of HCV via MSM has been frequent throughout the history of the HIV epidemic, and unprotected anal sex with more than one male partner was an independent predictor of HCV-seropositive status (incidence rate ratio 3.4, $p<0.001$), as well as HIV, syphilis, or hepatitis B coinfection, age, and heavy alcohol consumption. As with vertical transmission, HCV incidence was also predicted by HIV-positive status and inversely proportional to low-CD4 count among participants with less than 500 CD4+ T cells (Witt, Seaberg et al. 2013). A review by Yaphe and colleagues (2012) affirms this synergy between HIV and incident HCV among MSM, although they stop short of advising HCV screening for all individuals with a history of MSM, instead recommending to approach the question on an individualized basis.

Finally, a collection of primarily older studies points to possible permucosal transmission of HCV through shared use of personal hygiene items including toothbrushes, razor blades, manicure pliers, and even nail clippers, or so-called “intrafamilial” or “household” transmission (Honda, Kaneko et al. 1993; Tibbs 1995; Caporaso, Ascione et al. 1998; Cavalheiro Nde, De La Rosa et al. 2009). Taken together, the risk of HCV transmission by this route seems to be low and regionally variable (Ackerman, Ackerman et al. 2000). Nonetheless, a recommendation to avoid sharing personal hygiene items appears in the post-test counseling materials issued by CDC (1998) to be given to all individuals following an HCV-positive serotest.

2.2 Approaches to prevention

There is a fundamental dichotomy with regard to public health efforts aimed at mitigating the impact of infectious disease: *primary* prevention and *secondary* prevention. With regard to HCV, primary prevention addresses factors impacting major routes of disease transmission, whereas secondary prevention focuses primarily on managing existing cases of

HCV in order to prevent disease manifestations in the years to come (Thomas 2013). Given the reality of scientific challenges to discovery of an efficacious preventative vaccine (Torresi, Johnson et al. 2011), biomedical approaches to primary prevention of HCV remain unavailable. Thus, harm reduction approaches such as SEP, OST, and substance abuse treatment coupled with efforts to reduce transmission risk via modification of IDU behavior, remain the primary options available at the present time to reduce incidence of HCV. However, as previously described, there are no harm reduction programs and a scarcity of substance abuse and related social services in rural Central Appalachia.

Consensus is lacking regarding the impact of HCV screening on subsequent HCV transmission-related risk behaviors among people who use and inject drugs, and this question has not been previously studied in the rural context. Moreover, there are few prospective studies examining changes in drug-related transmission risk behavior in response to HCV serostatus disclosure over time. Additional longitudinal studies should help solidify public health understanding of the effectiveness of HCV antibody screening and CDC-recommended post-test counseling materials alone on disease transmission risk. Ultimately, this research question is highly pragmatic in nature, as HCV screening, when it occurs, is likely to be one of the few interactions with the healthcare system many members of the rural drug-using population may experience. Thus, examining what impact screening may have is vital in rural Central Appalachia, which as mentioned in chapter 1 features widespread drug injection and inhalation (Young, Havens et al. 2010), as well as HCV seroprevalence among PWID comparable to urban areas (Havens, Lofwall et al. 2013). For these reasons, the following chapter focuses on a behavioral approach to the primary prevention of HCV in medically underserved Eastern Kentucky. Analyses of transmission-related IDU risk behaviors among PWID in a rural cohort are presented before and after HCV serotesting and standard informational counseling.

Chapters 4 and 5, by contrast, focus on secondary prevention of HCV among rural people who use drugs by describing levels of treatment uptake and exploring key patient-level steps in engagement of the healthcare system, specifically the immediate steps study participants take, or do not take, following receipt of an HCV-positive serotest result and post-test counseling. While ostensibly these chapters are most relevant to the long-term clinical prognosis of HCV-positive individuals, there is important relevance to the prevention of future HCV transmission as well, as former CHC patients who have achieved SVR can no longer transmit the virus to others. In other words, successful treatment of CHC can prevent incident infections

as well as substantially improve the clinical course of individuals already infected (Marinho, Vitor et al. 2014). In this way, identifying factors predicting healthcare engagement among seropositive individuals has potential to inform both primary and secondary prevention. Similarly, effective primary prevention strategies to avoid re-infection of individuals who have already achieved SVR are critical for secondary prevention of CHC-related disease manifestations to be truly effective. In other words, both approaches to disease prevention are complementary parts of an effective strategy to containing the impact of HCV on society. Engagement in HCV management, treatment-seeking, and treatment uptake among in the rural Appalachian drug-using population are explored in more detail in Chapters 4 and 5.

Primary Prevention:
HCV screening and transmission risk behavior among rural Appalachian people who inject drugs

3.1 Introduction

As detailed in chapter 1, hepatitis C virus is a major global health challenge with myriad potential clinical consequences among individuals with chronic infection. HCV is hyperendemic in a variety of populations of PWID, and IDU is the primary route of transmission in developed nations worldwide (Hellard, Doyle et al. 2014). HCV screening, including testing and post-test informational counseling (T&C), has been proposed as a valuable means of reducing HCV prevalence among PWID (Clark and Muir 2012; Ward 2013), despite only weak support for the effectiveness of screening on IDU risk behavior (Chou, Cottrell et al. 2012). However, there are relatively few studies examining the potential impact of testing and standard counseling might have on subsequent risk behavior for HCV transmission, particularly within the context of rural America. Indeed, the impacts of screening and counseling were recently identified as one of six major areas in need of further study with regard to prevention modalities targeting HCV (Page, Morris et al. 2013).

Past research yields insight into the interplay of HCV status awareness and IDU risk, although findings often conflict and previously sampled populations have been primarily from major urban centers. An early study of 592 PWID in Paris undergoing drug abuse or other psychosocial treatment compared individuals reporting HCV-positive status to those reporting unknown or HCV-negative status. In a multivariate model, lack of HCV status awareness was associated with decreased probability of using new IDU equipment of any kind, suggesting heightened transmission risk among PWID who have not received a serotest for HCV (Vidal-Trecan, Coste et al. 2000). Similarly, in one of the first studies to address IDU risk specifically in relation to HCV-positive status awareness, Kwiatkowski and colleagues reported on 197 PWID in Denver, CO in a cross-sectional analysis. Individuals who were aware of being HCV-positive reported a longer duration of IDU but fewer HCV-related risk behaviors, including IDU with a used needle, sharing injection paraphernalia (cookers, cotton, or rinse water), and a greater self-perception of using "safe" injection techniques (Kwiatkowski, Fortuin Corsi et al. 2002). This finding contrasts with a recent study from Aspinall (2014) and colleagues reporting no change in

IDU sharing behavior following positive T&C, although there was a small but significant decline in overall IDU frequency.

Concordant with the findings of Aspinall, a study of more than 3000 PWID age 15-30 in five U.S. cities found that awareness of HCV-seropositive status was not associated with decreased sharing of syringes or cotton, nor with decreased syringe-mediated drug sharing. Interestingly, however, participants aware of their HCV-*seronegative* status were less likely to reporting recent sharing of a syringe (adjusted OR 0.8, 95% CI: 0.6-0.9) or filtration cotton (aOR 0.8, 95% CI: 0.6-0.9) (Hagan, Campbell et al. 2006). Similarly, Korthuis and colleagues (2012) examined the question cross-sectionally among PWID in drug treatment, comparing those aware of their HCV-positive status to those who were not aware or were HCV-seronegative. In a multivariate model, reporting awareness of being HCV-seropositive was associated with *increased* sharing of syringes and needles in the last 6 months (adjusted OR: 2.4, 95% CI: 1.2-4.9). Any opioid use, marijuana use, crack use via injection, and female gender were also associated with increased syringe/needle sharing (Korthuis, Feaster et al. 2012). Norden and colleagues (2009), however, reported that knowledge of HCV status and awareness of the personal health consequences of HCV were not associated with significant differences in prevalence of sharing needles and IDU equipment. Meanwhile, another study by Cox et al. (2008) used a theoretical approach to investigate correlates to the sharing of syringes and drug preparation equipment by adapting the AIDS Risk Reduction Model, originally designed to address HIV sexual risk behavior (Catania, Kegeles et al. 1990). In a multivariate model derived from 321 PWID in Montreal, lower perceived benefits of safe IDU practices and greater difficulty in practicing safe injection were associated with greater risk of syringe sharing, while lower perceived benefits of safe injection and lower self-efficacy to convince other PWID to inject safely increased risk of equipment sharing (Cox, De et al. 2008). Similarly, a study from Budapest found IDU equipment-sharing was associated with lower self-efficacy for the use of safe injecting procedures and higher peer pressure to share equipment, along with *higher* perceived susceptibility to HIV/AIDS and having a criminal record (Racz, Gyarmathy et al. 2007). However, the cross-sectional design of these studies limits causal interpretation of these findings, although it is probable that HCV infection and serotesting preceded most reports of drug injecting behavior as measure of recent sharing (last 3-6 months) were utilized.

In the first prospective study to address the question of transmission risk-related behavioral change among PWID, Ompad and colleagues (2002) interviewed 106 young PWID in

Baltimore six months after HCV serotesting. As with the majority of cross-sectional studies, no significant differences between individuals receiving HCV-positive T&C versus individuals with a negative result or no awareness of their status with regard to the sharing of syringes, needles, and other IDU-related paraphernalia (Ompad, Fuller et al. 2002). However, this analysis was bivariate in nature and did not control for potential confounders, such as demographic factors, illicit drug use patterns, and prior HCV status knowledge at baseline in particular. In another prospective study, Tsui and colleagues (2009) followed 112 initially PWID in San Francisco who seroconverted and received post-test counseling during the course of a 12-month study period. Incidence of IDU and sharing injection equipment decreased among all study participants, regardless of serotest result and counseling received. In a multivariate model, non-injection drug use decreased significantly among HCV seroconverters relative to HCV-negative participants immediately after status disclosure and counseling (OR 0.4, 95% CI: 0.2-0.8), although this decline was not sustained over 6- and 12-month follow-ups; no significant differences were observed between HCV groups with regard to IDU sharing. Thus, as with the above studies of Hagan, Aspinall, and Ompad, risky IDU practices did not seem to be affected by HCV seroconversion and brief counseling, and the initial decrease in non-IDU was not detected after 12 months of study (Tsui, Vittinghoff et al. 2009).

Although not specific to the impact of screening, PWID-targeted HCV interventions such as peer-driven counseling and integrated harm reduction programs have been shown to be highly effective among PWID. A systematic review of HCV primary prevention studies assessed the impact of targeted behavioral interventions on HCV incidence (3 studies) and IDU-related risk behaviors (6 studies). Of these latter studies, two reported significant decreases in IDU risk behavior, although disparities in study design and primary outcome measures prevented pooling of data (Sacks-Davis, Horyniak et al. 2011). A meta-analysis examining the impact of harm-reduction programs in the United Kingdom found that combined syringe-exchange and opioid substitution programs reduced needle sharing by 48% (adjusted OR=0.52, 95% CI: 0.32-0.83) and mean IDU frequency by 20.8 occasions per month (95% CI: 14.4-27.3). In addition, significant decreases in HCV incidence were reported for both SEP and OST programs, with an impressive 80% reduction in new cases observed among “full harm reduction” recipients in combined programs (aOR=0.2, 95% CI: 0.1-0.5). Finally, a small number of studies indicate that analysis of social network-level variables can be predictive of syringe, needle, and equipment sharing among PWID. These factors include measures of network structure, such as density and

turnover, along with compositional attributes including individual network member centrality and dyadic characteristics, behavioral norms, and local drug use patterns (De, Cox et al. 2007; Shaw, Shah et al. 2007).

Taken together, the majority of past research suggests that HCV screening and brief post-test counseling alone are unlikely to substantially reduce transmission-related risk among PWID. In fact, there is some evidence that awareness of HCV-positive serostatus may even increase IDU risk behavior. However, even more targeted educational and counseling interventions may be of limited benefit unless implemented in a multi-component fashion with integrated focus to education and as well as opioid addiction treatment , harm reduction programs, and accessible options for CHC medical care and treatment (Birkhead, Klein et al. 2007; Sacks-Davis, Horyniak et al. 2011; Page, Morris et al. 2013; Grebely and Dore 2014). This research question is particularly relevant to the unique setting of rural Appalachia, where public health efforts to address the burgeoning HCV crisis are almost non-existent and few local healthcare providers or hospitals (Stensland, Mueller et al. 2002; Zhang, Infante et al. 2008). Furthermore, as the state of Kentucky prohibits syringe-exchange programs (Kentucky Legislative Research Commission 2010), the region might be expected to feature particularly high rates of injection-related risk behavior among PWID (Vlahov and Junge 1998; Neaigus, Zhao et al. 2008). Finally, as expanded upon in later chapters, medical management of HCV is characterized by a variety of challenges on virological, individual, healthcare provider, and societal levels, so optimizing primary prevention strategies are particularly important. Therefore, the purpose of this study was to longitudinally assess whether HCV screening and counseling impacts IDU risk behavior among PWID in rural Central Appalachia.

3.2 Methods

Sampling

Data analyzed here were collected at the first four study occasions (baseline, 6-months, 12-months, and 18-months) during the ongoing longitudinal cohort study, *Social Networks among Appalachian People* (SNAP; R01DA024598 and R01DA033862), principal investigator Jennifer R. Havens. This purpose of this study was study epidemiology and risk factors of HCV, HIV, and herpes simplex virus type 2 (HSV-2) among people who use illicit drugs in the Central

Appalachian region of rural Eastern Kentucky. Individuals were eligible for enrollment in the study if they met the following criteria:

- 18 years of age or older at the time of enrollment
- Resident of a rural Appalachian county of Kentucky
- Used one or more of the following drugs to get high in the past 30 days: prescription opioids, heroin, cocaine or crack, or methamphetamine.
- Not currently receiving treatment for illicit drug use or other addiction problems

A storefront location in Hazard, KY (Perry County) was established for the purposes of recruitment and data collection. A baseline sample of 503 study participants was recruited between November 2008 and August 2010 using respondent-driven sampling (RDS). This sampling technique has been shown to be useful in the recruitment of difficult-to-access or "hidden" populations, such as drug users in both urban (Abdul-Quader, Heckathorn et al. 2006; Des Jarlais, Arasteh et al. 2007) and rural settings (Falck, Siegal et al. 2005; Frost, Brouwer et al. 2006; Wang, Falck et al. 2007). The RDS protocol developed and refined by Heckathorn offers substantial advantages over other techniques such as "snowball" sampling, which tend to be highly biased by non-random recruitment (Heckathorn 1997; Heckathorn 2002; Heckathorn 2007).

The recruitment process utilized informational flyers posted in public locations around Hazard, KY (Perry County, pop. 28,241) to collect an initial group of study "seeds," who were screened for eligibility and enrolled in the study if meeting eligibility requirements. This initial group was screened for eligibility as described above with the additional requirement that they had injected drugs with a needle in the past 6 months; this was confirmed by asking a set of detailed questions regarding specific injection techniques and performing a physical examination for evidence of track marks or other evidence of recent injection. Initial recruits were given three study coupons to recruit potentially eligible members of their drug use network (without the requirement of recent IDU), and later compensated $10 for each additional eligible study participant who enrolled. This secondary wave of new recruits was subsequently screened for eligibility, enrolled in the study if appropriate, and then given another set of coupons to initiate the recruitment of a third wave of potential study participants, and so on. This recruitment cycle continued until the sample reached the size determined to be necessary for adequate study power. 107 initial study seeds in total recruited, resulting in a final baseline sample of 503 participants. For each dependent measure assessed,

RDSAT software, version 7.1 (Ithaca, NY) was used to correct for residual non-randomness in the sample recruited during the course the RDS recruitment protocol. RDSAT yields individualized statistical weights for each study outcomes via 25,000 bootstrap iterations and enhanced data smoothing to appropriately adjust for potential bias and artificially induced sampling homogeneity (homophily) among recruitment chains, which can be introduced by the RDS protocol and result in inappropriately narrow confidence intervals (Heckathorn 2002; Volz and Heckathorn 2012; Volz, Wejnert et al. 2012). Participants were compensated $50 for their time in completing interviews, $20 for serotesting, and $20 for returning to receive serotest results. Study recruitment, serotesting procedures, pre- and post-test counseling, and interviewing procedures were approved by the University of Kentucky College of Medicine Institutional Review Board and a Certificate of Confidentiality was obtained. All study participants granted informed consent in order to participate.

HCV serotesting and data collection

All SNAP participants were tested at baseline and every subsequent 6-month visit for serum antibodies to HCV by trained study personnel using the Home Access® Hepatitis C Check serotest (Home Access Health Corporation, Hoffman Estates, IL). This test utilizes dried blood spot specimens collected by finger-stick and a 3rd-generation enzyme immunoassay (EIA) to detect antibodies to HCV in serum. Sensitivity and specificity of this test are 98.2% and 99.6%, respectively (US Food and Drug Administration 1999), and accuracy exceeds 99% (O'Brien, Kruzel et al. 2001). Four results are possible with this serotest (Home Access Health Corporation 2008):

- HCV-seropositive
- HCV-seronegative
- Indeterminate (antibodies but not necessarily specific to HCV)
- Result not available (inadequate blood volume/poor sample); participant retested

Participants were asked to return to the study site in approximately two weeks to receive their test results; if unable to return in person, participants were informed of their test result and counseled as described below by telephone. Participants with indeterminate or “reactive” test results were counseled as if testing seropositive (described below). Individuals testing seropositive or reactive were categorized as negative if they did not receive test results at least 30 days before subsequent interviewing. HCV status was then positive at the next interview with more than 30 days between HCV+ status disclosure and counseling. If participants received a

Table 3.1
Guidelines for pre-test counseling of individuals receiving an HCV antibody test

- Exposures associated with the transmission of HCV, including behaviors or exposures that might have occurred infrequently or many years ago
- Test procedures and the meaning of test results
- Nature of hepatitis C and chronic liver disease
- Benefits of detecting infection early
- Available medical treatment
- Potential adverse consequences of testing positive, including disrupted personal relationships and possible discriminatory action (e.g., loss of employment, insurance, and educational opportunities)

seronegative test after a previously reactive test, HCV status was amended to negative at the time the negative result was received to reflect the most recent counseling messages received.

Pre-test counseling messages were administered to all study participants, as advised by CDC guidelines (1998) and presented in Table 3.1 above. Post-test counseling and printed informational materials were given simultaneously with serotest results and tailored to individual serotest results. Table 3.2 below summarizes the recommendations from CDC (1998) for individuals testing HCV-seropositive. While these guidelines do not specifically address IDU behavior, AASLD guidelines published in 2009 include the recommendation that HCV-seropositive individuals stop using illicit drugs and avoid any sharing of syringes, needles, and injecting equipment including cookers, rinse water, spoons, or cotton filters. Trained SNAP study personnel advised participants accordingly regarding the risk of sharing syringes and injection equipment, and printed materials included specific statements regarding the high risk of HCV transmission through the sharing of *any* IDU paraphernalia (needles, syringes, and ancillary equipment) and a statement to always use one's own injecting equipment to eliminate the risk of HIV, HBV, and HCV transmission via IDU. Pamphlets with illustrated instruction were also distributed with information regarding "safe" methods of cleaning *all* IDU equipment using the "3x3" technique with bleach, including ancillary equipment, and to always use a new cotton filter and water. Finally, the standard counseling information for those testing positive for HCV included a list of local community clinics and hospitals offering further testing, physician assessment, and potential treatment options for HCV. This list included the Appalachian Regional Health Center hospital (Hazard, KY) and four additional nearby clinics located in Perry County, Kentucky.

Table 3.2
Guidelines for post-test counseling of individuals testing HCV-seropositive

• To protect their liver from further harm, HCV-positive persons should be advised to:
- Not drink alcohol - Not start any new medicines, including over-the-counter and herbal medicines, without checking with their doctor - Get vaccinated against hepatitis A if liver disease is found to be present
• To reduce the risk for transmission to others, HCV-positive persons should be advised to:
- Not donate blood, body organs, other tissue, or semen - Not share toothbrushes, dental appliances, razors, or other personal-care articles that might have blood on them - Cover cuts and sores on the skin to keep from spreading infectious blood or secretions
• HCV-positive persons with one long-term steady sex partner do not need to change their sexual practices. They should:
- Discuss the risk, which is low but not absent, with their partner (If they want to lower the limited chance of spreading HCV to their partner, they might decide to use barrier precautions [e.g., latex condoms]) - Discuss with their partner the need for counseling and testing
• HCV-positive women do not need to avoid pregnancy or breastfeeding.
• Other counseling messages
- HCV is not spread by sneezing, hugging, coughing, food or water, sharing eating utensils or drinking glasses, or casual contact - Persons should not be excluded from work, school, play, child-care or other settings on the basis of their HCV infection status - Involvement with a support group might help patients cope with hepatitis C
• HCV-positive persons should be evaluated for presence or development of chronic liver disease including:
- Assessment for biochemical evidence of chronic liver disease - Assessment for severity of disease and possible treatment according to current practice guidelines in consultation with, or by referral to, a specialist knowledgeable in this area - Determination of need for hepatitis A vaccination

A detailed questionnaire was administered at baseline and subsequent follow-up interviews (approximately every six months) by specially trained SNAP personnel at the study site in Hazard. Participants' responses were directly entered into a touch screen laptop using computer-assisted personal interviewing (CAPI) software (Questionnaire Development System, Nova Research Company, Bethesda, MD). Trained interviewers in the SNAP study all resided in the target rural area around Perry County, KY, and all were certified as HIV counselors who had undergone a thorough training program in the standardized interviewing procedures used throughout the study. Standard sociodemographic data including participant gender, race, age, education level (including classroom/academic settings and technical training), income (with

illegal sources specified), marital status, sexuality, religion, transportation status (access to vehicle and possession of driver's license), access to the internet, pattern of employment history were collected at baseline, along with participant responses to the MINI neuropsychiatric interview, version 5.0.31 (Sheehan, Lecrubier et al. 1998), to assess for symptoms of psychiatric disorders including major depressive disorder (MDD), generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), and antisocial personality disorder (ASPD). Participants who met the criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) for any of these four psychiatric diagnoses were given a standardized information sheet with detailed information on mental health resources available in the region. Finally, previous receipt of a positive test for HCV, hepatitis B virus, HIV, or HSV-2 from a healthcare professional was also asked at each interview.

A battery of time-varying measures were collected at each interview as well, including: health insurance status (dichotomized as no insurance or any insurance including private insurers, Medicaid, or Medicare), lifetime and recent incarceration, self-reported health status and frequency of health-related problems, substance abuse treatment, use in the last 30 days and 6 months of: alcohol (including to intoxication), legal and illegal methadone and buprenorphine, lifetime and recent illicit drug (including prescription opioids such as OxyContin® and other oxycodone -containing formulations, heroin, sedatives and tranquilizers, cocaine, crack, methamphetamine, oral amphetamines/prescription stimulants, barbiturates, hallucinogens, marijuana, and simultaneous use of multiple substances. Illicit use of prescription opioid was defined in concordance with the National Survey on Drug Use and Health (NSDUH) as use within the previous 6 months for the purpose of experiencing euphoria, or use of a prescription opioid not prescribed to the participant (SAMHSA 2003). Data on injection drug use including drugs injected, frequency of IDU, and year of first IDU, were collected at baseline and all subsequent interviews. Lifetime drug use history measures were also collected for reach substance above. Detailed questions regarding participants' recent HCV transmission risk via drug use behaviors, including sharing of syringes, needles, cottons, cookers, rinse water, were asked at all interviews. Sexual risk behavior was collected in the form of recent unprotected sex, recent unprotected sex with PWID, and recent unprotected transactional sex (for drug, money, or gifts). In addition, the following 6 true-false questions were asked at baseline to assess level of participant HCV knowledge:

- There is treatment for hepatitis C.
- Hepatitis C is passed from one person to another by sharing needles or syringes.
- Hepatitis C is passed from one person to another by sharing other injection equipment (cookers, cotton, etc.).
- Hepatitis C is passed from one person to another by coming into contact with infected blood.
- Hepatitis C is passed from one person to another through infected food or water.
- Hepatitis C is passed from one person to another by tattooing or body piercing instruments.

Lastly, a series of questions concerning HCV-seropositive individuals obtaining medical follow-up, seeking and obtaining HCV treatment from a healthcare professional were asked at the 6, 12, and 18-month interviews. These measures are described in detail in chapter 5.

Analysis

For the purposes of the specific analyses specific to this chapter (described below), a subsample of n=291 individuals returning for another interview after baseline HCV serotesting and reporting IDU in the past 6 months at any interview between 6 and 24 months and were included for analysis of IDU sharing (needles, syringes, and ancillary equipment, including cookers, cotton filters, and rinse water). For analysis of IDU cessation, included participants reported IDU at any time point between baseline and 18 months and must have returned for at least one interview between 6 and 24 after initial report of recent IDU to enable longitudinal analysis of IDU cessation, yielding a sample size of n=324. 22 recent PWID were excluded under these criteria. These individuals and any participants missing any interview between 6 and 24-month study occasions were assessed for significant differences with regard to major sociodemographic or time-invariant measures reported at baseline.

The primary dependent measure in this analysis was sharing of syringes, needles, and/or any other ancillary IDU equipment (cookers, cotton filters, or rinse water) in the 30 days preceding each 6-month interview. Thus, in order to capture the effect of HCV testing and counseling over time independent of baseline sharing habits, a binary change variable was created indicating *decreased* frequency of IDU sharing relative to baseline levels reported by each participant. A corresponding variable capturing *increased* IDU sharing frequency was also created to capture deleterious effects. In addition, *any* engagement in IDU during each 6-month intervals following was also assessed in a secondary analysis of IDU cessation during the study period. In addition, descriptive statistics for IDU sharing and IDU frequency in the last 6 months,

sources of needles and syringes, and syringe cleaning using bleach were also calculated at baseline and compared at 6 months by HCV serotest results for select variables.

In light of the research question, receipt of HCV test results and counseling were considered for inclusion in all multivariate models. Other covariates listed above were considered in a bivariate screening step for potential inclusion in multivariate modeling as outlined below. Potential associations between each covariate and the outcome of interest were assessed in a bivariate manner using generalized estimating equations (GEE; described below), with an unstructured specifications of covariance considered as described below. Covariates found to be associated with an outcome at the $p<0.10$ level of significance were considered for inclusion in the multivariate modeling procedures described in the following section. The main effect of time and standard sociodemographic measures including sex, age, race, education, and income were also considered in all multivariate models and retained if coefficients for significant independent measures changed by 10% or more (Hosmer and Lemeshow 1989).

Longitudinal data are characterized by within-subject correlation between data collection occasions, violating the assumption of independent observations key to conventional statistical techniques within the framework of generalized linear models. Failing to account for this within-subject correlation across observations can result in misleading statistical inferences stemming from overestimation of sampling variability, inflating standard error and 95% confidence intervals, and limiting meaningful statistical inference (Hardin and Hilbe 2003; Fitzmaurice, Laird et al. 2004). For this reason, statistical methodologies designed to account for within-subject correlation in data are required. Since informing pragmatic public health strategies at the level of the sampled population is the primary objective of this study, generalized estimating equations (GEE) were used for bivariate and multivariate analysis of the outcomes described above. Proposed in 1986 as an extension of generalized linear models, GEE accounts for within-subject correlation over time by explicitly modeling pairwise covariance structures as exchangeable, autoregressive, unstructured, and so on. Unstructured and autoregressive covariance structures were considered in this analysis, although GEE is relatively robust to misspecification of covariance (Fitzmaurice, Laird et al. 2004) and offers significant relaxation of conventional generalized linear model assumptions that would otherwise restrict analysis of longitudinal data. However, use of GEE remains subject to a few important assumptions, namely: log-odds of the dependent variable is linearly related to the predictors,

total count of clusters (individuals in this case) is relatively high (>30), and between-cluster observations are independent (Hardin and Hilbe 2003; Ghisletta and Spini 2004). Importantly, GEE yields population-averaged ("marginal") coefficients for independent variables, meaning that inferences are applicable to the background population sampled via the RDS protocol described above (Liang and Zeger 1986; Zeger, Liang et al. 1988; Fitzmaurice, Laird et al. 2004). Regression parameters in the GEE modeling were derived using robust ("sandwich") standard error estimates and Wald tests with a significance threshold of $p<0.05$. To assess model fit and compare nested multivariate models in a hierarchical fashion, the quasi-Akaike Information Criterion (QIC), a quasi-likelihood-based score test which balances goodness-of-fit with parsimony by penalizing each additional regression parameter, was used select the model with optimal goodness-of-fit and parsimony using the *qic* add-on algorithm for Stata (Pan 2001; Cui 2007). Again, as the GEE modeling procedure yields only population-averaged inferences, regression parameters are not appropriate for individual-specific inferences among participants within a study sample (Hardin and Hilbe 2003). Stata, version 13.1 (College Station, TX) was used for all statistical analyses.

Table 3.3

Drug-related behavior and baseline HCV test result and counseling received (T&C) among recent PWID (n=288)

Behavior	**Overall sample** n (%)	**HCV+ T&C** n=154 n (%)	**HCV- T&C** n=134 n (%)	**p-value**
IDU sharing (last 30d): Baseline				
Any paraphernalia	115 (39.9)	67 (43.5)	48 (35.8)	0.184
Needles/syringes	65 (22.6)	42 (27.3)	23 (17.2)	0.041
Other IDU equipment	103 (35.8)	60 (38.9)	43 (32.1)	0.225
IDU sharing (30d): 6m after test (n=267)[1]				
Any paraphernalia	46 (17.2)	33 (22.4)	13 (10.8)	0.012
Needles/syringes	23 (8.6)	18 (12.2)	5 (4.2)	0.027[2]
Other IDU equipment	42 (15.7)	30 (20.4)	12 (10.0)	0.020
IDU 6 months after HCV test (n=267)[1]	181 (67.8)	117 (79.5)	64 (53.3)	<0.0001
IDU frequency (last 6m): Before test				
Less than once per month	66 (22.9)	19 (12.3)	47 (35.1)	<0.0001
1-3 times per month	50 (17.4)	17 (11.0)	33 (24.6)	0.002
1-6 times per week	70 (24.3)	42 (27.3)	28 (20.9)	0.208
Daily or more	102 (35.4)	76 (49.7)	26 (19.7)	<0.0001
Daily or more IDU: 6m after test (n=181)[3]	81 (44.8)	61 (52.1)	20 (31.3)	0.007
Days of Rx opioid IDU (30d):				
Before test - mdn (IQR)	7 (1-25)	20 (2-30)	2 (0-10)	<0.0001
6 months after test (n=181)[3] – mdn (IQR)	10 (0-30)	15 (1-30)	2 (0-20)	0.004
Drugs injected (6m): Before test				
Prescription opioids	266 (92.4)	145 (94.2)	121 (90.3)	0.219
Heroin	31 (10.8)	16 (10.4)	15 (11.1)	0.826
Sedatives/tranquilizers	13 (4.5)	4 (2.6)	9 (6.7)	0.081[2]
Methamphetamine	8 (2.8)	3 (1.9)	5 (3.7)	0.479[2]
Prescription stimulants	13 (4.5)	9 (5.8)	4 (3.0)	0.271[2]
Drugs injected (6m): After test (n=181)[3]				
Prescription opioids	172 (95.0)	114 (97.4)	58 (90.6)	0.044
Heroin	9 (5.0)	7 (6.0)	2 (3.1)	0.398[2]
Sedatives/tranquilizers	3 (1.7)	1 (0.9)	2 (3.1)	0.286[2]
Methamphetamine	5 (2.8)	2 (1.7)	3 (4.7)	0.348[2]
Prescription stimulants	1 (0.6)	0 (0)	1 (1.6)	0.354[2]
Primary needle source: Before test				
Pharmacy or clinic	13 (4.5)	8 (5.2)	5 (3.7)	0.551
Drug dealer/street	53 (18.4)	33 (21.4)	20 (14.9)	0.155
Family member	33 (11.5)	11 (7.1)	22 (16.4)	0.014
Friend/acquaintance	93 (32.3)	46 (29.9)	47 (35.1)	0.346
Diabetic	93 (32.3)	54 (35.1)	39 (29.1)	0.281
Syringe exchange program	1 (0.3)	1 (0.6)	0 (0)	1.000[2]
No source given	2 (0.7)	1 (0.6)	1 (0.7)	1.000[2]
Cleaned syringes with bleach (6m):				
Before test	96 (33.3)	60 (39.0)	36 (26.9)	0.030
6 months after test (n=181)[3]	56 (30.9)	42 (35.9)	14 (21.9)	0.051
Straw sharing (6m): Before test	232 (80.6)	120 (77.9)	112 (83.6)	0.226
Straw sharing (6m): 6m after test (n=267)[1]	148 (55.4)	75 (51.0)	73 (60.8)	0.109

[1] n=267 PWID interviewed after 6 months (147 HCV+, 120 HCV-)

[2] Fisher's exact test

[3] n=181, excluding missing participants and those denying recent IDU at 6 months (117 HCV+, 64 HCV-)

3.3 Results

Description of IDU risk behavior

Of 503 individuals interviewed and serotested for HCV at baseline, participant follow-up rate was 94.4% (n=475) after 6 months, 93.2% (n=469) after 12 months, 95.0% (n=478) after 18 months, and 86.5% (n=435) after 24 months. Table 3.3 on the preceding page describes IDU habits and risk behavior among all study participants reporting recent (past 6-month) IDU at baseline (n=288) compared by HCV test result and counseling received. Note that serotest result and counseling *received* can differ from actual HCV serostatus, as some seropositive participants did not receive their test result at least 30 days prior to 6 month interviewing and were categorized as negative with regard to testing and counseling. 40% of PWID were sharing any IDU equipment at baseline and 35% reported injecting daily or more often in the last 6 months. After testing, overall proportion sharing any IDU paraphernalia had declined to 17% of the 267 individuals who returned after 6 months. Of note, despite an overall decline in IDU over the 6 month period, receiving HCV-positive T&C at baseline was associated with reporting continued IDU at 6 months in bivariate chi-squared analyses. 80% of those receiving HCV-positive T&C at baseline continuing to inject after 6 months, compared to just 53% of PWID receiving negative T&C ($p<0.0001$).

IDU sharing overall as well as sharing of ancillary equipment displayed similar patterns of *increased* risk following a positive test and counseling, although sharing of needles and syringes was significantly higher in the positive T&C group before testing as well ($p=0.041$). Daily IDU among active injectors (n=181 at 6 months) was associated with HCV-positive T&C both before ($p<0.0001$) and after testing ($p=0.007$), as was number of days of prescription opioid IDU out of the last 30 ($p<0.0001$ and $p=0.004$, respectively). The primary sources of needles and syringes at baseline were friends or acquaintances (32%) and diabetics (32%), which included diabetic acquaintances as well as study participants themselves. A smaller proportion of participants receiving HCV-positive T&C reported obtaining needles and syringes from family members (7.1%) relative to the HCV-negative group (16.4%; $p=0.014$), although baseline associations are not temporally ordered with regard to assessing impact of T&C. Finally, a greater proportion of participants testing HCV-positive reported cleaning used syringes with bleach before T&C (39% vs. 27%, $p=0.030$), whereas the proportion cleaning with bleach 6

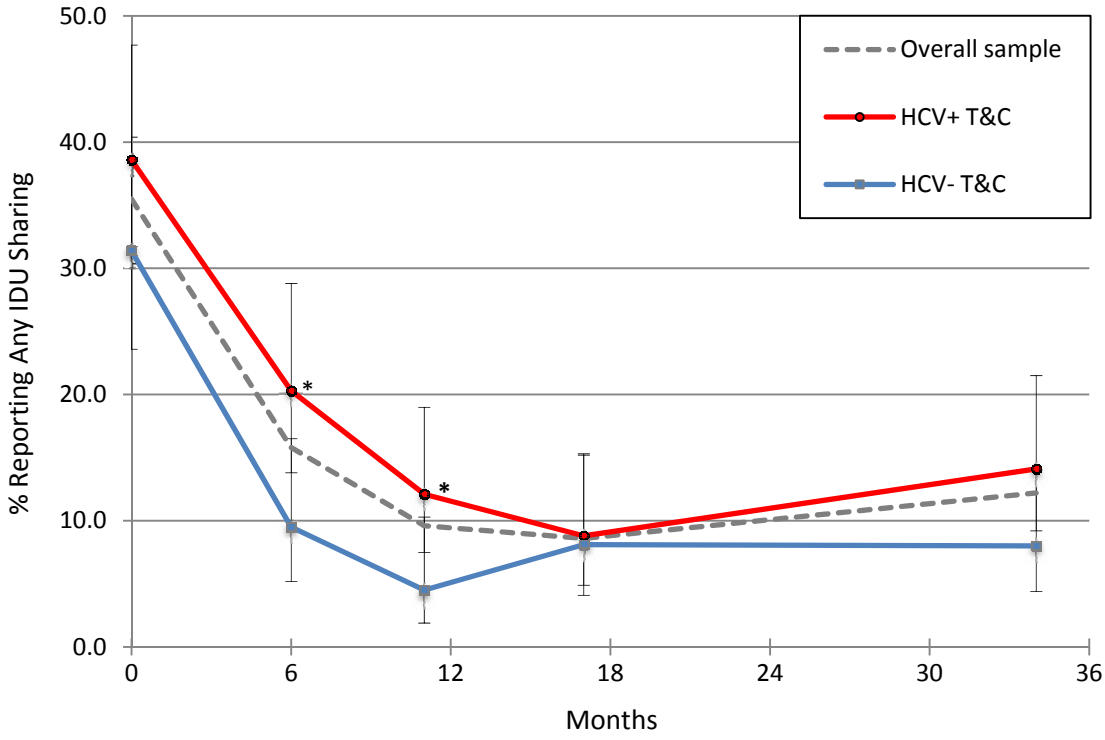

Figure 3.1: RDS-adjusted population estimates and 95% confidence intervals for proportion of PWID sharing any IDU paraphernalia. HCV serotest results and post-test counseling were received at least 30 days prior to interviews, with the exception of 0 months (*p<0.05)

months after HCV-positive T&C was higher as well but of only marginal significance (36% vs. 22% of HCV-negative; p=0.051).

288 (57.3%) participants reported IDU in the 6 months preceding baseline, and 283 of these individuals (98.3%) returned for at least one interview after baseline. Figure 3.1 depicts RDS-adjusted population estimates of proportion of PWID sharing any IDU paraphernalia over time compared by results of HCV status from previous screening and post-test counseling. Time since study enrollment is represented continuously as the mean number of months between the five interviews. An overall decline in IDU sharing was observed between baseline (35.5%) and 18 months (8.6%) among baseline PWID regardless of HCV status, followed by an overall increase at 24 months (12.2%) driven by rising absolute risk among individuals receiving HCV-positive T&C between baseline and 18 months. Despite insignificant differences before serotesting (p=0.25), IDU sharing prevalence between HCV groups differed significantly after 6 and 12 months (20.3% of HCV-positive vs. 9.5% of HCV-negative and 12.1% of HCV-positive vs. 4.5% of HCV-negative, respectively; p<0.05). Sharing prevalence at 18 months was nearly identical in the two groups

Table 3.4

Baseline sample characteristics of recent PWID and RDS-adjusted bivariate associations with any IDU sharing (n=283)

Characteristic	**Sample total** n (%)	**% IDU Sharing** (95% CI)	**% Not Sharing** (95% CI)	**p-value**
Male	167 (59.0)	50.4 (40.1-60.6)	60.1 (51.4-68.2)	0.155
White	265 (93.6)	93.4 (86.2-97.0)	94.8 (89.8-97.4)	0.662
Age (years) - mean (SD)	32.7 (7.9)	32.7 (31.0-34.4)	32.6 (31.2-34.1)	0.944
Any religious affiliation reported	81 (28.6)	32.7 (24.0-42.7)	21.2 (15.5-28.2)	0.042
Married	68 (24.0)	20.6 (13.1-30.8)	24.8 (18.6-32.3)	0.468
Bisexual or homosexual	27 (9.5)	12.2 (7.2-20.1)	6.0 (3.2-11.1)	0.789
Number of dependents - mean (SD)	1.0 (1.4)	0.7 (0.5-0.9)	1.1 (0.8-1.3)	0.012
Education (years) - mean (SD)	11.7 (2.4)	11.7 (11.3-12.1)	11.6 (11.2-11.9)	0.665
Monthly income (US $) - mean (SD)	1340.5 (2014.0)	1267.2 (901.6-1632.8)	1278.0 (970.6-1585.3)	0.965
Most often unemployed (last 3 years)	84 (29.7)	37.0 (27.6-47.5)	25.9 (19.1-34.0)	0.078
Driver's license and vehicle	93 (32.9)	37.0 (27.3-47.7)	33.8 (26.1-42.5)	0.639
Major depressive disorder	77 (27.2)	29.8 (21.5-39.7)	25.8 (19.1-33.8)	0.492
Generalized anxiety disorder	84 (29.0)	32.8 (24.2-42.8)	28.4 (21.0-37.3)	0.486
Antisocial personality disorder	97 (34.3)	33.3 (24.6-43.4)	34.5 (26.8-43.1)	0.855
Post-traumatic stress disorder	39 (13.8)	13.6 (8.4-21.2)	11.2 (7.1-17.3)	0.563
Received HCV+ test prior to study	63 (22.3)	39.1 (29.3-49.8)	15.4 (10.2-22.6)	0.0001
HCV+ serotest at baseline	171 (60.4)	71.1 (61.3-79.2)	59.5 (50.9-67.5)	0.069
≥5 of 6 general HCV questions correct	257 (90.8)	94.4 (88.4-97.4)	89.7 (83.5-93.7)	0.170
3 of 3 HCV transmission questions correct	271 (95.8)	98.2 (93.2-99.6)	95.3 (91.1-97.6)	0.185
Health insurance coverage	85 (30.0)	22.4 (15.2-31.7)	35.1 (27.4-43.8)	0.038
"Poor" to "fair" health status	127 (44.9)	49.4 (39.2-59.7)	40.2 (32.3-48.5)	0.169
Days with health problems[1] - mean (SD)	5.8 (10.1)	5.6 (3.7-7.6)	5.3 (3.8-6.9)	0.853
Reported chronic medical condition	91 (32.2)	33.9 (24.7-44.6)	32.0 (24.7-40.4)	0.768
Taking legally prescribed medication	72 (25.4)	23.3 (15.3-33.9)	27.5 (20.6-35.7)	0.499
Receiving physical disability pension	35 (12.4)	4.5 (2.0-10.2)	17.0 (11.7-24.1)	0.002
Substance use treatment (last 6m)	33 (11.7)	15.1 (9.3-23.5)	8.3 (5.0-13.4)	0.080
Legal methadone use (last 6m)	17(6.0)	4.8 (2.1-10.7)	6.0 (3.3-10.8)	0.676
Recent incarceration[1]	25 (8.8)	6.0 (2.9-11.9)	9.7 (5.9-15.7)	0.262
Lifetime behaviors				
Incarceration	241 (85.2)	83.1 (71.0-90.8)	82.3 (74.0-88.3)	0.895
Substance abuse treatment	186 (65.7)	63.9 (53.4-73.3)	68.3 (59.8- 75.8)	0.499
Drug overdose	104 (36.8)	37.2 (28.1-47.4)	34.1 (26.6-42.6)	0.628
Years of IDU - mean (SD)	8.0 (7.0)	8.3 (6.7-9.9)	7.7 (6.6-8.9)	0.547
Heroin use	123 (43.5)	47.3 (37.2-57.6)	37.0 (29.5-45.3)	0.122
Illicit methadone use	261 (92.2)	93.5 (86.0-97.1)	91.0 (85.1-94.7)	0.493
Legal methadone use	45 (15.9)	15.1 (9.4-14.8)	14.8 (10.0-21.3)	0.951
Illicit buprenophine use	201 (71.0)	80.3 (71.3-87.0)	65.3 (56.6-73.0)	0.013
Legal buprenorphine use	41 (14.5)	18.0 (11.0-28.2)	11.6 (7.4-17.9)	0.186
OxyContin® use	272 (96.1)	96.3 (91.3-98.5)	97.1 (92.9-98.8)	0.701
Other oxycodone use	273 (96.5)	96.7 (91.0-98.8)	96.8 (92.9-98.6)	0.949
Any other prescription opioid use	231 (81.6)	80.9 (71.9-87.6)	80.3 (71.9-86.7)	0.913
Sedative, hypnotic, or tranquilizer use	246 (86.9)	93.7 (87.4-97.0)	84.2 (77.5-89.2)	0.019
Barbiturate use	31 (11.0)	9.0 (4.6-16.6)	13.0 (8.2-19.8)	0.344
Crack use	212 (74.9)	76.1 (65.6-84.1)	74.9 (67.0-81.4)	0.842
Cocaine use	267 (94.4)	95.6 (89.4-98.2)	94.5 (90.0-97.1)	0.694
Methamphetamine use	128 (45.2)	49.4 (39.2-59.7)	38.2 (30.4-46.5)	0.095

Prescription stimulant use	110 (38.9)	44.0 (34.3-54.3)	33.3 (25.7-41.9)	0.105
Marijuana use	276 (97.5)	96.2 (80.8-99.4)	97.6 (94.1-99.1)	0.639
Hallucinogen use	142 (50.2)	56.6 (46.0-66.6)	38.4 (30.8-46.6)	0.007
Inhalant use	59 (20.9)	21.2 (14.2-30.5)	17.6 (12.5-24.1)	0.463
Multiple substance use	264 (93.3)	94.1 (87.1-97.4)	93.8 (89.2-96.5)	0.912
Recent risk behaviors (last 6m unless noted)				
Unprotected sex[1]	231 (81.6)	84.9 (76.2-90.7)	79.8 (72.3-85.7)	0.323
Unprotected sex with PWID[1]	102 (36.0)	56.8 (46.6-66.5)	27.5 (20.5-35.8)	<0.0001
Unprotected transactional sex[1]	18 (6.4)	3.7 (1.5-8.6)	5.8 (3.2-10.3)	0.389
Drug overdose	8 (2.8)	4.3 (1.8-9.8)	0.8 (0.2-3.3)	0.029
Alcohol use to intoxication	58 (20.5)	11.3 (6.8-18.2)	25.4 (18.4-34.0)	0.005
Daily or greater IDU frequency	101 (35.7)	51.5 (41.2-61.7)	26.4 (19.7-34.3)	0.0001
Days of IDU[1] - mean (SD)	12.4 (11.8)	17.4 (14.9-20.0)	9.7 (7.9-11.6)	<0.0001
Heroin use	48 (17.0)	15.3 (9.7-23.4)	14.3 (9.6-20.8)	0.824
Heroin IDU	31 (11.0)	9.9 (5.5-17.4)	9.3 (5.6-15.1)	0.863
Illicit methadone use	212 (74.9)	65.0 (53.6-74.9)	76.5 (68.6-82.9)	0.074
OxyContin® use	268 (94.7)	97.4 (89.6-99.4)	93.5 (88.8-96.3)	0.219
Other oxycodone use	242 (85.5)	91.9 (85.4-95.6)	80.3 (72.5-86.4)	0.009
Any other prescription opioid use	278 (98.2)	98.0 (92.1-99.5)	98.0 (93.5-99.4)	0.996
Any prescription opioid IDU	262 (92.6)	93.9 (85.7-97.6)	91.4 (85.7-94.9)	0.499
Days of opioid IDU[1] - mean (SD)	12.1 (11.9)	17.1 (14.5-19.6)	9.6 (7.7-11.4)	<0.0001
Sedative, hypnotic or tranquilizer use	272 (96.1)	97.4 (89.6-99.4)	94.5 (89.1-97.3)	0.340
Sedative, hypnotic or tranquilizer IDU	13 (4.6)	5.7 (2.7-11.8)	3.3 (1.2-8.6)	0.370
Barbiturate use	12 (4.2)	2.4 (0.5-9.7)	5.1 (2.6-9.7)	0.331
Crack use	92 (32.5)	32.5 (24.0-42.4)	25.7 (19.5-33.1)	0.240
Cocaine use	158 (55.8)	56.4 (45.9-66.3)	52.4 (43.8-60.9)	0.562
Cocaine IDU	112 (39.6)	39.1 (29.4-49.7)	40.8 (32.7-49.5)	0.801
Methamphetamine use	37 (13.1)	12.5 (7.5-20.2)	10.5 (6.7-16.0)	0.597
Methamphetamine IDU	8 (2.8)	2.5 (0.9-7.0)	1.9 (0.7-5.4)	0.735
Prescription stimulant use	47 (16.6)	18.0 (11.6-26.9)	12.9 (8.6-18.9)	0.257
Prescription stimulant IDU	11 (3.9)	2.1 (0.6-6.9)	3.9 (1.9-8.0)	0.384
Marijuana use	204 (72.1)	73.3 (62.5-81.9)	70.4 (62.3-77.3)	0.640
Hallucinogen use	19 (6.7)	8.9 (4.8-15.9)	4.2 (2.1-8.3)	0.106
Multiple substance use	268 (94.7)	90.8 (80.1-96.0)	94.7 (88.2-97.7)	0.345

[1] Last 30 days

(8.8% of HCV-positive and 8.1% of HCV-negative; p=0.844), and while sharing among PWID counseled as HCV-positive began to rise during the final study interval (14.1%), this proportion was not significantly different from the HCV-negative group (8.0%; p=0.127).

Correlates of IDU sharing at baseline

Table 3.4 above describes sociodemographic and baseline behavioral characteristics of the 283 recent PWID who returned for at least one interview and were eligible for longitudinal analyses. Participants predominantly male (59%), white (94%), single (76%), uninsured (70% uninsured at baseline; 51% reported no insurance throughout the study), with a mean age of

32.7 years. Of 171 (60%) total seropositive tests, 151 participants (53%) received positive test results and post-test counseling at least 30 days before 6-month follow-up; by the end of 18-month serotesting, 195 participants had tested positive at any study visit (68%). 241 participants (85%) had a lifetime history of incarceration and 104 (37%) had ever experienced a drug overdose. Over 96% reported having ever used either OxyContin® or another form of oxycodone non-medically, and the mean duration of IDU in the cohort was 8 years. 93% of participants reported injecting any prescription opioid over the course of the study, and the mean number of days of opioid IDU out of the last 30 was 12 over the course of the study. 113 participants (39.9%) reported sharing IDU needles, syringes, or other equipment in the 30 days preceding baseline interviews. 63 participants (22%) reported receiving an HCV-positive test prior to study enrollment, a characteristic strongly associated with IDU sharing in the 30 days preceding baseline (39% of HCV+ versus 15% of HCV-; $p<0.0001$). Other significant negative associations with IDU sharing at baseline included number of dependents ($p=0.012$), having any form of health insurance coverage ($p=0.038$), receiving a physical disability pension ($p=0.002$), and recent alcohol use to intoxication ($p=0.005$). Measures significantly associated with increased IDU sharing included prior HCV-positive testing ($p=0.0001$), recent unprotected sex with PWID ($p<0.0001$), lifetime history of using buprenorphine ($p=0.013$), prescription sedatives ($p=0.019$) or hallucinogens ($p=0.007$), recent drug overdose ($p=0.029$), recent non-medical use of oxycodone formulations aside from OxyContin® ($p=0.009$), and both measures of recent IDU frequency: daily IDU during the last 6 months ($p=0.0001$) and days injecting during the last 30 days ($p<0.0001$).

An RDS-adjusted multivariate logistic model for independent associations with recent IDU sharing reported at baseline is presented below in Table 3.5. A positive HCV test prior to study entry tripled the odds of reporting recent IDU sharing (95% confidence interval [CI]: 1.4-6.2), while recent unprotected sex with PWID conferred a 6.4-fold increased risk of IDU sharing 95% CI: 3.9-10.4). Reporting more dependents (adjusted OR [aOR]=0.7 per individual, 95% CI: 0.6-0.9) and receiving a pension for disability (aOR=0.2, 95% CI: 0.1-0.6) were negatively associated with IDU sharing. Illicit drug use measures increasing risk of IDU sharing included lifetime history of using sedatives (aOR=2.9, 95% CI: 1.1-7.2) or hallucinogens (aOR=2.8, 95% CI: 1.5-5.2), recent use of non-OxyContin® forms of oxycodone (aOR=2.9, 95% CI: 1.1-7.5), and frequency of IDU during the last 30 days (4% increased odds per day, 95% CI: 1.0-1.1). Of note, recent drug

Table 3.5
Baseline correlates of IDU sharing among recent PWID (n=283)[1]

Characteristic	Adjusted Odds Ratio	95% CI	p-value
Received HCV+ test prior to study	2.97	1.43 – 6.21	0.004
Number of dependents (per individual)	0.74	0.60 – 0.91	0.004
Currently receiving pension for physical disability	0.20	0.07 – 0.58	0.003
Unprotected sex with PWID (last 30 days)	6.36	3.89 – 10.41	<0.0001
Ever used sedatives, hypnotics, tranquilizers (lifetime)	2.86	1.13 – 7.22	0.026
Ever used hallucinogens (lifetime)	2.78	1.50 – 5.16	0.001
Oxycodone use of other than OxyContin® (last 6m)	2.87	1.11 – 7.45	0.030
Days of IDU out of last 30 (per day)	1.04	1.01 – 1.07	0.001

[1] Logistic regression model adjusted for RDS

overdose was also predictive of IDU sharing if included in the model, but the low number of participants reporting an overdose in the last 6 months (n=8) severely impacted the precision of this estimate (95% CI: 2.4-77.0), so the measure was dropped from the multivariate model. This change in model specification resulted in little apparent impact on goodness-of-fit (BIC=339.6 with recent drug overdose measure vs. 340.8 without). Logistic regression diagnostics were performed using the *linktest* command in Stata, which rebuilds the model using the linear predicted value squared to indicate potential errors in specification of predictors or link function. No significant errors in specification or with regard to omitted variables were detected in this diagnostic test (p=0.682), and the mean variance inflation factor (VIF) for this model calculated using Stata's *collin* command was 1.05, indicating no issues with regard to multicollinearity in this model.

Predictors of change in IDU sharing frequency

Table 3.6 summarizes sample characteristics and bivariate population-averaged associations with improved risk of HCV transmission risk parameterized as *decreased* frequency of IDU sharing following HCV test result disclosure and counseling. In light of the robust bivariate association of receiving an HCV+ test prior to study entry with decreased sharing among baseline PWID (OR=3.1, 95% CI: 1.8-5.6), participants reporting previous receipt of a positive test were excluded from analysis of the dependent change variable of interest in order to improve inferences regarding the potential effect of HCV screening on decreased IDU sharing frequency, resulting in a sample of 220 baseline PWID with no prior knowledge of HCV-positive

Table 3.6

Description of sample and population-averaged bivariate associations with decreased IDU sharing among recent PWID with no previous HCV+ test (n=220)[1]

Characteristic	Sample total n (%)	Odds Ratio	95% CI	p-value
Time-invariant				
Received HCV+ test prior to study[2]	63 (22.3)	3.13	1.76 – 5.57	<0.0001
Male	134 (60.9)	0.56	0.30 – 1.07	0.079
White	205 (93.2)	1.33	0.41 – 4.31	0.639
Age (years) - mean (SD)	32.5 (8.2)	1.00	0.96 – 1.05	0.832
Any religious affiliation reported	55 (25.0)	1.93	1.01 – 3.70	0.048
Married	74 (25.4)	0.63	0.26 – 1.55	0.317
Bisexual or homosexual	20 (9.1)	3.13	1.20 – 8.19	0.020
Number of dependents - mean (SD)	0.9 (1.3)	0.80	0.62 – 1.02	0.074
Education (year) - mean (SD)	11.7 (2.5)	1.07	0.95 – 1.21	0.237
Monthly income (per $100 US) - mean (SD)	1250.4 (1832.9)	0.99	0.98 – 1.01	0.399
Most often unemployed (last 3y)	63 (28.6)	1.77	0.94 – 3.36	0.079
Transportation	70 (31.8)	1.01	0.50 – 2.05	0.971
Major depressive disorder	57 (25.9)	1.27	0.65 – 2.49	0.483
Generalized anxiety disorder	57 (25.9)	1.53	0.76 – 3.08	0.237
Antisocial personality disorder	78 (35.5)	1.14	0.60 – 2.18	0.694
Post-traumatic stress disorder	33 (15.0)	2.30	1.04 –5.12	0.041
≥5 of 6 general HCV questions correct	196 (89.1)	1.59	0.58 – 4.37	0.369
3 of 3 HCV transmission questions correct	209 (95.0)	2.27	0.46 – 11.18	0.312
Time-varying				
HCV+ T&C at any study visit (0-18m)	134 (60.9)	1.12	0.91 – 1.38	0.288
Study occasions since HCV+ T&C: 1	107 (48.6)	0.93	0.81 – 1.07	0.302
2	120 (54.6)	0.94	0.81 – 1.08	0.356
3	128 (58.2)	1.17	1.00 – 1.36	0.047
4	134 (60.9)	0.81	0.64 – 1.03	0.081
Followed up with clinician after HCV+ test	74 (33.6)	1.08	0.94 – 1.24	0.257
Sought treatment after HCV+ test	11 (5.0)	0.95	0.92 – 0.98	0.001
Received HCV treatment after HCV+ test[3]	8 (3.6)	n/a	n/a	0.054
Health insurance coverage	109 (49.6)	0.94	0.84 – 1.05	0.283
“Poor” to “fair” health status	127 (57.7)	1.03	0.90 – 1.18	0.683
Days with health probs[4] - mean (SD)	5.1 (7.9)	0.99	0.99 – 1.00	0.228
Reported chronic medical condition	109 (49.6)	0.99	0.75 – 1.22	0.965
Taking legally prescribed medication	104 (47.3)	0.83	0.61 – 1.14	0.253
Receiving physical disability pension	59 (22.7)	0.99	0.87 – 1.13	0.860
Substance use treatment (last 6m)	64 (29.1)	1.07	0.87 – 1.32	0.512
Legal methadone use (last 6m)	24 (10.9)	1.12	0.87 – 1.44	0.380
Legal buprenorphine use (last 6m)	31 (14.1)	0.89	0.75 – 1.04	0.144
Incarceration[4]	87 (39.6)	1.08	0.92 – 1.26	0.335
Lifetime behavior				
Incarceration	184 (83.6)	1.26	0.44 – 3.60	0.670
Substance abuse treatment	141 (64.1)	0.74	0.58 – 2.13	0.752
Drug overdose	73 (33.2)	1.00	0.95 – 1.05	0.999
Years of IDU - mean (SD)	7.6 (7.0)	1.02	0.98 – 1.06	0.348
Heroin use	89 (40.5)	1.50	0.80 – 2.81	0.209
Illicit methadone use	201 (91.3)	2.26	0.66 – 7.69	0.192
Legal methadone use	32 (14.6)	0.77	0.31 – 1.91	0.571
Illicit buprenophine use	153 (69.6)	1.90	0.95 – 3.83	0.071

Legal buprenorphine use	25 (11.4)	0.93	0.35 – 2.47	0.891
Illicit OxyContin® use	209 (95.0)	0.43	0.12 – 1.60	0.209
Other illicit oxycodone use	211 (95.9)	0.88	0.20 – 3.87	0.871
Any other prescription opioid use	180 (81.8)	1.20	0.53 – 2.73	0.668
Sedative, hypnotic, or tranquilizer use	187 (85.0)	4.15	1.32– 13.11	0.015
Barbiturate use	21(9.6)	0.39	0.12 – 1.28	0.120
Crack use	159 (72.3)	1.08	0.54 – 2.15	0.825
Cocaine use	205 (93.2)	0.65	0.20 – 2.10	0.472
Methamphetamine use	93 (42.3)	1.48	0.80 – 2.75	0.216
Prescription stimulant use	85 (38.6)	1.43	0.76 – 2.70	0.267
Marijuana use	215 (97.7)	3.51	0.38 – 32.65	0.270
Hallucinogen use	110 (50.0)	1.96	1.03 – 3.75	0.039
Inhalant use	47 (21.4)	1.35	0.65 – 2.81	0.417
Multiple substance use	202 (91.8)	0.55	0.18 – 1.62	0.276
Recent risk behavior (last 6m unless indicated)				
Recent unprotected sex[4]	200 (90.9)	0.75	0.59 – 0.95	0.016
Recent unprotected sex with PWID[4]	82 (37.3)	0.72	0.51 – 1.00	0.053
Recent unprotected transactional sex[4]	7 (3.2)	0.98	0.93 – 1.04	0.605
Drug overdose	14 (6.4)	1.72	0.55 – 5.33	0.348
Alcohol use to intoxication	142 (64.6)	0.87	0.74 – 1.03	0.118
Daily or greater IDU frequency	98 (44.6)	0.77	0.58 – 1.01	0.060
Days of IDU[4] - mean (SD)	11.6 (10.5)	0.99	0.98 – 1.00	0.017
Heroin use	25 (11.4)	1.00	0.68 – 1.46	0.983
Heroin IDU	14 (6.4)	0.79	0.50 – 1.25	0.322
Illicit methadone use	172 (78.2)	0.97	0.81 – 1.17	0.766
Illicit buprenorphine use	159 (72.3)	0.85	0.67 – 1.06	0.153
OxyContin® use[5]	189 (85.9)	0.87	0.75 – 1.01	0.183
Any other oxycodone use	208 (94.6)	0.89	0.80 – 0.99	0.035
Any other prescription opioid use	192 (87.3)	0.96	0.82 – 1.13	0.653
Any prescription opioid IDU	162 (73.6)	0.78	0.62 – 0.98	0.036
Days of opioid IDU[4] - mean (SD)	6.5 (8.4)	0.99	0.98 – 1.00	0.017
Sedative, hypnotic or tranquilizer use	187 (85.0)	0.84	0.72 – 0.98	0.028
Sedative, hypnotic or tranquilizer IDU	5 (2.3)	0.58	0.14 – 2.38	0.453
Barbiturate use	19 (8.6)	0.97	0.93 – 1.02	0.218
Crack use	57 (25.9)	0.90	0.78 – 1.05	0.187
Cocaine use	107 (48.6)	0.90	0.71 – 1.13	0.347
Cocaine IDU	56 (25.5)	0.57	0.26 – 1.23	0.152
Methamphetamine use	36 (16.4)	0.89	0.65 – 1.23	0.484
Methamphetamine IDU	11 (5.0)	0.55	0.14 – 2.20	0.399
Prescription stimulant use	67 (30.5)	0.81	0.62 – 1.08	0.149
Marijuana use	181 (82.3)	1.05	0.83 – 1.35	0.663
Hallucinogen use	16 (7.7)	0.97	0.91 – 1.04	0.440
Multiple substance use	203 (92.3)	1.09	0.97 – 1.23	0.140

[1] GEE models with unstructured correlation, adjusted for RDS

[2] n=283 (participants who reported IDU in the 6 months preceding baseline and returned after 6 months

[3] GEE did not converge; zero PWID with reduced IDU sharing received HCV treatment compared to 8 (5.5%) reporting no treatment (p-value via Fisher's exact test)

[4] Last 30 days

[5] Includes original and abuse-deterrent formulations

status. Sample proportions for time-invariant measures are reported from baseline data collection. Sample totals for time-varying measures reflect proportion of participants reporting *any* occurrence between 6 and 24 months for dichotomous variables; means for reported continuous measures were calculated for the same period. Similar to the previous analysis including all baseline PWID (Table 3.4), the 220 participants included in this analysis were again largely male (61%), white (93%), single (75%), and uninsured over the course of the study (50%). Prescription sedatives and opioids were the most commonly reported drugs used illicitly during the last 6 months across all time points, with 85% reporting sedative use, 86% OxyContin®, 95% other forms of oxycodone, and 87% other prescription opioids. 162 participants (74%) reported prescription opioid IDU over the course of the study, compared to lower proportions of those reporting recent IDU of cocaine (26%), heroin (6%), methamphetamine (5%), sedatives (2%), and the one participant reporting prescription stimulant IDU (0.5%; not shown).

74 individuals in this sample (33.6%) reported decreased IDU-related equipment sharing at any interview between 6 and 24 months. In bivariate GEE analyses specifying unstructured covariance, decreased IDU sharing was associated with HCV-positive T&C 18 months after receipt of test results and counseling (OR=1.2, 95% CI: 1.0-1.4), but there were no significant associations at any other time point or with overall HCV T&C received at any point during the course of the study. Participants reporting any religious affiliation were more likely to report decreased IDU sharing (OR=1.9, 95% CI: 1.0-3.7), as were those reporting bisexuality or homosexuality (OR=3.1, 95% CI: 1.2-8.2), ever having used prescription sedatives (OR=4.2, 95% CI: 1.3-13.1) or hallucinogens (OR=2.0, 95% CI:1.0-3.8), and those meeting the DSM-IV criteria for PTSD (OR=2.3, 95% CI: 1.0-5.1). Variables negatively associated with decreased IDU sharing included seeking treatment after testing HCV-positive (OR=0.95, 95% CI: 0.92-0.98), recent unprotected sex (OR=0.8, 95% CI: 0.6-1.0), IDU frequency in the last 30 days (OR=0.99 per day, 95% CI: 0.98-1.00), recent non-medical use of any oxycodone formulation except OxyContin® (OR=0.9, 95% CI: 0.9-1.0) or sedatives (OR=0.8, 95% CI: 0.7-1.0), and frequency of prescription opioid IDU in the last 30 days (OR=0.99, 95% CI: 0.98-1.00). No other IDU measures had negative associations with decreased IDU sharing.

Table 3.7 presents adjusted odds ratios for decreasing IDU sharing from a multivariate GEE model with unstructured covariance specified. This model was statistically weighted to adjust for RDS and incorporated time elapsed since HCV-positive test disclosure and counseling

Table 3.7
Predictors of decreased IDU sharing among recent PWID with no previous HCV+ test (n=220)[1]

Characteristic		Adjusted Odds Ratio	95% CI	p-value
Male		0.38	0.19 – 0.75	0.006
Number of dependents (per individual)		0.73	0.55 – 0.97	0.029
Any religious affiliation		2.63	1.32 – 5.22	0.006
Study intervals since HCV+ test & counseling:	1	1.17	0.87 – 1.58	0.291
	2	1.26	0.92 – 1.73	0.152
	3	1.40	1.01 – 1.92	0.042
	4	1.01	0.72 – 1.43	0.940
Unprotected sex (last 30 days)		0.82	0.67 – 0.99	0.043
Sedative, hypnotic or tranquilizer use (last 6m)		0.81	0.70 – 0.95	0.007
Days of prescription opioid IDU (last 30 days)		0.99	0.97 – 1.00	0.026

[1] GEE model with unstructured correlation, adjusted for RDS

in discrete study intervals along with other significant covariates. Having previously received an HCV+ test before study enrollment was not significant at any time except 3 study intervals (approximately 18 months) after serotesting (aOR=1.4, 95% CI: 1.0-1.9). Men were 62% less likely to decrease their IDU sharing (95% CI: 0.2-0.8). Reported number of dependents was negatively associated with improvements in sharing behavior in this population (aOR=0.7 per individual, 95% CI: 0.6-1.0), whereas having a religious conferred more than 2.5 times the odds of decreasing IDU sharing over the course of the study (aOR=2.6, 95% CI: 1.3-5.2). Those reporting unprotected sex in the last 30 days were 18% less likely to reduce IDU sharing during the same period (95% CI: 0.7-1.0). Recent of frequency prescription opioid IDU also had a harmful effect on IDU sharing (aOR=0.99 per day of IDU, 95% CI: 0.97-1.0) independent of overall IDU frequency, which was not significant and dropped from the model. Finally, recent non-medical users of sedatives, hypnotics, or tranquilizers were nearly 20% less likely to report a reduction in frequency of IDU sharing (95% CI: 0.7-1.0).

The above model assumed an unstructured (US) specification for the covariance matrix quantifying within-subject correlation, with a quasi-Akaike information criteria (QIC) measure of goodness-of-fit of 1700.5. Given the nature of longitudinal data, an autoregressive (AR) covariance structure was also considered for the final model, as presented in the Appendix (Table A3.1). Because missed "middle" interviews are restricted from models specifying autoregressive covariance, the sample size for this alternative model was n=203. Number days of prescription opioid IDU was not significant and replaced with any prescription opioid IDU in the last 6 months (aOR=0.8, 95% CI: 0.6-1.0). As with the unstructured correlation model, HCV-

positive T&C conferred higher likelihood of decreasing sharing after 3 study intervals (aOR=1.2, 95% CI: 0.9-1.4), but the effect was of marginal significance in the autoregressive model (p=0.068). Because the QIC value for this reduced autoregressive model suggested no improvement in goodness-of-fit (QIC_{AR}=1775.5 versus QIC_{US}=1700.5), the unstructured specification presented above was selected as the final model. Mean VIF for final predictors in the unstructured model was 1.21, indicating no issues with multicollinearity.

To investigate potentially deleterious changes in IDU sharing frequency over time, a multivariate GEE model for *increased* IDU sharing in the last 30 days is presented in Table 3.8. As summarized in the Appendix in Table A3.2, receipt of an HCV-positive test prior to study enrollment was not significantly associated with risk of increased IDU sharing in bivariate analyses (OR=1.1, p=0.85), thus these 63 participants were included in this analysis. 55 study participants reporting recent baseline IDU (19.4%), or an RDS-adjusted population estimate of 18.1% (95% CI: 13.7-23.6), increased their frequency of IDU sharing between 6 and 24-month interviews. HCV-positive T&C had statistically marginally negative associations with increased IDU risk only in the HCV-positive T&C had statistically negative associations with increased IDU risk only in the third and fourth study intervals (p=0.062 and p=0.079, respectively). Length of time in the study was positively associated with increasing IDU sharing frequency (aOR=1.04 per month, 95% CI: 1.01-1.07), as recent unprotected sex with a PWID (aOR=5.2, 95% CI: 2.8-9.4), illicit use of prescription stimulants (aOR=3.3, 95% CI: 1.5-7.6), and frequency of prescription

Table 3.8
Predictors of increased IDU sharing among recent PWID (n=283)[1]

Characteristic		**Adjusted Odds Ratio**	**95% CI**	**p-value**
Time since study enrollment (per month)		1.04	1.01 – 1.07	0.013
Monthly income (per $100)		0.97	0.95 – 1.00	0.032
Study intervals since HCV+ test & counseling:	1	1.38	0.58 – 3.28	0.465
	2	1.04	0.44 – 2.46	0.923
	3	0.38	0.14 – 1.05	0.062
	4	0.31	0.08 – 1.14	0.079
Unprotected sex with PWID (last 30 days)		5.17	2.84 – 9.42	<0.0001
Ever used marijuana (lifetime)		0.40	0.19 – 0.87	0.021
Prescription stimulant use (last 6m)		3.31	1.45 – 7.58	0.005
Days of prescription opioid IDU in last 30 days (per day)		1.09	1.07 – 1.11	<0.0001

[1] GEE model with unstructured correlation, adjusted for RDS

opioid IDU (aOR=1.09 per day, 95% CI: 1.07-1.11). The unstructured covariance model fit equally as well as the autoregressive model (n=264) presented in Appendix Table A3.3, with QIC values of 588.9 for both models and similar magnitudes and directions of associations and levels of significance for all independent measures in the multivariate models. Finally, mean VIF with the unstructured specification was 1.22, suggesting no multicollinearity between predictors in the final model.

Predictors of IDU cessation

In light of the association of HCV-positive T&C with *increased* frequency of IDU after 6 months observed among baseline PWID (Table 3.5) and the nested nature of injection drug paraphernalia sharing within IDU itself, a secondary analysis of injection cessation over time was undertaken to further explore this protective behavior. Receiving an HCV-positive test prior to study enrollment was negatively associated with IDU cessation in the bivariate analyses presented in Table A3.4 among the 283 baseline PWID, thus analysis of this outcome was undertaken excluding the 63 individuals reporting a prior positive test. 166 of these 220 participants (75.5%) reported at least one 6 month break from IDU between 6 and 24-month interviewing. Bivariate GEE analysis adjusted with RDS weights also appears in Table A3.4 of the Appendix. Given the high prevalence of IDU as a preferred route of drug administration in this sample and the robust correlation observed between IDU and illicit drug use during the same study interval, two multivariate models are presented with regard to IDU cessation over the course of the study: one excluding recent illicit drug use to assess non-drug-related time-varying measures, and another including significant recent illicit drug use measures in order to differentiate drug-specific associations with likelihood of IDU cessation. Of note, inferences regarding the principal research question of interest (impact of HCV screening on IDU cessation) were similar between these two model specifications.

Table 3.9 presents a multivariate GEE model with an unstructured covariance specification and recent illicit drug use measures excluded (n=220). HCV-positive testing and counseling conferred a 40% reduction in odds of IDU cessation during the interval following serotesting (aOR=0.6, 95% CI: 0.4-1.0). The most robust predictor of reporting continuous IDU at each interview was recent unprotected sex with PWID, which was associated with an 84% decrease in odds of cessation (95% CI: 0.1-0.3). Other independent predictors of increased odds of IDU cessation included receiving substance abuse treatment in the last 6 months (aOR=2.2,

Table 3.9
Predictors of IDU cessation among recent PWID, excluding recent illicit drug use measures (n=220)[1]

Characteristic		Adjusted Odds Ratio	95% CI	p-value
Study intervals since HCV+ test & counseling:	1	0.59	0.35 – 1.00	0.049
	2	1.60	0.90 – 2.84	0.111
	3	1.48	0.80 – 2.71	0.210
	4	1.94	0.89 – 4.23	0.097
Number of dependents		1.31	1.09 – 1.56	0.004
Lifetime history of incarceration		0.23	0.10 – 0.53	0.001
Currently receiving disability pension		2.86	1.63 – 5.02	<0.0001
Substance abuse treatment (last 6m)		2.23	1.22 – 4.04	0.009
Unprotected sex with PWID (last 30d)		0.16	0.09 – 0.30	<0.0001
Alcohol use to intoxication (last 6m)		0.64	0.43 – 0.96	0.029
Ever used illicit OxyContin® (lifetime)		0.24	0.09 – 0.62	0.003
Days of Rx opioid IDU in last 30d (per day)[2]		0.93	0.91 – 0.95	<0.0001

[1] GEE model with unstructured correlation, weighted for RDS
[2] At baseline

95% CI: 1.2-4.0), number of dependents reported (aOR=1.3 per individual, 95% CI: 1.1-1.6), and current receipt of a pension for physical disability (aOR=2.9, 95% CI: 1.6-5.0). Lifetime histories of incarceration (aOR=0.2, 95% CI: 0.1-0.5) and non-medical OxyContin® use (0.2, 95% CI: 0.1-0.6) decreased the likelihood of IDU cessation, as did frequency of prescription opioid IDU in the 30 days preceding baseline (aOR=0.93 per day, 95% CI: 0.9-1.0) and recent alcohol use to intoxication (aOR=0.6, 95% CI: 0.4-1.0). Table A3.5 in the appendix presents a GEE model with autoregressive covariance specified (n=203). The QIC value of this alternative model suggested marginal improvement in goodness-of-fit (QIC_{AR}=1746.1 vs. QIC_{US}=1753.3). The significance and direction of associations agreed in both models with the exception of recent use of alcohol to intoxication, which was dropped from the autoregressive model. Associations of all other covariates were of the same direction and similar in magnitude between the two models.

Finally, Table 3.10 below summarizes multivariate odds ratios for IDU cessation including recent illicit drug use measures with an unstructured covariance matrix for GEE. Directions and magnitude of associated covariates were unaffected with the exception of recent alcohol use to intoxication and substance abuse treatment, which were dropped from the recent illicit drug use model. Unprotected sex with PWID in the last 30 days remained the strongest predictor of continuous IDU, conferring an 80% reduction in odds of IDU cessation (95% CI: 0.1-0.4), largely in agreement with the recent drugs-excluded model in Table 11. Drug-

Table 3.10
Predictors of IDU cessation among recent PWID, including recent illicit drug use measures (n=220)[1]

Characteristic		Adjusted Odds Ratio	95% CI	p-value
Time since study enrollment (per month)		0.98	0.95 – 1.00	0.086
Study intervals since HCV+ test & counseling:	1	0.40	0.21 – 0.73	0.003
	2	1.10	0.60 – 2.02	0.747
	3	1.05	0.53 – 2.08	0.882
	4	1.29	0.49 – 2.42	0.827
Number of dependents (per individual)		1.29	1.05 – 1.57	0.015
Lifetime history of incarceration		0.23	0.11 – 0.50	<0.0001
Currently receiving disability pension		2.66	1.46 – 4.83	0.001
Unprotected sex with PWID (last 30d)		0.20	0.11 – 0.37	<0.0001
Days of Rx opioid IDU in last 30d (per day)[2]		0.93	0.91 – 0.95	<0.0001
Illicit OxyContin® use (last 6m)		0.22	0.13 – 0.39	<0.0001
Other oxycodone use (last 6m)		0.33	0.20 – 0.54	<0.0001
Cocaine use (last 6m)		0.48	0.28 – 0.81	0.006

[1] GEE model with unstructured correlation, weighted for RDS
[2] At baseline

specific illicit use in agreement with the recent drugs-excluded model in Table 3.9. Drug-specific illicit use measures independently associated with decreased likelihood of IDU cessation in this model were OxyContin® (aOR=0.2, 95% CI: 0.1-0.4), other formulations of oxycodone (aOR=0.3, 95% CI: 0.2-0.5), and cocaine (aOR=0.5, 95% CI: 0.3-0.8). The QIC value for this model was 1498.02, suggesting superior fit to the model without recent illicit drug use measures in Table 3.9 (QIC=1753.3), as expected given the strong correlation between recent illicit drug use and IDU in this sample. Regarding the independent measure of interest, HCV-positive T&C at the previous study visit was again associated with decreased odds of IDU cessation during the subsequent interval (aOR=0.4, 95% CI: 0.2-0.7). An alternate GEE model specifying an autoregressive covariance structure (n=203; see Table A3.6 of Appendix) resulted in no changes of significance or direction of any associations, with adjusted odds ratios similar in magnitude and no improvement in goodness-of-fit (QIC_{AR}=1506.7 vs. QIC_{US}=1498.0). Therefore, the unstructured covariance specification in Table 3.10 was selected as the final model for statistical inference.

3.4 Discussion

This study is the first to examine longitudinal patterns of IDU risk behavior in a rural population of PWID, and among the first to assess the impact of drug-specific illicit use. Consistent themes emerged across various metrics of IDU behavior pursuant to assessment of impact of screening and counseling on risk behaviors for HCV transmission. In concordance with the majority of previous studies addressing this question, HCV testing and post-test counseling had minor apparent positive impact on IDU-related risk behavior in this rural Appalachian population, with mixed findings among individuals testing positive in particular. At time of study enrollment, prior HCV-positive status awareness was strongly associated with sharing any IDU paraphernalia in the past 30 days. Because this association held true for two other measures of IDU behavior (decreased IDU frequency and IDU cessation), 63 participants reporting a previous HCV-positive test were excluded from multivariate analyses of these outcomes to enhance inferences regarding HCV testing and counseling received specifically during the course of this study. Following suggestions of a trend at 6 and 12-month interviews, a modest positive association with *decreased* frequency of IDU sharing was observed among individuals testing positive 18 months previously. This effect was transient, however, and no significant effect of HCV-positive T&C detected at the following interview. Similarly, HCV-positive T&C did not significantly impact on *increased* IDU sharing during any study period, although marginally protective associations ($p<0.10$) were observed 18 and 24 months after serotesting. However, it is important to bear in mind that these results reflect *change* in IDU frequency, and a nominally higher proportion of HCV-seropositive individuals were sharing IDU paraphernalia at every study occasion, with significantly higher proportions at 6 and 12 months. Moreover, with regard to IDU continuity regardless of sharing patterns, positive T&C had a clear harmful effect in the short term, with a significant reduction in odds of IDU cessation seen in both the drug-excluded and recent drug use-specific longitudinal models. This effect was also transient, however, and no associations with the occurrence of IDU were significant beyond 6 months. In sum, these results suggest that HCV screening and brief post-test counseling has modest impact on IDU risk in the setting of rural Appalachia. However, the behavioral changes observed were not sustained over time and may be unlikely to significantly reduce HCV incidence among rural Appalachian PWID in the absence of further intervention.

Cross-sectional associations with lower risk of IDU sharing at baseline included number of dependents reported and receipt of a disability pension. Interestingly, while these factors also

emerged as protective in longitudinal analysis as significant predictors of IDU cessation, number of dependents was *negatively* associated with reporting a decreased frequency of IDU sharing, suggesting a complex role of family-related financial obligations in risk calculation among rural PWID. In addition to HCV-positive status awareness, measures associated with increased IDU sharing at baseline included recent unprotected sex with a drug injector and various illicit drug use measures, including lifetime use of sedatives and hallucinogens, recent use of oxycodone-containing prescription opioids, and frequency of recent opioid IDU. Of these, unprotected sex with another PWID and frequency of prescription opioid IDU were repeatedly associated with greater IDU risk quantified as sharing and continuous injection in longitudinal analyses, whereas recent non-medical use of OxyContin® and other oxycodone-containing drugs predicted diminished likelihood of IDU cessation only.

Of the sociodemographic factors were associated with changes in IDU behavior, gender was the most notable. Men were significantly less likely to decrease IDU sharing over the course of the study, suggesting that women could be more responsive targets of IDU risk reduction education efforts, regardless of HCV serostatus. Moreover, interventional efforts may need to consider gender-specific approaches and focus particular attention to IDU risk behavior among men. Of note, this finding is in direct contrast to other studies of IDU sharing behavior, which have reported women being more likely to share injection paraphernalia (Evans, Hahn et al. 2003; Korthuis, Feaster et al. 2012). Reported number of dependents exhibited a negative association with decreasing IDU sharing, whereas those reporting any religious affiliation were more likely to reduce IDU sharing over the course of the study. These findings are novel in the field of IDU risk behavior research, and the latter association is of particular interest given the importance of religion in Appalachian culture (Pew Forum on Religion & Public Life 2008) and the key role of altruism among HCV-positive PWID who elect to reduce IDU risk behavior. Moreover, religion-based public health interventions (Studts, Tarasenko et al. 2012; Schoenberg, Bundy et al. 2014) have been effective in rural Appalachia, although 75% of individuals in this sample reported no religious affiliation. In addition, while income was not associated with IDU risk reduction in this population, higher income did significantly reduce risk of *increased* IDU sharing, a finding supported by the sharing-protective association reported in a French sample of HCV-seronegative PWID (Vidal-Trecan, Coste et al. 1998). Other sociodemographic measures had little impact on IDU sharing, including age, despite previously reported protective

associations (Norden, Saxon et al. 2009; Korthuis, Feaster et al. 2012) and education, although Korthuis et al (2012) reported a protective effect of higher education.

Recent unprotected sex with another PWID displayed robust risk associations across metrics of IDU risk, including a strong positive association with increased frequency of IDU sharing and decreased likelihood of IDU cessation. Similarly, *any* unprotected sex in the last 30 days was negatively associated with reducing IDU sharing frequency. The influence of sexual risk on IDU behavior has been reported in previous studies, with increased risk of IDU sharing among individuals reporting transactional sex (Wood, Li et al. 2005), sex partners who currently inject (Shaw, Shah et al. 2007), and among women, recent sex with PWID (Evans, Hahn et al. 2003). Furthermore, Evans et al. (2003) also reported that recent sexual contact with PWID explained concomitant IDU risk better than gender alone. Despite very low risk of transmission by sexual contact (Terrault, Dodge et al. 2013), risky sexual behavior such as transactional sex (Hahn, Page-Shafer et al. 2002; Ward 2013) is a commonly associated with HCV infection, suggesting correlation between sexual and IDU risk behaviors given the very low likelihood sexual transmission. The robust association in this population between IDU sharing and unprotected sex with partners known to be injecting further supports this connection.

In one of the few studies to report associations of using specific drugs with IDU sharing, Korthuis et al. (2012) reported that use of any opioid, marijuana, and crack via IDU were positively associated with IDU sharing. In this analysis, frequency of injecting prescription opioids in particular conferred greater risk of IDU sharing, independent of overall IDU frequency, whereas recent crack IDU had no significant associations and lifetime marijuana users were actually less likely to increase sharing. Moreover, recent non-medical use of prescription stimulants predicted increased IDU sharing, whereas non-medical sedative uses were less likely to decrease sharing frequency. However, non-medical use of prescription OxyContin® and other oxycodone formulations, particularly via IDU, was consistently associated with elevated IDU risk quantified as either increased or decreased sharing frequency. As with IDU cessation, this further attests to the unique behavioral risk relationships of non-medical prescription drug use in general and prescription opioid IDU in particular among rural Appalachian PWID relative to their urban counterparts (Young, Havens et al. 2010; Havens, Oser et al. 2011; Havens, Lofwall et al. 2013).

Previous studies have suggested “breaks” from IDU to be effective as a pragmatic approach to reducing HCV incidence in high-risk populations, even if only in the short-term

(Hahn, Page-Shafer et al. 2002; Evans, Hahn et al. 2009; Page, Morris et al. 2013). A recent longitudinal study reported a small but significant decrease in IDU frequency among PWID testing HCV-positive (Aspinall, Weir et al. 2014). Among rural PWID in this study, by contrast, HCV-positive T&C reduced the likelihood of taking a break from IDU in the short-term. This also implies that receiving a *negative* HCV test result may have a beneficial effect on IDU cessation in the 6 months following testing. However, this pattern was not sustained over time, implying that the impact of testing and counseling alone is transient regardless of serostatus, and that focused multidisciplinary interventions with peer-driven approaches are more likely to effect lasting decreases in IDU risk (Latka, Hagan et al. 2008). Although there were no significant associations between alcohol use and IDU sharing as reported in other studies (Vidal-Trecan, Coste et al. 1998; Le Marchand, Evans et al. 2013), recent alcohol use to intoxication was a risk factor for continuous IDU. This finding echoes previous research (Shah, Galai et al. 2006; Evans, Hahn et al. 2009), suggesting that IDU is best reduced via complete abstinence from *any* drug use, whether illicit or legal in nature. Incarceration also substantially reduced the likelihood of IDU cessation in this population, similar to findings in an urban population of PWID in Baltimore (Galai, Safaeian et al. 2003) and related to prior associations with both IDU sharing (Wood, Li et al. 2005) and hepatitis C itself (Neff 2003; Larney, Kopinski et al. 2013). Lower IDU frequency was another key predictor of cessation reported by Evans et al. (2009), and in this cohort baseline IDU frequency of prescription opioids in particular was negatively associated with IDU cessation, whereas overall IDU frequency was not significant. Similarly, while heroin use also predicted decreased chance of cessation among urban PWID in San Francisco (Evans, Hahn et al. 2009), OxyContin® and oxycodone were important predictors of continuous IDU in the rural population studied here. This finding reinforces important differences in IDU preference between urban and rural populations as reported in previous research of Appalachian PWID (Young, Havens et al. 2012). Finally, illicit benzodiazepine use was negatively associated with IDU cessation in the urban San Francisco cohort (Evans, Hahn et al. 2009), while in this population recent non-medical use of sedatives decreased the likelihood of reducing IDU sharing frequency, but had no apparent impact on occurrence of IDU itself.

Less than a third of this study sample reported receiving substance abuse treatment during any study interval. Encouragingly, however, recent substance abuse treatment in this population decreased risk of engaging in IDU, supporting arguments to expand access such programs in the rural Appalachian region and reiterating reports from Galai (2003) and Evans et

al. (2009). As with baseline prevalence of IDU sharing, receiving a disability pension again conferred a protective effect. Whether this association resulted from substance abuse treatment and support structure of this government program, habitual reporting bias stemming from program eligibility criteria, or associated drug testing is unknown. Furthermore, although no previous studies have investigated the impact of government support such as disability insurance program on IDU risk, the protective association observed here is striking given that nearly a quarter of this population reporting receiving disability over the course of the study, and Appalachian Kentucky has among the highest proportions of disability recipients nationwide (Flippen 2014). Echoing the findings of Shah and colleagues (2006), risky sexual relationships with PWID were a robust predictor of continuous IDU in this population. As with IDU sharing as discussed above, this further suggests considerable overlap of injecting and sexual risk relationships in this population and supports the application of network-based approaches to the study of IDU among risk rural PWID. Finally, an association between number of dependents and increased likelihood of IDU cessation was observed, independent of recent illicit drug use. This finding implies that family responsibilities could be important points of social leverage with regard to targeting and implementation intervention efforts aimed at diminishing IDU risk behavior in Central Appalachia.

Prior research of HCV prevention modalities often refers to the hypothesis that increasing HCV screening reduces injection risk behavior among PWID (Page, Morris et al. 2013), although the strength of evidence that HCV screening reduces transmission risk behaviors was rated "low" in a comparative effectiveness review from the Agency for Health and Research Quality (Chou, Cottrell et al. 2012). Furthermore, it has been noted that HCV testing and counseling creates opportunities to decrease IDU risk behavior on two levels: 1. *individual*, among those testing HCV-negative; 2. *population*, or the network of PWID connected via IDU to those testing positive (Hagan, Campbell et al. 2006). If the concept of *risk* is defined as "the chance you take of becoming injured by a hazard" (Norden, Saxon et al. 2009), then PWID already infected with HCV receive no primary preventive benefit in reducing IDU-related risk behavior. Thus, population-level primary prevention is optimized only if HCV-positive PWID place value in reducing or eliminating IDU sharing behavior. However, concordant with another study of PWID in substance abuse treatment reported an association of HCV-positive status awareness (Korthuis, Feaster et al. 2012), HCV-positive status awareness conferred increased risk of IDU sharing in cross-sectional cross-sectional analysis (Table 3.5), and the magnitude of

association was similar between the studies, with multivariate odds ratios of 3.0 in this sample and 2.4 in the Korthuis (2012). By contrast, a recent study of HCV seroconverters reported no change in frequency of injecting with used equipment among PWID recently acquiring antibodies to HCV, although overall frequency of any IDU did show a modest decrease (Aspinall, Weir et al. 2014). Another major study differentiated risk behaviors on the basis of HCV-positive awareness versus HCV-negative awareness in a cross-sectional analysis, acknowledging that HCV "risk" has distinctly different meanings between HCV-seropositive and HCV-seronegative PWID—specifically, infection versus disease manifestation, respectively. Using this approach, Hagan and colleagues (2006) reported that PWID who were aware of their HCV-*negative* status were less likely to share syringes or cotton filters. Related patterns of *increased* risk among HCV-seropositive PWID aware of their status have been reported in cross-sectional analysis (Norden, Saxon et al. 2009). By contrast, other researchers have found no effect of HCV screening and/or seropositive status on IDU risk (Ompad, Fuller et al. 2002; Miller, Mella et al. 2003; Tsui, Vittinghoff et al. 2009), whereas just two have reported decreased IDU sharing among HCV-seropositive PWID (Vidal-Trecan, Coste et al. 2000; Kwiatkowski, Fortuin Corsi et al. 2002), implying that the net population-level effect of HCV screening and post-test counseling with regard to primary prevention behaviors among seropositive PWID is most often null or even potentially negative in the absence of further interventional effort, but these negative effects can be offset by prevention "reminders" among seronegative PWID (Hagan, Campbell et al. 2006).

Overall, findings from the rural population studied here suggest a similar pattern, with HCV-positive testing and counseling weakly associated with reduced injecting risk behaviors or of null effect and short-term tendency among those testing seronegative to cease IDU. This implies there could be modest population-level benefit to screening among HCV-seropositive PWID, as suggested by Kwiatkowski (2002) and Vidal-Trecan (2000), and a short-lived individual-level effect among HCV-seronegative PWID with regard to IDU cessation. However, as all apparent benefits were ephemeral in nature, the overall preventive gains of screening are likely minimal or null in this population, in agreement with the preponderance of conclusions from other longitudinal studies (Ompad, Fuller et al. 2002; Tsui, Vittinghoff et al. 2009; Aspinall, Weir et al. 2014). In this analysis, sharing proportions presented in Figure 4.1 became nearly identical between HCV groups after 18 months, when a beneficial effect of positive T&C on IDU sharing become significant, but this preventive gain was not sustained. This trajectory suggests that the

entire sample substantially decreased IDU sharing after baseline regardless of serostatus, but individuals testing negative were somewhat less likely to decrease sharing relative to those testing positive 18 months previously. Moreover, this preventive benefit was not sustained beyond 18 months, and the proportion of HCV-seropositive individuals sharing IDU paraphernalia at the final study occasion showed signs of increase from the preceding visit. Furthermore, individuals testing HCV-positive were more likely to report continuing to engage in IDU in the 6 months following their serotest. Thus, while HCV-positive testing and counseling had a potentially beneficial effect on IDU sharing frequency in this population, these behavioral gains may be offset by a concomitant tendency to continue injecting 6 months after positive screening. Moreover, no associations in IDU risk behavior were observed beyond 18 months, although there was marginally significant trend among individuals who received HCV-positive T&C to cease IDU 24 months or more following serotesting. Regardless, HCV screening was not clearly effective in decreasing IDU risk in this population, and as suggested in other studies among PWID, more intensive targeted interventions are likely required to meaningfully decrease HCV incidence via behavior change.

The study of primary HCV prevention is predicated on understanding the concept of "risk" among seropositive PWID—individuals with substantial IDU risk who are likely infected with HCV. Risk perception and aversion theory offers valuable insight into the culture of HCV risk and IDU behavior among injectors. In the first application of psychometric scaling methods (Slovic, Fischhoff et al. 1985) to a drug-using sample, Marsch and colleagues (2007) found the three most significant components impacting risk perception among PWID to be (ranked in descending order of importance in accounting for perception variance): 1. potential severity of consequences related to the risk; 2. degree of certainty with regard to experiencing potential consequences of risk; and 3. extent to which consequences of risk are delayed versus immediate. In theory, HCV screening and counseling should ameliorate both factors 1 and 2, first by reducing the uncertainty of future consequences by providing status awareness, and second by educating PWID with regard to the potential severity of untreated HCV in the long term—namely, morbidity and mortality due cirrhosis and HCC, as well as extrahepatic morbidity. However, the third component in this model of risk perception is largely unaffected by HCV testing and counseling. Moreover, HCV risk would presumably rank very low in this category regardless of serostatus, given that the disease manifestations of CHC take upwards of two decades to manifest, if symptoms appear at all. It is logical to surmise that many PWID are likely

concerned with the more immediate consequences of IDU-related risk, namely managing the symptoms of opiate addiction, maintaining adequate food and shelter, avoiding incarceration and other legal concerns, and more rapidly progressing health problems caused by IDU. Furthermore, among individuals already infected with HCV, the notion of risk compensation becomes relevant, given that these individuals' "risk" of acquiring HCV is effectively negated, eclipsed perhaps by other more clear and present medical risks of IDU, such as drug overdose and infective endocarditis, although it has been reported that the health risks of IDU are not high-priority concerns of daily life among most PWID (Miller 2005). Even among seronegative individuals, the threat of HCV acquisition may seem minor compared to other risks routinely faced by PWID. HCV has been referred to as "ordinary" and "ubiquitous" by PWID (Rhodes, Davis et al. 2004; Rhodes and Treloar 2008), to the extent that HCV has assumed a normative status in many communities of injectors (Davis, Rhodes et al. 2004; Treloar and Rhodes 2009). Many PWID and even some public health officials regard HCV as an "inevitable" consequence of IDU not worth the effort of preventing (Page, Morris et al. 2013). Moreover, "hepatitis" as a potentially hazardous construct was ranked only intermediate in a scale of perceived risk among PWID: position 20 out of 53, just ahead of "police work," "barbiturates," and "motorcycles," but behind "dynamite," "terrorism," and "nuclear power," with HIV and AIDS ranked first and second (Marsch, Bickel et al. 2007). This further suggests that the potentially severe, but very gradual health threats that affect "only" 1 out of 4 individuals with CHC are not sufficient to substantially deter injection-related risk among PWID after basic screening without more focused intervention.

Despite this low HCV risk perception, the modest effect of screening observed in this Appalachian cohort suggest that scaling up of HCV screening and counseling among rural PWID do offer a moderate benefit to behavioral targets of primary prevention. Perhaps reflective of the poor access to healthcare and disease screening services characterizing Central Appalachia, it appears that *any* intervention is likely better than none with regard to HCV risk among rural PWID. However, many researchers suggests that one intervention in isolation—even those requiring significant government or other financial support such as syringe exchange and opioid substitution programs)—are unlikely to significantly reduce high HCV incidence among PWID (Page-Shafer, Hahn et al. 2007; Rhodes and Hedrich 2010; Hagan and Schinazi 2013; Grebely and Dore 2014; Hellard, Doyle et al. 2014). By contrast, *combined* interventions incorporating integrated addiction treatment, focused counseling, peer support, opioid substitution, syringe

exchange, and convenient medical care for HCV have been demonstrated to effect sustained decreases in IDU risk behavior and HCV transmission (Wright and Tompkins 2006; Birkhead, Klein et al. 2007; Latka, Hagan et al. 2008; Zule, Costenbader et al. 2009; Vickerman, Martin et al. 2012; Martin, Hickman et al. 2013). Meta-analysis of SEP and OST in the UK reached the same conclusion, finding that combined OST and high-coverage SEP together resulting in a 48% reduction in needle sharing and an 80% reduction in odds of acquiring HCV (Turner, Hutchinson et al. 2011). The superiority of combined interventions seems likely to hold true in rural Appalachia as well, though unfortunately both the funding and political will to support implementation of such programs in the Central Appalachian region is unlikely in the foreseeable future. As was noted earlier, Kentucky is one of 18 states in the U.S. without SEPs (Foundation for AIDS Research 2013), as such programs are prohibited by state law (Kentucky Legislative Research Commission 2010). Thus despite the tremendous economic burden projected from public health impacts of HCV (Davis, Alter et al. 2010), a pragmatic approach to prevention such as the scaling-up of existing HCV testing options, expanded access to substance abuse therapy and mental health services, and invigorated public health education campaigns are likely the most realistic hope to contain HCV in rural Appalachia, barring substantial changes in political culture and availability of funding.

Although this study provides important insights into the nature of injection-mediated HCV transmission risk among rural PWID, there are limitations to consider. First, while the data are longitudinal in nature, some covariates do not temporally precede the dependent variables assessed. Collection of time-invariant data including sociodemographic measures and lifetime behavioral and drug use measures preceded assessment of IDU sharing at each time point, as did HCV testing and potential post-test counseling. However, other time-varying measures including self-reported health-related measures, illicit drug use during the last 6 months, and so on, were analyzed concurrently with the reported outcome (IDU sharing), limiting causal inference. Nonetheless, this strategy was deemed appropriate in light of these measures reflecting conditions closer to the outcome of interest. Moreover, IDU sharing was assessed in the last 30 days, lending support to causal inferences made from behaviors covering the entire 6-month study interval and diminishing recall bias with regard to the primary outcome. Assessing IDU sharing within the last 30 days also reduced the influence of HCV test result disclosure date variance between participants, as the Home Access serotest used between baseline and 18 months came before the era of instant point-of-case testing such as the

OraQuick® "instant" serotest (implemented at 24 months in this cohort), requiring instead 2 weeks or more before test results were available and potential counseling received, dependent upon participant's return for test results and patterns of attrition. In addition, a choice was presented between assessing sharing of needles/syringes, ancillary IDU equipment (cookers, cotton filters, water, spoons), or a combination of both. In light of considerable research demonstrating the importance of so-called "indirect" sharing of equipment and syringe-mediated sharing in HCV transmission (Hagan, Thiede et al. 2001; Thorpe, Ouellet et al. 2002; Pouget, Hagan et al. 2012) and widespread awareness of HCV risk via needles/syringes as well as ancillary equipment sharing methods in this cohort at baseline (99.7% and 97.2% respectively), combining sharing of *any* IDU equipment was deemed justifiable and most physiologically relevant with regard to HCV transmission. Furthermore, as described in chapter 2, the study survey instrument captured baseline status awareness among participants testing HCV-seropositive, but not among those testing negative. Although there was no apparent impact of baseline status awareness among seropositive participants, it is unknown whether previous awareness of HCV-*negative* status might have influenced IDU sharing and continuity at later study occasions. Finally, lifetime and recent behavioral measures used in this analysis relied on self-report from study participants, potentially subjecting the data to reporting, social desirability, and recall biases. Nonetheless, self-reported risk behavior from PWID was determined to be a reliable indicator of actual behavior in a comprehensive review (Weatherby, Needle et al. 1994; Darke 1998), and the possibility recall bias was minimized by the primary use of 6-month measures of drug use and 30-day for the primary outcome measured concerned IDU sharing.

The data presented here illuminate several important pathways for future research of HCV risk in this population. Given the dynamic interplay of sexual and injection behaviors reported here, one avenue for further study in this population is to incorporate dyadic and sociometric network measures in relation to IDU risk behavior over time. Moreover, while this analysis accounts for awareness of one's own HCV status in impacting future risk behavior, it does not assess whether an individual's awareness of serostatus of other members in an IDU network may influence risk behavior. Network-oriented analysis and modeling of HCV risk has produced important insights with regard to HCV transmission, treatment, and reinfection (Rolls, Sacks-Davis et al. 2013) and HIV risk behavior and norms (Latkin, Forman et al. 2003; Latkin, Kuramoto et al. 2010), including demonstrated efficacy of network-based risk reduction

interventions (Latkin, Donnell et al. 2009; Latkin, Donnell et al. 2013). However, there have been relatively few studies examining network factors and network-oriented interventions on IDU risk behavior in populations with high HCV prevalence, although the impact of social network factors on both IDU risk behavior (De, Cox et al. 2007; Shaw, Shah et al. 2007) and HCV transmission (Sacks-Davis, Daraganova et al. 2012) has been substantial in past research. Finally, there have been no longitudinal studies of straw-sharing during inhalational drug use, specifically what impact HCV testing and counseling might have on straw sharing over time. In light of the finding that intranasal administration is higher among rural Appalachian prescription opioid users relative to urban users (Young, Havens et al. 2010), sharing of straws used for drug inhalation could represent an important mode of viral transmission in this population and another viable target for intervention.

In sum, the results from this sample build upon most previous studies of the topic suggesting that HCV screening and post-test informational counseling in isolation are unlikely to have a strong lasting effect on IDU risk behavior among PWID in most settings, including that of rural Central Appalachia. On the other hand, screening for HCV may have a positive short-term effect on maintaining "safer" IDU behaviors among seronegative PWID, and modest improvement in IDU sharing frequency were observed among those receiving a positive test and counseling. Moreover, the opportunities for promotion of secondary prevention via lifestyle modification (particularly reduction of alcohol intake) and medical management and potential treatment of HCV are substantial (Marinho, Vitor et al. 2014). As discussed in the following chapters, widespread HCV treatment uptake targeted to the right individuals has considerable potential to act as a cost-effective means of primary prevention (Martin, Pitcher et al. 2011; Martin, Vickerman et al. 2011; Hagan, Wolpe et al. 2013; Grebely and Dore 2014). Rapidly evolving and potent drug agents specifically targeting HCV are increasingly likely to result in viral clearance in the form of SVR, which in turn represents a vital isthmus between primary and secondary HCV prevention. Thus, regardless of impact on transmission risk behavior, HCV screening has potential benefit among high-risk populations if only to increase the probability of chronically infected individuals engaging the healthcare system to receive active clinical management of CHC. Of course, individuals infected with HCV must first know their disease status in order to seek care from a healthcare provider, and the newest drug agents do not come without a hefty a price tag for those eligible to be treated. In the following chapter, the

many challenges, barriers, and clinical issues marking the path to medical care and treatment among individuals with CHC are explored in detail.

Secondary Prevention:
Factors impacting progression of chronic HCV

4.1 Overview

Once hepatitis C establishes chronic infection in the liver of an exposed individual, the virus induces a nonspecific immune response resulting in chronic hepatic inflammation, high levels of oxidative stress, and variable degrees of fibrosis (Feld and Liang 2006). A body of research also indicates the virus is also likely responsible for direct activation of hepatic stellate cells, apoptosis, and oncogenic activity mediated primarily by the viral core protein (Okuda, Li et al. 2002; Chou, Tsai et al. 2005). Beyond the increasingly efficacious drug treatment options, an array of biological, behavioral, and environmental factors are known to dictate progression of hepatic fibrosis, development of hepatocellular carcinoma (HCC), and long-term clinical prognosis of patients with CHC. Age is perhaps the most important non-modifiable predictor of CHC progression, with age at time of infection robustly predicting rate of hepatic fibrosis, even controlling for the effect of duration of infection and exceeding the impact of viral genotype (Poynard, Bedossa et al. 1997). This pattern is reflected in concerns among public health officials as the American "baby boomer" cohort born between 1945 and 1965 advances in age and the clinical impacts among individuals infected with HCV expand (Davis, Alter et al. 2010). The pathological mechanism at play between aging and HCV remain uncertain, although hypotheses include declining immune function, loss of mitochondrial capacity, and reduced vascular perfusion (Missiha, Ostrowski et al. 2008). Similarly, male sex has also been reported as a predictor of accelerated progression to cirrhosis in many studies (Poynard, Bedossa et al. 1997; Wright, Goldin et al. 2003), doubling the rate of fibrosis progression in one study even controlling for other established factors impacting disease progression (Ratziu, Munteanu et al. 2003). Higher rates of HCC among men as well as greater numbers of liver transplantations are also observed. This gender differential risk is mediated primarily by protective effects of estrogen, although important gender differences in IL-10 and IL-6 expression have also been reported (Missiha, Ostrowski et al. 2008). Some evidence also indicates that race impacts the likelihood and rate of CHC progression, particularly with regard to U.S. studies demonstrating increased risk of HCC (El-Serag 2004) and poor response to conventional HCV treatment (Muir,

Bornstein et al. 2004) among African-American patients. Surprisingly, however, this trend among Black patients with CHC has not translated to increased risk of cirrhosis, perhaps instead indicating poor access to medical care among African-Americans (Nguyen, Segev et al. 2007). In addition, sporadic data indicate accelerated progression among American Latinos (Bonacini, Groshen et al. 2001), whereas Native Americans have exhibited higher rates of spontaneous viral clearance (Scott, McMahon et al. 2006). Other potential non-modifiable factors include source of infection and a variety of host genetic polymorphisms detected via genome-wide scanning (Missiha, Ostrowski et al. 2008). Although viral genotype exerts well-established effects on sustained virologic response (SVR) in response to conventional ribavirin-interferon treatment regimes, particularly with regard to genotype 1, reports of accelerated fibrosis among patients with genotypes 1 and 3 have been largely discredited (Missiha, Ostrowski et al. 2008). Nonetheless, genotype 3 has been positively associated with spontaneous clearance of acute infection in the absence of treatment in (Lehmann, Meyer et al. 2004).

An important and frequently overlooked aspect of HCV management is that many severe manifestations of chronic hepatitis C are strongly correlated to patient behavioral factors and other modifiable characteristics. Foremost among these behaviors is alcohol consumption among individuals with CHC. Over 20 years of research have unequivocally demonstrated a deadly synergy between alcohol consumption and HCV, with clearly elevated rates of hepatic fibrosis, cirrhosis, and HCC among individuals who consume alcohol after infection (Hutchinson, Bird et al. 2005; Mallat, Hezode et al. 2008), even at moderate levels (Khan and Yatsuhashi 2000). Of note, receiving an HCV-positive serotest and post-test counseling did not significantly reduce frequency of alcohol consumption 6 months after testing among baseline drinkers in the cohort studied in this report, suggesting that more intensive interventions are needed in the setting of rural Appalachia (Stephens and Havens 2013). In addition to alcohol, smoking tobacco is another well-established risk factor for HCC (Mori, Hara et al. 2000) and potentially accelerated fibrosis (Missiha, Ostrowski et al. 2008) among CHC patients, and marijuana smoking has been reported to increase risk of steatosis and potentially fibrosis (Hezode, Roudot-Thoraval et al. 2005; Hezode, Zafrani et al. 2008; Mallat, Hezode et al. 2008). Hepatic iron levels have also been established as an important predictor of liver disease progression (Shedlofsky 1998; Fujita, Sugimoto et al. 2007). Therapeutic phlebotomy is effective in the management of CHC for hemochromatosis patients and the 30-40% of HCV-infected individuals who become iron overloaded (Yano, Hayashi et al. 2002). Proposed histopathological mechanisms for iron's

deleterious effect include increased inflammation and viral-mediated changes in iron trafficking (Missiha, Ostrowski et al. 2008). Next, with particular relevance to the medical setting of Eastern Kentucky, a variety of interrelated metabolic factors including obesity, insulin resistance, and non-alcoholic steatohepatitis exhibit strong associations with advanced liver disease among CHC patients (Fierro, Gonzalez-Aldaco et al. 2014; Huang, Yang et al. 2014); interestingly, these appear to be HCV genotype-specific. Finally, an array of co-infections can substantially accelerate disease progression, including hepatitis B, HIV, and schistosomiasis, with the latter pathogen being particularly relevant to the epidemic levels of HCV in the developing world (Missiha, Ostrowski et al. 2008). The pathological synergy observed with regard to HIV stems from viral suppression of CD4+ T-cells, leading to attenuated cell-mediated immunity and elevated HCV viral loads among co-infected individuals.

4.2 HCV treatment and barriers to care

Along with the modifiable and non-modifiable factors impacting disease progression described above, medical treatment holds substantial power to avert severe clinical manifestations of CHC. This is increasingly true as new all-oral, interferon-free and potentially ribavirin-free treatment options make impressive strides in terms of vastly increased efficacy and decreased toxicity. However, HCV presents obstacles to effective disease management at multiple levels: molecular, individual (patients and their physicians), and at the macro scale of the healthcare system and society itself (Morrill, Shrestha et al. 2005; Thomas 2013; Treloar, Rance et al. 2013). Once chronic infection has been established, as is the case in approximately 75% of exposed individuals (NIH 2002), the virus can obscure its presence from the host immune response for decades and even actively downregulate signaling process of host cell machinery (Foy, Li et al. 2005) that would otherwise have resulted in viral eradication. Similarly, in most individuals with CHC, symptoms are subtle and rarely recognized—if symptoms are present at all (NIH 2002; Seeff 2002). Even among those individuals who are diagnosed with HCV and seek medical care, the many contraindications outlined in Table 1.3 coupled with physician-level barriers can block the path to treatment and viral eradication, despite rapid advances in HCV pharmacotherapy. However, most of the reasons to delay or withhold care have been reported as perceived at the patient-level, including concerns of non-adherence, psychiatric comorbidity, toxicity, threat of reinfection, and inability to afford treatment, along with numerous

organizational/institutional obstacles, (Edlin, Seal et al. 2001; McGowan, Monis et al. 2013; Robaeys, Grebely et al. 2013). Furthermore, it is worth noting that in McGowan and colleagues' (2013) survey of 697 physicians in 29 countries, reported reasons for deferring treatment among physicians varied substantially between geographic regions.

Thomas (2013) suggested that all necessary virologic and therapeutic factors for HCV eradication are present: HCV can be effectively cleared from infected individuals, transmission can be controlled by behavioral modification and harm-reduction policies, and HCV does not have a non-human reservoir, which prevents the complete elimination of some other pathogens. Moreover, treatment of a sufficient number of individuals with CHC could reduce the exclusively human-borne reservoir for HCV to the point that, in theory, the HCV epidemic could be brought to an end. However, inadequate investment in public health intervention efforts, insufficient financial resources to subsidize the expense of treatment, prevention and harm reduction programs, and a general lack of socioeconomic and political will in many parts of the world obstruct widespread eradication of the virus at present (Thomas 2013).

Largely because of the insidious clinical course fostering low status awareness combined with marginalized social status of many individuals with CHC (Conrad, Garrett et al. 2006), most previously reported HCV treatment uptake rates in the general population have been very low. For instance, rates worldwide have varied from 16% in France to less than 1% in Romania, Poland, Greece, and Russia (Lettmeier, Muhlberger et al. 2008). The United States falls in the middle of this spectrum, with one study finding 11.6% of 99,166 veterans with CHC initiating treatment, but only 6.4% of them completing it (Kramer, Kanwal et al. 2012), despite this patient population having essentially free access to medical care for HCV. A sobering model predicting the impact of HCV treatment on health outcomes in the United States estimated that just 14% of future mortality due to progressive hepatic disease resulting from CHC will be prevented by drug therapy at current levels of treatment uptake (Volk, Tocco et al. 2009).

As for status awareness among individuals with CHC, population-based data in the U.S. indicate that HCV screening and treatment uptake are relatively low across multiple socioeconomic strata. In an analysis of 170 HCV-seropositive individuals recruited from those participating in the National Health and Nutrition Examination Survey (NHANES) between 2001 and 2008, just 49.7% were aware of the HCV-positive serostatus before being notified by NHANES, although 80% of these individuals had seen a doctor after receiving their initial positive HCV test result. Unfortunately, data on seeking or receiving treatment were not reported.

Notably, participants 40-59 years of age, non-Hispanic whites, and those who reported seeing a physician following status disclosure also scored higher on a survey assessing their knowledge level of HCV (Denniston, Klevens et al. 2012). Volk and colleagues (Volk, Tocco et al. 2009) reported data from a subsample of 133 HCV-infected respondents taken from NHANES (2003-2008), 11 individuals (sampling weight-adjusted proportion: 12%, 95% CI: 4-19%) were treated for HCV. The most frequently cited reasons for not receiving treatment were as follows: 69 (adjusted 49%, 95% CI: 39-60%) were unaware of their HCV-seropositive status prior to NHANES participation, 33 (adjusted 24%, 95% CI: 15-33%) were advised by their physician not to be treated, 12 (adjusted 9%, 95% CI: 3-16%) did not follow-up with a physician following status disclosure, and 8 (adjusted 6%, 95% CI: 1-9%) refused treatment. Unsurprisingly, poor access to healthcare and lack of insurance emerged as major barriers to HCV status awareness and treatment, with sampled individuals lacking any form of health insurance more likely to be unaware of their HCV status (OR 4.8, 95% CI: 1.8-12.7) and marginally less likely to receive treatment (OR 0.3, 95% CI: 0.03-2.6). Moreover, NHANES participants without a usual source of medical care were more likely to be unaware of their status (OR 19.0, 95% CI: 2.4-148.1), and none of these respondents had received treatment for HCV (Volk, Tocco et al. 2009).

Other studies reiterate low rates of treatment uptake across multiple settings. In a study of 2118 residents of inner-city Vancouver, Canada, just 15 of 1360 (1.1%) of HCV-seropositive individuals had initiated treatment between January 2000 and December 2004—an alarming proportion in a population with access to government-sponsored healthcare (Grebely, Raffa et al. 2009). A retrospective analysis of 196 Irish patients receiving opioid substitution therapy found that 151 (77%) had been previously screened for HCV, and of these HCV seroprevalence was 69%. 24 (23%) of the 104 individuals with a positive test result had followed up with a physician and just 3 (3%) had received HCV treatment (Cullen, Stanley et al. 2007). This represents a somewhat anomalous pattern, in that a large proportion of individuals in this sample were screened and aware of their HCV status, yet very few of those testing positive had followed up with a physician or received treatment. In a non-population-based sample, Morrill and colleagues (2005) investigated barriers to care among 208 HCV RNA-positive patients under the care of a primary physician in community health centers. 57 (27.4%) individuals had undergone treatment, with individual-level and physician-level barriers cited, as outlined in the following sections.

People who use and/or inject drugs face additional barriers to care relative to the general population (Grebely, Genoway et al. 2008) and are generally characterized by lower levels of treatment uptake for CHC relative to the general population. Australian health researchers in one study found treatment uptake among HCV-positive PWID to be just 4% (National Centre in HIV Epidemiology and Clinical Research 2009). Other researchers in Australia reported an increase from the proportion of 9478 PWID who had received treatment from 3.4% to 8.6% between 1999 and 2001 (Iversen, Grebely et al. 2013), though it is worth noting that Australian public health and government officials have been aggressively confronting the HCV epidemic among PWID. Another study of 597 PWID living in Baltimore reported treatment initiation rates of just 6%, with 22% aware that HCV was curable, and only 21% reporting that they had received evaluation by a healthcare provider and discussed treatment (Mehta, Genberg et al. 2008). Similarly, Strathdee and colleagues (2005) found that just 27% of PWID aged 18-35 years in three U.S. cities had followed up with a healthcare provider following the disclosure of their HCV-seropositive status.

In light of these data, there are barriers to HCV medical care for infected individuals across multiple levels: the often asymptomatic nature of acute and early chronic HCV, the perceptions and preferences of individuals infected with the virus, and the attitudes and clinical judgment of clinicians providing care for HCV-positive individuals, who are in turn subject to complex contraindications to treatment along with restrictions and financial constraints of the overall healthcare system, although vast differences can exist both within and between countries (McGowan, Monis et al. 2013). Finally, society itself presents many obstacles to HCV eradication, including social stigmatization and discrimination with regard to HCV-positive individuals and PWID in particular (Zacks, Beavers et al. 2006; Treloar, Rance et al. 2013), as well as a general lack of resources and energy allocation for effectively managing a global public health crisis caused by what theoretically should be an eradicable disease agent (Thomas 2013).

Individual-level

Data presented in chapter 5 are principally focused on individual-level barriers to HCV care, specifically those with potential to influence the decision to seek medical care after being diagnosed HCV-seropositive and receiving informational post-test counseling. As reported in many prior studies (Fraenkel, McGraw et al. 2005; Khokhar and Lewis 2007; Nguyen, Dore et al. 2007; Swan, Long et al. 2010), fear of treatment adverse effects and lack of concern for the

potential long-term health consequences of CHC were suggested as the most pressing personal concerns with regard to initiating HCV treatment in a sample of 120 HCV-positive individuals. By contrast, physician recommendations were cited as a common motivating factor (Fusfeld, Aggarwal et al. 2013). Race has also been suggested to be an important effect modifier in the decision to begin treatment (Khokhar and Lewis 2007), although as yet this question remains inadequately studied in minority populations (Borum, Igiehon et al. 2009). Morrill et al. (2005) found that single individuals, women, current heavy alcohol users, and patients with low attendance to appointments with their physician were less likely to receive treatment for HCV; a positive association with declining therapy among women was also suggested in another study (Khokhar and Lewis 2007). By contrast, in a study of HCV-positive individuals in Australia, Stoove and colleagues (2005) found the opposite association with regard to gender and HCV specialist referral; female gender conferred increased likelihood of referral, along with a longer period of time since HCV diagnosis, longer consultation times at diagnosis, and the experiencing of HCV-related symptoms. In a multivariate model, absence of current IDU and seeing a general practitioner specifically for HCV care were strongly associated with referral to a specialist for HCV treatment, whereas current IDU was associated with diminished probability of receiving treatment. Thus, current IDU was negatively associated with both HCV specialist referral and subsequent treatment (Stoove, Gifford et al. 2005).

As these previous findings from Stoove and colleagues suggests, among active PWID, healthcare barriers are likely to be more pronounced and potentially distinct from those faced by the general population, although much overlap exists given the high prevalence of IDU in the HCV-positive population (Grebely, Genoway et al. 2008). In a qualitative study, Treloar and colleagues (2010) examined patient-level barriers to care and treatment initiation in a small sample (n=27) of HCV-infected PWID receiving opioid substitution therapy (OST) in Australia. Among the factors OST clients reported were competing responsibilities such as caring for children, concerns regarding adverse effects of treatment, perceived low efficacy of HCV drug therapy, homelessness and unstable living arrangements, medical and psychiatric comorbidities including HIV, stroke, myocardial infarction, diabetes, epilepsy, hepatitis B, depression, and antisocial behavior. In a related quantitative study, younger age (adjusted OR=0.9, 95% CI: 0.9-1.0), higher formal education (aOR=7.8, 95% CI: 1.6-37.7), and participation in opioid substitution therapy (aOR=4.5, 95% CI: 2.2-8.2) were independently associated with receiving medical assessment for potential HCV treatment in a cross-sectional analysis of Australian PWID

(Treloar, Hull et al. 2012). Swan and colleagues (2010) qualitatively explored barriers to HCV care among Irish PWID in a variety of settings, finding that several patient perceptions and characteristics inhibited access to HCV care, including the notion that HCV is a benign disease, fear of invasive tests and treatments, lack of symptoms, and a general perception of HCV drug therapy as undesirable circulated in the form of negative anecdotes through peer networks. Other life responsibilities also competed with treating participants HCV infection, such as keeping a job and housing, attaining education, and addiction problems, whereas experiencing HCV symptoms, having obligations to children, and expressing the desire to quit using illicit drugs were all commonly reported as factors motivating HCV treatment initiation (Swan, Long et al. 2010). The demotivating impact of CHC's often asymptomatic course was also reported in another qualitative study of 95 racial minorities who use drugs, in addition to reluctance from physicians to initiate treatment and recommendations against treatment from both healthcare providers and peer networks. Moreover, low HCV knowledge levels were reported among study participants with regard to the meaning of a positive HCV serotest, the long-term health implications of CHC, the necessity of clinical follow-up and active HCV monitoring, and the availability of efficacious treatment (Jordan, Masson et al. 2013).

The individual-level barriers above are repeated across many studies in the field. Among 216 treatment-naïve PWID in 3 U.S. cities, researchers found that higher levels of awareness of the threat of advanced liver disease, having a regular source of healthcare, absence of alcohol dependency, and higher levels of readiness to quit drug use were associated with greater interest in initiating HCV drug therapy. Moreover, PWID who had been told by a healthcare professional that they were at risk for cirrhosis or liver cancer had seven-fold greater levels of interest in HCV treatment (Strathdee, Latka et al. 2005), suggesting the priority of physician-level advocacy for treatment of eligible patients, as described in the following section. In qualitative assessment of participants the large Australian Trial in Acute Hepatitis C (ATAHC) study, treatment toxicity, current substance use, mental health contraindications were reported as common barriers to HCV treatment among active drug injectors, but financial and transportation problems, lack of social support, and legal system difficulties (criminalization of IDU) also emerged as frequently cited barriers to medical care and treatment adherence (Nguyen, Dore et al. 2007). A later analysis from the same study found a treatment uptake level of 76% (111 of 146) in this highly interventional setting, with HCV RNA level and duration of HCV

infection being independently associated with treatment uptake, while current IDU was not (Grebely, Petoumenos et al. 2010).

Finally, by using Geographic Information Systems (GIS) software technology, distance of residence from available HCV care facilities has recently been shown to be strongly associated with HCV diagnosis and status awareness in French PWID (Monnet, Collin-Naudet et al. 2006; Monnet, Ramee et al. 2008). Thus poor geographic access might also be expected to impact access to HCV care and treatment-seeking, particularly in the rural setting. In a related study controlling for the system-level factor of healthcare resource deprivation, the same association was suggested in a model for PWID in the United States, although this finding was specific to PWID with a history of receiving OST (Astell-Burt, Flowerdew et al. 2011).

Healthcare provider-level

In light of the complex set of contraindications, the lengthy and demanding nature of the treatment, and many adverse effects surrounding treatment, it is inherent to the nature of HCV pharmacotherapy that the decision between a patient and physician to initiate therapy is difficult and beset with potential barriers, even among individuals who are aware of their status and seek medical care. However, adherence to basic HCV screening guidelines among physicians was found to be poor in a sample of 154 U.S. physicians, with numerous barriers at the level of clinician knowledge and attitudes (Southern, Drainoni et al. 2013), potentially exacerbating what is already a cumbersome and challenging process in terms of medical management. With a regard to initiation of HCV treatment, McGowan and colleagues (2013) found in a global review of 697 physicians in 29 countries that patient-level issues were the most commonly reported barriers to care, including concerns regarding toxicity, duration of treatment, and cost of therapy, as alluded to in the previous section. However, in this study physician knowledge of the principles of HCV treatment was again found to be deficient across healthcare settings, with less than 50% of providers providing correct responses to questions covering treatment paradigms such as treatment stoppage in responses to HCV RNA levels at various stages of therapy and the impact of patient fibrosis staging and HCV viral load (RNA titer) on the probability of achieving SVR. Commonly cited barriers at the healthcare provider- and system-levels included insufficient reimbursement for services, lack of access to necessary medications and labs, lack of administrative and office support to treat patients, insufficient training lack of referral from other physicians, and limitation of HCV treatment to government-controlled centers (McGowan,

Monis et al. 2013). In addition, in Morrill and colleagues' retrospective analysis (2005), reluctance among physician to treat patients with a history of substance abuse was reported as a provider-level barrier, along with other typical patient-related factors such as current substance abuse, psychiatric contraindications, and treatment refusal.

Given the high prevalence of illicit drug use and IDU among HCV-positive individuals, several potential barriers arise from the impact of these behaviors on patient lifestyle. In a study of 4318 HCV-positive patients in the Veteran's Administration system, 2611 (61%) were former PWID, although former IDU was not associated with candidacy for HCV treatment or efficacy of treatment (Seal, Currie et al. 2007). Nonetheless, among physicians managing the care of active drug users in particular, many potentially valid arguments against treatment initiation are frequently cited, including: poor adherence to long and demanding treatment regimes; high burden of adverse effects, particularly with regard to interferon use among patients with comorbid psychiatric conditions such as major depressive disorder, and concerns of HCV reinfection among active PWID following SVR (Edlin, Seal et al. 2001).

Some researchers have argued that current the treatment eligibility criteria remain too restrictive, despite a relaxing of rules to permit treatment of active people who use and even inject drugs on a "case-by-case" basis with careful monitoring and concomitant substance abuse treatment (Ghany, Strader et al. 2009). A study of 404 HCV-infected PWID aged 18-35 found that 96% exhibited conditions that could exclude them from treatment on the basis of eligibility criteria that were argued by the authors to be overly stringent in many cases (Hagan, Latka et al. 2006). Indeed, many studies have demonstrated that PWID can achieve rates SVR comparable to non-drug-using samples if treatment is delivered in the right setting (Birkhead, Klein et al. 2007; Grebely, Knight et al. 2010; Aspinall, Corson et al. 2013). Nonetheless, the probability of achieving SVR when treating people who are actively using or injecting drugs is highly context-dependent and must be considered individually in light of the standard eligibility criteria, including individual housing situation, psychiatric health, alcohol consumption habits, and presence of a social support network, in addition to access to ancillary PWID-specific services such as substance abuse treatment, opioid substitution therapy, and even clean syringes in some situations (Birkhead, Klein et al. 2007). At one extreme, delaying therapy has been suggested to be ethical as a patient care decision only in certain stages of HCV infection and if an achievable plan is proposed to address a patient's illicit drug use issues (Edlin, Seal et al. 2001). Lastly, in light of substantial concerns of HCV reinfection following SVR, rates of reinfection are

generally low (Micallef, Macdonald et al. 2007; Grebely, Knight et al. 2010; Grebely, Prins et al. 2012; Grady, Schinkel et al. 2013), and treatment of active PWID has been modeled to be cost-effective in populations with HCV prevalence below 60% (Martin, Vickerman et al. 2012). Unfortunately, these studies do not address system-level barriers such as the high cost of treatment, restrictive coverage from insurers, and regional scarcity of harm reduction programs as outlined in the following section, particularly in countries such as the United States that lack a national healthcare system and comprehensive policy to manage the problem of widespread HCV among PWID.

Healthcare system-level and societal barriers

In a review by McGowan colleagues (2013), the most commonly cited barriers at the level of the healthcare system or government included the high cost of HCV treatment, restrictions on treatment as per government policy, insufficient public funding for HCV management, and inadequate public promotion of treatment. In addition, numerous barriers related to health insurance providers were reported, including: refusal to cover HCV treatment, coverage limitations for HCV-positive patients; refusal of plans to cover RNA quantification, HCV genotyping, hepatic fibrosis testing, or medications to manage adverse effects; restrictions regarding which physicians could treat HCV; requirement for liver biopsy to begin treatment; and excessive paperwork (McGowan, Monis et al. 2013). Morrill and colleagues (2005) also reported system delays in patient referral to HCV specialists as a common barrier to treatment in their retrospective study. Another recent review by Harris and Rhodes (2013) of the most significant social barriers to HCV care among PWID cited discrimination and stigma, housing instability and homelessness, geographic access and localized resource deprivation problems, criminalization of IDU lifestyle, health care system obstacles and government policy restrictions, and gender-related cultural issues. In an analysis of NHANES data from 2005-2008, 54% HCV RNA-positive individuals had health insurance, but only 36% of HCV-seropositive individuals were both covered by health insurance and potentially eligible for treatment. Insurance status was protective against being HCV RNA-positive in a multivariate model (adjusted OR=0.4, 95% CI: 0.2-0.8) (Stepanova, Kanwal et al. 2011), suggesting that lack of universal healthcare in the climate of increasingly costly treatments for HCV is likely to be an important factor in HCV treatment uptake in the United States. What effect the Affordable Care Act may have health insurance coverage expands to previously uninsured individuals remains to be seen.

Two additional societal factors may play a role with regard to the treatment of actively injecting individuals with CHC: size of the community in which physicians practice and social stigma. Myles and colleagues (2011) found that size of the population in which Canadian physicians practice was a robust predictor of whether or not HCV therapy was initiated, with specialists in communities with a population of 500,000 or greater having nearly 4 times the odds of treating current PWID relative to those practicing in smaller communities (OR 3.89, 95% CI [1.06, 14.26]). This finding has obvious implications for the rural Appalachian study population examined in the following chapter using data collected in the setting of Perry County (pop. 28,241) in Eastern Kentucky. Finally, HCV-positive individuals and PWID frequently cite social stigmatization as a major barrier to seeking treatment for their infection-related and substance abuse problems (Zickmund, Ho et al. 2003; Zacks, Beavers et al. 2006; Janke, McGraw et al. 2008; Treloar, Rance et al. 2013), which in turn acts as a barrier to both treatment initiation as well as medication adherence among patients with CHC (Modabbernia, Poustchi et al. 2013).

Barriers to Care:
HCV treatment uptake and predictors of healthcare engagement among rural Appalachian people who use drugs

5.1 Introduction

As previously described, HCV is a major source of morbidity and mortality worldwide, estimated to cause more than 483,000 deaths globally in 2010 (Lim, Vos et al. 2012) and over 16,000 in the United States in 2011 (Centers for Disease Control and Prevention 2011), with a U.S. a mortality rate exceeding that of HIV since 2007 (Ly, Xing et al. 2012). The virus hyperendemic among people who inject drugs, with a midpoint seroprevalence of 73% worldwide (Nelson, Mathers et al. 2011), and efforts to enhance primary prevention among PWID have been met with mixed results (Page, Morris et al. 2013). In a study reporting no impact of HCV-positive status awareness on transmission risk behavior, Hagan and colleagues (2006) commented that perhaps the most pragmatic benefit of HCV screening is "to facilitate access to medical monitoring and treatment of HCV infection." Indeed, although HCV screening and post-test counseling alone have been generally insufficient to reduce transmission risk among seropositive PWID, increased screening retains important potential applications to secondary disease prevention among high-risk individuals. While other modifiable factors related to HCV disease progression, particularly reducing or eliminating alcohol consumption, are vital in the management of individuals with CHC, pharmacotherapy for HCV continues to advance rapidly, offering the promise of decreased toxicity and contraindications, and of particular relevance among PWID, shortened treatment durations and the imminent availability of all-oral, interferon- and even ribavirin-free options achieving sustained virologic response (SVR) in more than 98% of genotype 1 patients, whether treatment-naïve or experienced (Afdhal, Reddy et al. 2014; Afdhal, Zeuzem et al. 2014). Moreover, beyond individual-level benefits, treatment also represents another potential form of primary prevention in itself by reducing the pool of viremic individuals able transmit the virus to others (Martin, Vickerman et al. 2011; Hagan, Wolpe et al. 2013; Grebely and Dore 2014). However, despite being the crucial first step in CHC care among seropositive individuals, medical follow-up with HCV RNA

quantification to assess for active infection is frequently not undertaken, even in the general population (Spradling, Tong et al. 2014). Therefore, understanding factors impacting the decision to see a healthcare provider after receiving a positive serotest and counseling are vitally important, particularly in medically underserved populations such as PWID (Grebely, Genoway et al. 2008) and individuals living in rural Central Appalachia (Stensland, Mueller et al. 2002).

Several studies have addressed the question of factors associated with seeing a healthcare provider and seeking treatment for HCV, but few have specifically assessed recently-diagnosed seropositive individuals or drug-using populations. Moreover, there are no prior studies focused specifically on the resource-deprived setting of rural Appalachia. In a sample taken from four major U.S. healthcare organizations, Spradling and colleagues (2014) found that just over half (61%) of 5,860 seropositive individuals had received follow-up RNA testing within 6 months of serotesting, with a significantly increasing trend from 2003 to 2010 ($p<0.001$). Men, patients with lower income, those born between 1945 and 1965 were less likely to receive and RNA test within 6 months of serotesting (Spradling, Tong et al. 2014). Similarly, in a study of 245 seropositive patients sampled from medical facilities, detoxification programs, jails, and prisons, McGibbon et al. (2013) reported that 164 individuals (67%) received follow-up testing, although 21% of these tests were administered at the request of the investigators. Missed follow-up appointments, unavailability of RNA testing, and patient incarceration were the commonly cited reasons for lack of follow-up testing. The researchers concluded that HCV management guidelines should be amended to recommend routine RNA testing after a positive serotest, similar to confirmatory Western blot following a positive screening test for HIV (McGibbon, Bornschlegel et al. 2013).

In population-based NHANES data collected from 2001 to 2008, lack of HCV status awareness was the most common barrier to treatment among HCV-exposed individuals, with only 84 of 169 individuals (49.7%) aware of their HCV-seropositive status prior to NHANES testing and just 3 (3.6%) of previously aware individuals reporting that their doctor had tested them because of perceived HCV risk (Denniston, Klevens et al. 2012). Having health insurance ($p<0.001$), a regular source of healthcare ($p<0.001$), and being aged 40-59 ($p<0.05$) were significant predictors of HCV-positive status awareness in bivariate analyses. With regard to medical follow-up among HCV-seropositive individuals, 131 (77.1%) had seen a doctor or healthcare provider following their positive serotest result. Health insurance status (80.6% versus 64.9%; $p=0.04$) and having a regular source of healthcare (91.6% versus 76.3%; $p=0.01$)

were associated with receiving medical follow-up following positive serostatus disclosure. Among individuals seeing a healthcare professional following HCV-positive status disclosure, 51.6% were told they needed regular medical care for HCV, while 31.2% were told they did not need to do anything now with regard to HCV, and 9.4% reported being advised against starting treatment for HCV. Of the individuals who were told they needed regular care for HCV, 61.8% received medical treatment for HCV, representing 12.9% of the original 170 HCV-seropositive individuals responding to the survey. Finally, an 11 -item survey was given to assess HCV knowledge level. Correct responses to two disease progression-related questions and one transmission-related question were associated with following up with a healthcare provider following HCV-seropositive status disclosure (Denniston, Klevens et al. 2012).

In a related study of HCV-positive secondary survey responders recruited via NHANES between 2002 and 2007, status awareness emerged the largest barrier to treatment, with 69 out of 133 individuals (estimated 49% with adjustment for sampling) previously unaware of their status (Volk, Tocco et al. 2009). Just 12 (adjusted 9%) did not follow-up with a physician from this subsample of survey respondents, although non-response bias was a potential limitation. 33 respondents (adjusted 24%) were advised by their physician not to be treated, and 8 (adjusted 6%) refused treatment. 11 respondents (adjusted 12%) received treatment (Volz and Heckathorn 2012). In related retrospective analysis of treatment uptake among patients screened for HCV, 24% of 681 treatment-eligible (RNA-positive) patients in the U.S. Veterans Affairs (VA) hospitals received treatment (Groom, Dieperink et al. 2008), whereas just 15% of 122 recently diagnosed viremic patients in a similar retrospective analysis, despite cost of treatment not being a significant barrier among patients in the VA system. However, population-based NHANES and VA patient samples differ substantially from individuals engaging in active drug use, so these findings are not directly applicable to the setting of rural Appalachia or to active drug users and PWID, who as outlined below are typically characterized by lower levels medical care and treatment initiation for HCV.

In a community-based study specific to people reporting current illicit drug use, Strathdee and colleagues (2005) reported that just 59 of 216 (27%) treatment-naïve PWID age 18-35 in Baltimore, Seattle, and New York City obtained medical follow-up following disclosure of HCV-seropositive status, although 81.5% reported interest in receiving treatment. Interest in treatment was associated with reporting greater than 50% perceived risk of cirrhosis or HCC in the next 20 years (adjusted OR=3.7, 95% CI: 1.1-12.7), having a usual source of care (aOR=6.0,

95% CI: 1.8-19.4), lack of alcohol dependency as determined by an AUDIT score ≥ 8 (aOR=0.2, 95% CI: 0.1-0.6), and reporting higher readiness to stop illicit drug use (aOR=7.5, 95% CI: 1.8-32.3) (Strathdee, Latka et al. 2005). Mehta and colleagues (2008) also investigated treatment uptake among 597 urban PWID with HCV antibodies, finding that 86 (21%) had been evaluated for HCV treatment by a healthcare provider and just 36 (6%) had initiated treatment. 70% of participants knew that HCV treatment was available, but only 22% were aware than HCV was a potentially curable. Commonly reported barriers to HCV treatment were perceptions of severe adverse effects, low treatment efficacy, and low priority of treatment due to the absence of symptoms (Mehta, Genberg et al. 2008).

In another study of treatment willingness, Stein et al. (2001) reported that 162 of 306 (53%) former PWID who were HCV-seropositive were "definitely" or "probably" interested in initiating HCV treatment, but there was considerable disparity in knowledge levels with regard to HCV natural history and management. In addition, 82% of individuals who did not know their HCV status or had never received an HCV serotest were HCV-seropositive, again suggesting status awareness is a significant barrier to HCV treatment among PWID (Stein, Maksad et al. 2001). In a study of 2913 PWID in Vancouver, Canada between 2003 and 2004, HCV treatment was reported in just 15 of 1360 seropositive individuals (1.1%), among which just 4 completed treatment and 3 achieved SVR. Strikingly, incident HCV seroconversions occurred at a rate 25 times greater than the rate of HCV treatment (Grebely, Raffa et al. 2009); unfortunately, predictors of treatment uptake were not reported in this study. With regard to the impact of current IDU on receiving specialist care and initiating treatment for HCV, Stoove and colleagues (2005) reported that in a sample of 690 Australian PWID, current and former PWID were less likely to be referred to an HCV specialist than patients with no history of IDU (adjusted OR=3.4, 95% CI: 1.8-6.2). In addition, current PWID were significantly less likely to initiate treatment for HCV ($p<0.001$) (Stoove, Gifford et al. 2005). A review of HCV care uptake among PWID cited PWID-specific healthcare barriers on multiple levels commonly associated with low levels of HCV-related healthcare uptake. In addition to an array of issues and biases both among providers and endemic to overall healthcare systems, prominent barriers among patients included lifestyle instability and poor social functioning, psychiatric comorbidity (particularly depression), HIV co-infection, low HCV knowledge level, lack of status awareness, fear of diagnosis and medical procedures, concerns regarding drug toxicity and low efficacy, and problems related to finances and transportation (Mravcik, Strada et al. 2013). Finally, as

mentioned in chapter 4, both shorter travel distance from clinic (Monnet, Collin-Naudet et al. 2006; Monnet, Ramee et al. 2008) and greater community size quantified as population (Astell-Burt, Flowerdew et al. 2011) have been reported as predictors of increased access to HCV-related healthcare among HCV-seropositive PWID.

Given the many barriers to HCV care among people who use drugs, understanding factors impacting treatment-seeking after positive serotesting and counseling are vital to enhancing the effectiveness of HCV screening and targeting individuals at highest risk for severe liver disease. This is particularly true in medically underserved regions such as rural Appalachia, where access to harm reduction, substance abuse programs, and integrated disease management recommended to address widespread HCV among people who use and inject drugs (Birkhead, Klein et al. 2007; Grebely, Knight et al. 2010) is often limited. By contrast, these programs are often accessible to PWID in urban centers and in national healthcare systems with comprehensive HCV intervention policies in place, and the majority of prior research on HCV care initiation has occurred in this context. Past research has revealed several factors associated with HCV healthcare engagement, but as yet there is little consensus with regard to which are most relevant with regard to targeting public health intervention, and many predictors are likely to be highly population- and context-specific. Moreover, few studies have addressed the question longitudinally in the period just after serostatus disclosure, and no studies have addressed the question in the context of rural Appalachia. Thus, the purpose of this study is to describe HCV care engagement, treatment seeking and uptake in Central Appalachia, and to identify predictors of receiving secondary medical assessment from a healthcare provider following a positive HCV serotest and counseling.

5.2 Methods

Sampling

As described in chapter 3, data analyzed here were collected at the first four study occasions (baseline, 6-months, 12-months, and 18-months) during the ongoing longitudinal cohort study, *Social Networks among Appalachian People* (SNAP; R01DA024598 and R01DA033862), the purpose of which was to describe epidemiology and risk factors of HCV, HIV, and herpes simplex virus type 2 (HSV-2) among people who use illicit drugs in the Central Appalachian region of Eastern Kentucky. A baseline sample of 503 study participants was recruited between November 2008 and August 2010 using respondent-driven sampling (RDS) as described in detail in chapter 3. Participants were 18 years of age or older, not currently in substance use treatment, and must have used prescription opioids, heroin, crack/cocaine, or methamphetamine in the last 6 months. For this analysis, participants testing HCV-seropositive at baseline, 6-month, or 12-month study occasions and receiving test results and counseling at least 30 days prior to subsequent interviewing were included. Participants testing "reactive" were counseled as if HCV-seropositive and included as well; reactive participants who received a definitive seronegative test upon subsequent testing were censored from analysis at that point in time. Participants receiving HCV-positive T&C at baseline (n_0=226), six months (n_6=21), or twelve months (n_{12}=8) were followed through 18-month interviews. Participants who did not return for at least one follow-up interview following their first positive serotest were excluded; there were no significant sociodemographic differences with regard to these participants. All participants gave informed consent and were compensated for their time in completing questionnaires, serotesting, and returning for test results. All study procedures were approved by the University of Kentucky Institutional Review Board, and a Certificate of Confidentiality was obtained.

HCV serotesting and data collection

HCV screening was completed at each interview session using the Home Access® Hepatitis C Check serum antibody test with standard pre-test counseling given to all participants. This test uses dried blood spot specimens obtained by finger-stick and 3rd-generation enzyme immunoassay (EIA) to detect HCV serum antibodies. Sensitivity and specificity of this test are 98.2% and 99.6%, respectively (US Food and Drug Administration 1999), and accuracy exceeds 99% (O'Brien, Kruzel et al. 2001). Post-test counseling given to

participants testing seropositive was tailored to their result as detailed in Chapter 3, including specific recommendations to seek further medical assessment from a healthcare provider and contact information provided for Appalachian Regional Health Center hospital in Hazard and four other nearby clinics offering HCV-related assessment.

The dependent variable of interest was following up with a healthcare professional for medical assessment following receipt of a positive HCV serotest and post-test counseling obtained at baseline, 6-month, or 12-month study occasions. Numbers of participants reporting seeking and receiving treatment for HCV were also collected. To adjust appropriately for potential bias introduced by non-randomness inherent to respondent-driven sampling (Volz, Wejnert et al. 2012), individualized sampling weights were calculated using RDSAT software, version 7.1 (Ithaca, NY) for the dichotomous medical follow-up variable described above and applied to all bivariate and multivariate analyses.

Sociodemographic and behavioral data were collected via interviewer-administered questionnaires using computer-assisting personal interviewing (CAPI) software. Standard sociodemographic measures including sex, race, age, education level (including classroom/academic settings and technical training), income (with illegal sources specified), marital status, sexuality, and religion were collected. In addition, medical insurance (including private insurance, Medicaid or Medicare), transportation (access to vehicle and possession of driver's license), access to the internet, pattern of employment history were collected at baseline, and participant responses to the MINI neuropsychiatric interview, version 5.0.31 (Sheehan, Lecrubier et al. 1998), to assess for symptoms of psychiatric disorders including major depressive disorder (MDD), generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), and antisocial personality disorder (ASPD) were also collected. Participants meeting the criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) for any psychiatric conditions were given a standardized information sheet with detailed information on mental health resources available in the region. Recent (last 6 month) and lifetime non-medical use of the following substances was collected at each interview: heroin, OxyContin® (including old and newer abuse-deterrent formulations as these entered the market), other forms of oxycodone, all other prescription opioids, illicit methadone and buprenorphine, cocaine, crack, methamphetamine, barbiturate, sedatives (including hypnotics and tranquilizer), hallucinogens, marijuana, and simultaneous use of multiple substances. Recent and lifetime use of alcohol, alcohol to intoxication, legal methadone, and legal

buprenorphine were also collected, along with lifetime and recent (past 6-month and 30-day) history of substance use treatment, drug overdose, and incarceration. In addition, shortest driving distance from each study participant's addresses to the nearest infectious disease specialist offering HCV treatment (located at Appalachian Regional Health Center hospital in Hazard KY, as listed in the HCV post-test counseling materials) was computed at each study occasion using geocoded North American Street Map data (Environmental Systems Research Institute 2010) and the Network Analyst tool in ArcGIS, version 10.2 (Redlands, CA). Participants who moved away from the area over the course of the study were excluded from analysis of this measure. HCV knowledge level was assessed using the 6 true-false questions described in chapter 3, including participant awareness of HCV treatment availability.

In addition, given the importance of social support in seeking and adhering to HCV treatment, number of named members offering support in each participant's social support network was also calculated from social network data at each time point. Study participants reported the first name, surname initial, gender, and approximate age of other individuals (or "alters") from whom they had received social support. Named alters were later cross-referenced with existing demographic information from SNAP baseline data to determine if these individuals were also enrolled in the study and thus a member of the sociometric network, or individuals outside of the study. From the network representing social support, total number of individuals from which the participant received social support ("social support network out-degree") was calculated from time-varying data reported at each interview. Finally, previous receipt of a positive test for HCV, hepatitis B virus, HIV, or HSV-2 from a healthcare professional was also asked of study participants at each interview.

Analysis

Given the large number of covariates with potential to impact HCV care engagement, a bivariate screening step was used to select variables for multivariate model-building. Longitudinal bivariate odds ratios were calculated in discrete time as described below; analyses were conducted controlling for the main effect of time with individualized weights to adjust for RDS. Independent variables with a significance level of $p<0.10$ were considered for potential inclusion in the multivariate model. In addition, standard sociodemographic measures (sex, race, age, education, and income) were considered for inclusion in the multivariate model regardless of significance in bivariate analysis and retained in the model if their inclusion changed

coefficient estimates for other independent measures by more than 10% (Hosmer and Lemeshow 1989). Likewise, previously reported factors impacting healthcare access in drug-using populations were also considered in the final model, including current injection drug use, recent substance abuse and opioid substitution therapy (methadone or buprenorphine), and DSM-IV psychiatric measures.

All bivariate and multivariate analyses utilized discrete-time survival analysis (DTSA). DTSA was developed for dichotomous dependent variables that are "interval-censored" in nature, meaning that the outcome of interest either occurs or does not occur during discrete intervals defined by two points in time, with no information as to precisely when an event occurs during each interval (Allison 1982; Singer and Willett 1993; Singer and Willett 2003). In effect, DTSA is a modified form of survival analysis techniques adapted for the study of interval-censored outcomes. Moreover, DTSA yields a familiar odds ratio (OR) measure of association that is interpretable by a researchers and clinicians across a broad array of scientific and biomedical disciplines. This approach is ideally suited to non-repeatable dichotomous outcomes, such as the outcome primary outcome described here, receiving initial medical assessment from a healthcare provider after a positive a serotest, a non-repeatable event that could occur at any time during the course of the study after testing HCV-antibody positive: baseline to 6 months, 6 to 12 months, and 12 to 18 months. As serotest results and counseling, if appropriate, were not received by participants in a homogenous fashion, some individuals were not eligible to obtain medical follow-up until after 6-month interviewing had passed. Similarly, 21 individuals seroconverted by 6 months and received test results and counseling after that time, followed by another 8 participants after 12 months. DTSA is ideally suited to leveraging information from such study designs featuring "staggered" study entry, as well as utilizing the data from individuals who may have returned for an interview following a positive test result and reported behavioral data, but were censored from the study because of a missed a subsequent interview.

DTSA approaches interval-censored data much like a conventional survival analysis, utilizing life-tables to calculate hazard probabilities for the dependent measure during each time interval, conditional on the outcome event *not* having occurred during a previous interval. From this, a discrete-time hazard function can be derived depicting the set of hazard probabilities observed during each time interval. Discrete-time hazard functions can then be assessed for dependence on predictor variables using a series of "dummy" time period indicators (Singer and Willett 1993). Unlike conventional logistic regression models, there is no single intercept term,

but instead multiple α parameters serving as intercepts for each respective time interval observed. Together, these interval-specific α coefficients represent the baseline logit-hazard function subject to the main effect of time for the entire sample assuming a homogenous population of individuals. For this analysis, More parsimonious approximations of the main effect of time (constant and linear hazard in this case, as just three time intervals were assessed) on hazard were assessed in a hierarchical fashion as described by Singer and Willet (2003). Reduced models were compared to the fully discrete "general" model for significant changes in goodness-of-fit by assessing change in deviance (-2[log likelihood]) on a chi-square distribution with $N - k$ (number of time parameters in the fully-discrete minus parameters in the compared model) degrees of freedom and a critical value 3.84 ($p<0.05$). Nested time parameterizations that did not differ significantly from the fully discrete model were then compared on 1 degree of freedom (as there is a one unit difference in number of time parameters) using the same distribution and critical value (3.84), along with two likelihood-based measures of goodness-of-fit, Akaike and Bayesian Information Criteria (AIC and BIC).

In order to capture heterogeneity between participants, time-invariant and time-varying independent measures were considered using a manual forward-selection process assessing significance of additional covariates via Wald testing on a chi-squared distribution with a significance level of $p<0.05$. Because DTA employs maximum-likelihood estimation, conventional hierarchical methods can be used to compare proposed models with the iterative addition of covariates, including evaluation of goodness-of-fit using AIC and BIC. As with conventional logistic and other generalized linear models, odds ratios for particular covariates were calculated by taking the anti-log of the respective β coefficient. Finally, there are assumptions inherent to DTSA, summarized as follows: 1. Censoring of participants is independent of the dependent variable of interest; 2. Relationship between predictors and logit-hazard is linear, which can be explored graphically and addressed via transformation, categorical re-representation, or dichotomization of independent variables; 3. No unobserved heterogeneity, as DTSA models have no error term (i.e., multivariate model are assumed to be acceptably "complete" as specified); 4. Odds are proportional across time for a given predictor, similar to the proportional hazards assumption of conventional survival analysis-based Cox regression (Singer and Willett 2003). Of note, interactions between significant independent variables and time were assessed in order to test the latter assumption with a $p<0.05$ level of significance. Finally, DTSA also assumes homogeneity in interval length between and within individuals.

Therefore, for fully discrete and linear time specifications, models adjusted for individual number of eligible days for follow-up during each interval were also considered using the following ratio: participant's number of days eligible for follow-up / mean number of days for follow-up for the overall sample. This ratio then served as time-weighted indicator and was compared to discrete-time and linear-time models using likelihood-based goodness-of-fit statistics as described above.

5.3 Results

254 of the 503 participants enrolled at baseline (50.5%) received a positive HCV serotest and counseling at baseline, 6, or 12-month study visits. As summarized in Table 5.4, these individuals were predominantly male (60%), white (95%), and single (76%), with a mean age of 33 years. 95% reported a lifetime history of injection drug use. 98% reported ever having used OxyContin® non-medically, whereas 94% and 95% reported a lifetime history of illicit use of sedatives and cocaine, respectively. 87% had ever been incarcerated, and 28% reported ever having experienced a drug overdose. For these longitudinal data, dichotomous time-variant measures are summarized as *any* reporting of the respective characteristic between baseline and 18 month interviews, whereas continuous measures are reported as means during the study period. 80 participants (32%) reported having any form of health insurance over the course of data collection between baseline and 12 months, and just 42 (17%) received substance abuse treatment during the 18 months of data collection.

Table 5.1 below summarizes sample and estimated population proportions of HCV-related healthcare events reported at any study interview between 6 and 18 months among these individuals receiving a positive serotest result and post-test counseling. 150 participants (59.1%) reported seeing a healthcare professional after receiving their positive test result, as advised during informational counseling; adjusting for RDS, these individuals represent an

Table 5.1
Medical follow-up, treatment seeking, and treatment receipt after HCV-positive serotest and counseling (n=254)

Aspect of HCV Care	**Sample Total** n (%)	**Population Estimate** % (95% CI)
Followed up with provider for medical assessment	150 (59.1)	51.8 (44.5 – 58.9)
Sought treatment for HCV	35 (13.8)	12.4 (8.4 – 18.1)
Received treatment for HCV	21 (8.3)	7.8 (4.5 – 13.1)

Table 5.2
Life table with sample hazard and survival probabilities for receiving medical follow-up after HCV+ testing and counseling

Study intervals[1]	Time since HCV+ T&C	HCV+ T&C before interval	Followed up with provider	Censored at end of interval	Proportion following up with provider *p(Hazard)*	Proportion remaining with no follow-up *p(Survival)*
1	0 - 6 months	254	97	20	0.382	0.618
2	6 - 12 months	137	31	11	0.226	0.478
3	12 - 18 months	95	22	73	0.232	0.367

[1] Since HCV+ test and counseling

estimated 51.8% of the sampled population. Of these 150 participants, 35 (13.8%) described themselves as "seeking treatment" following HCV-positive T&C (12.4% estimated population proportion). 21 of these participants (8.3% of sample; 7.8% estimated population proportion) reported receiving treatment for HCV between 6 and 12 months. To illustrate the longitudinal course of obtaining medical follow-up in discrete time, life tables, hazard and survivor functions for these 150 individuals obtaining medical assessment after testing seropositive are presented in Table 5.2. The conditional probability (hazard) of seeing a clinician for medical assessment in this rural sample was greatest in the 6 months immediately following HCV-positive T&C (0.38), followed by nearly uniform lower values after 12 (0.23) and 18 months (0.23).

Table 5.3 below presents RDS-adjusted estimates for hazard and survival probability in the sampled population. As with sample values, conditional probability of obtaining medical assessment for HCV decreased after 6 months (0.37) to lower values of reported follow-up at 12 (0.18) and 18 months (0.16), when examined in the context of fully discrete time presented in the table below. Other parameterizations for the main effect of time were also considered in the interest of improving statistical efficiency, including models specifying the main effect of time as constant and linear functions. A quadratic time model was also assessed for pedagogical purposes only, as with three data collection occasions the quadratic specification provides no statistical advantage in terms of total parameters estimated and can only diminish precision relative to the fully discrete model (3 degrees of freedom in both cases). Table A5.1 in the Appendix summarizes goodness-of-fit statistics used to evaluate these four candidate models of time. Deviance of the constant time model increased significantly from the fully discrete model ($p=0.002$), so this model was rejected. Deviance for the linear time model did not significantly increase relative to the discrete model ($p=0.158$) and dropped significantly from the constant

Table 5.3. RDS-adjusted population estimates for hazard and survival probabilities of receiving medical follow-up after HCV+ testing and counseling

Months since testing	p(Hazard)	SE	95% CI	p(Survival)	SE	95% CI
0				1	0	1 – 1
6	0.366	0.036	0.296 – 0.436	0.634	0.036	0.563 – 0.704
12	0.177	0.033	0.112 – 0.242	0.522	0.036	0.451 – 0.592
18	0.161	0.035	0.092 – 0.230	0.438	0.035	0.368 – 0.507

model ($p<0.0001$). In addition, AIC and BIC goodness-of-fit measures in the linear specification were at least as low or lower than all other candidate models (558.0 and 566.4, respectively), suggesting the optimal balance of model fit and parsimony. Deviance statistics for the quadratic time model did not significantly differ from the linear specification ($p=0.331$), suggesting no improvement in fit, and as expected, AIC and BIC values were inferior to the fully discrete general model (AIC: 559.1 versus 558.0; BIC: 571.6 versus 570.6, respectively). Finally, discrete-time and linear time models weighted for number of eligible days in each interval relative to mean interval length exhibited inferior goodness-of-fit statistics compared to unweighted discrete and linear model specifications and were dropped from consideration. In light of these analyses, the linear parameterization of time was selected for final multivariate modeling and all statistical inferences presented henceforth. Hazard functions for the general discrete and linear time parameterizations are depicted graphically in Figure 5.1 below.

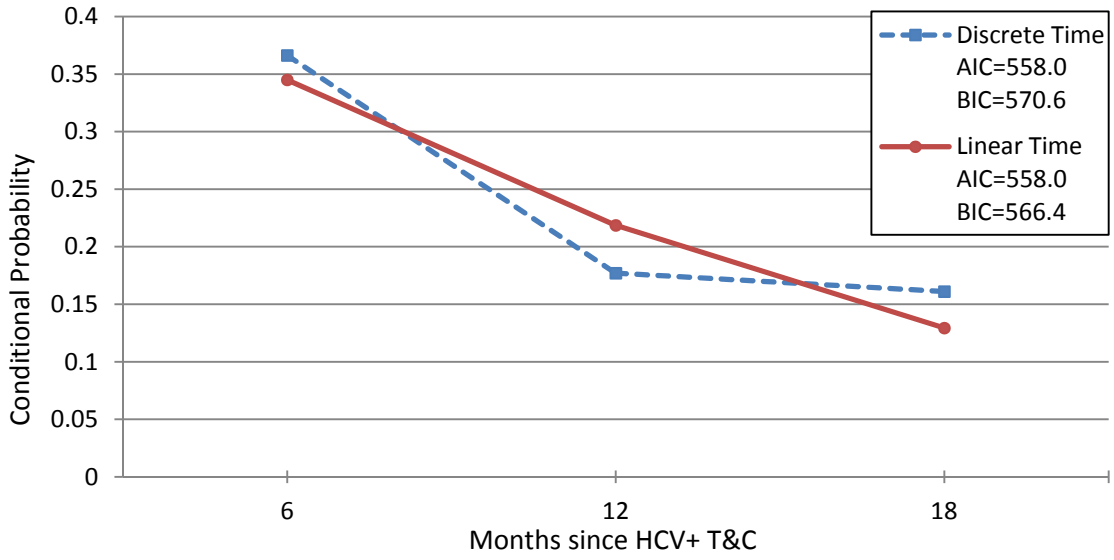

Figure 5.1
RDS-adjusted population hazard functions of following up with a healthcare provider after HCV-positive testing and counseling

Table 5.4

Description of sample and bivariate associations with receiving medical follow-up after HCV-positive test and counseling (n=254)[1]

Characteristic	Sample total n (%)	Odds Ratio	95% CI	p-value
Time-invariant				
Male	152 (59.8)	0.73	0.44 – 1.20	0.209
White	241 (94.9)	0.92	0.32 – 2.66	0.874
Age (years) - mean (SD)	33.1 (8.0)	0.99	0.96 – 1.02	0.213
Any religious affiliation reported	71 (28.0)	1.39	0.83 – 2.35	0.255
Heterosexual	23 (9.1)	0.58	0.32 – 2.66	0.198
Married	60 (23.6)	0.73	0.42 – 1.27	0.270
Number of dependents - mean (SD)	0.9 (1.4)	1.03	0.86 – 1.25	0.716
Education (months) - mean (SD)	137.3 (29.3)	1.00	0.99 – 1.01	0.454
Monthly income (US $) - mean (SD)	1283.6 (1949.6)	1.01	0.99 – 1.01	0.284
% of income legal - mean (SD)	93 .8 (19.8)	0.98	0.97 – 1.00	0.036
Most often unemployed (last 3 years)	78 (30.7)	0.95	0.56 – 1.59	0.832
Transportation	92 (36.2)	0.98	0.58 – 1.64	0.930
Major depressive disorder	68 (26.8)	0.95	0.55 – 1.62	0.839
Generalized anxiety disorder	73 (28.7)	1.78	1.04 – 3.05	0.036
Antisocial personality disorder	76 (29.9)	0.86	0.51 – 1.47	0.589
Post-traumatic stress disorder	35 (13.8)	0.89	0.44 – 1.83	0.754
Incident HCV during SNAP	30 (11.8)	0.88	0.37 – 2.08	0.770
Previous HCV+ test outside of study[2]	68 (26.8)	1.45	0.84 – 2.50	0.185
≥5 of 6 general HCV questions correct	234 (92.1)	1.56	0.62 – 3.94	0.343
Aware of HCV treatment	218 (85.8)	1.22	0.63 – 2.36	0.558
Time-varying				
Health insurance coverage[3]	80 (31.5)	1.97	1.19 – 3.27	0.008
"Good" to "excellent" health status	164 (64.6)	0.90	0.56 – 1.56	0.679
Days w/medical probs (last 30d) - mean(SD)	5.7 (8.9)	0.99	0.97 – 1.01	0.470
Chronic medical condition	106 (41.7)	1.11	0.67 – 1.83	0.691
Taking legally prescribed medication	86 (33.9)	1.44	0.81 – 2.56	0.216
Receiving physical disability pension	36 (14.2)	1.97	0.99 – 3.92	0.055
Access to internet	151 (59.5)	1.88	1.19 – 2.97	0.007
Incarceration (last 30d)	68 (26.8)	1.18	0.66 – 2.11	0.574
Distance to hospital (km) - mean (SD)	11.3 (10.2)	0.99	0.96 – 1.01	0.246
Moved to new address	135 (53.2)	1.77	1.12 – 2.78	0.014
Social support out-degree - mean (SD)	2.0 (1.2)	1.12	0.93 – 1.34	0.222
Lifetime behavior (reported at time of initial HCV+ test)				
Received substance abuse treatment	152 (59.8)	1.96	1.20 – 3.20	0.008
Incarceration	222 (87.4)	1.35	0.62 – 2.94	0.450
Drug overdose	72 (28.4)	1.55	0.89 – 2.67	0.119
Injection drug use	240 (94.5)	1.88	0.60 – 6.11	0.293
Heroin use	107 (42.1)	1.13	0.70 – 1.83	0.621
Illicit methadone use	240 (94.5)	0.32	0.13 – 0.76	0.010
Legal methadone use	63 (24.8)	0.91	0.53 – 1.56	0.733
Illicit buprenophine use	183 (72.1)	1.05	0.62 – 1.76	0.868
Legal buprenorphine use	30 (11.8)	1.53	0.69 – 3.41	0.295
Illicit OxyContin® use	249 (98.0)	2.44	0.34 – 17.42	0.374
Any other illicit oxycodone use	245 (96.5)	0.81	0.29 – 2.32	0.701

Any other prescription opioid use	245 (96.5)	0.31	0.06 – 1.67	0.172
Sedative, hypnotic, or tranquilizer use	238 (93.7)	0.58	0.26 – 1.33	0.199
Barbiturate use	43 (16.9)	0.83	0.45 – 1.51	0.537
Crack use	197 (77.6)	0.92	0.47 – 1.82	0.819
Cocaine use	240 (94.5)	0.64	0.23 – 1.82	0.405
Methamphetamine use	113 (44.5)	0.87	0.54 – 1.44	0.630
Oral amphetamine use	86 (33.9)	0.83	0.49 – 1.40	0.480
Marijuana use	247 (97.2)	0.34	0.08 – 1.39	0.133
Hallucinogen use	139 (54.7)	1.01	0.62 – 1.65	0.954
Multiple substance use	246 (96.9)	0.84	0.14 – 4.92	0.845
Recent behavior (last 6 months)				
Substance abuse treatment	42 (16.5)	1.01	0.59 – 1.74	0.973
Drug overdose	10 (3.9)	1.63	0.46 – 5.74	0.446
Alcohol use to intoxication	128 (50.4)	1.02	0.63 – 1.64	0.946
Injection drug use	170 (66.9)	0.95	0.59 – 1.52	0.818
Shared any IDU equipment	72 (28.4)	1.08	0.59 – 1.98	0.803
Shared any IDU or snorting equipment	165 (65.0)	1.25	0.78 – 2.00	0.355
Heroin use	12 (4.7)	2.19	0.65 – 7.43	0.208
Illicit methadone use	144 (56.7)	1.48	0.93 – 2.35	0.100
Legal methadone use	9 (3.5)	0.44	0.10 – 1.95	0.277
Illicit buprenorphine use	130 (51.2)	1.55	0.97 – 2.50	0.068
Legal buprenorphine use	23 (9.1)	1.69	0.66 – 4.34	0.275
OxyContin® use[4]	194 (76.4)	1.35	0.80 – 2.28	0.258
Any other oxycodone use	219 (86.2)	1.08	0.62 – 1.88	0.793
Any other prescription opioid use	201 (79.1)	1.22	0.75 – 1.98	0.431
Sedative, hypnotic or tranquilizer use	195 (76.8)	1.43	0.86 – 2.39	0.166
Barbiturate use	8 (3.2)	2.89	0.93 – 8.99	0.066
Crack use	40 (15.8)	1.67	0.85 – 3.26	0.134
Cocaine use	80 (31.5)	1.05	0.61 – 1.82	0.849
Methamphetamine use	20 (7.9)	1.60	0.62 – 4.15	0.329
Oral amphetamine use	38 (15.0)	1.51	0.74 – 3.05	0.257
Marijuana use	170 (66.9)	1.72	1.07 – 2.78	0.026
Hallucinogen use	5 (2.0)	1.38	0.18 – 10.70	0.756
Multiple substance use	225 (88.6)	1.35	0.76 – 2.40	0.310

[1] Discrete-time survival analysis adjusted for respondent-driven sampling
[2] At time of HCV+ serotest
[3] Private insurance, Medicaid, or Medicare
[4] Includes original and abuse-deterrent formulations of OxyContin®

Table 5.4 summarizes RDS-adjusted bivariate analyses used to select potential covariates considered in multivariate modeling. No sociodemographic measures were associated with medical follow-up except the percentage of reported monthly income derived from legal sources (OR=0.98, 95% CI: 0.97-1.00). Meeting the DSM-IV criteria for generalized anxiety disorder (GAD) was associated with increased odds of medical follow-up (OR=1.8, 95% CI: 1.0-3.1), as was having health insurance coverage (OR=2.0, 95% CI: 1.2-3.3) and access to the internet (OR=1.9, 95% CI: 1.2-3.0) at the onset of the study interval during which follow-up was

obtained. Lifetime behaviors associated with medical follow-up included substance abuse treatment (OR=2.0, 95% CI: 1.2-3.2) and illicit methadone use (OR=0.3, 95% CI: 0.1-0.8). The only recent behavior significantly associated with medical follow-up was illicit use of marijuana in the last 6 months (OR=1.7, 95% CI: 1.1-2.8).

Table 5.5
Predictors of medical follow-up after HCV-positive test and counseling: Linear time model (n=254)[1]

Variable	Adjusted Odds Ratio	95% CI	p-value
Time (per study interval)	0.59	0.43 – 0.80	0.001
Previous HCV+ status awareness	1.70	0.93 – 3.08	0.083
Health insurance[2]	2.06	1.20 – 3.53	0.009
Access to internet	1.83	1.15 – 2.92	0.011
Major depressive disorder	0.47	0.23 – 0.96	0.039
Generalized anxiety disorder	2.63	1.33 – 5.18	0.005
Ever received substance abuse treatment	1.67	1.01 – 2.75	0.045
Ever used illicit methadone	0.33	0.14 – 0.82	0.016
Legal methadone use (last 6 months)	0.21	0.05 – 0.90	0.035
Marijuana use (last 6 months)	1.76	1.09 – 2.84	0.021

[1] Discrete-time survival analysis adjusted for RDS
[2] Includes private insurance, Medicaid, or Medicare reported at onset of study interval

Independent associations with visiting a healthcare provider following an HCV-seropositive test and counseling are presented above in Table 5.5. The main effect of the linear time parameter independently predicted 40% decreased odds of receiving medical follow-up for each 6-month study interval elapsed since positive testing and counseling (95% CI: 0.4-0.8). Having any form of health insurance at the onset of study interval more than doubled the odds of receiving medical assessment during the interval (adjusted OR=2.1, 95% CI: 1.2-3.5), and meeting the DSM-IV criteria for generalized anxiety disorder at baseline interviewing exhibited a similar strong positive association (aOR=2.6, 95% CI: 1.3-5.2). By contrast, major depression more than halved the odds of medical follow-up (aOR=0.5, 95% CI: 0.2-1.0). Interestingly, two measures methadone use conferred decreased odds of follow-up, whether use was legal and recent (aOR=0.2, 95% CI: 0.1-0.9) or illegal and at any previous time (aOR=0.3, 95% CI: 0.1-0.8). By contrast, recent marijuana use was associated with 1.7-fold increase in odds of receiving medical assessment following HCV-positive T&C (95% CI: 1.1-2.8). Lastly, previous HCV-positive status awareness (aOR=1.7, 95% CI: 0.9-3.1) was retained in the model, despite marginal

statistical significance ($p<0.10$), due to meaningful impact on other coefficients of other significant covariates (>10% change) and improvements in goodness-of-fit suggested by decreased AIC and BIC. Finally, no evidence of significant interactions with time was detected in assessment of all final independent covariates, suggesting the proportional odds assumption was not violated.

5.4 Discussion

This is the first report of HCV medical follow-up, treatment seeking, and treatment uptake in a rural drug-using population and one of the few observational studies to assess factors impacting initiation of HCV medical management in a longitudinal context. Nearly 60% of this rural sample visited a healthcare professional for medical assessment after receiving an HCV-positive serotest and standard counseling. After adjustment for respondent-driven sampling, this represents an estimated 51% of HCV-seropositive individuals in the sampled population. This is unexpectedly higher than medical follow-up proportions reported in most other studies of urban drug-using populations, which have ranged from 21% among PWID in Baltimore (Mehta, Genberg et al. 2008) to 27% among young PWID in thre3 US cities (Strathdee, Latka et al. 2005). These proportions offer stark contrast with the 75% OST participants following up in Australia (Treloar, Hull et al. 2012), a nation offering relatively accessible treatment programs for people who use drugs and government-subsidized HCV treatment options. In a large clinic-based sample in the U.S., reported proportions range from 45% in 2003 up to 57% in 2010 in a significant upward trend (Spradling, Tong et al. 2014), and similar to the level of follow-up observed in this sample. Another study of 245 seropositive patients sampled from the New York City health department reported that 67% obtained RNA testing, although this number was artificially inflated by investigator requests (McGibbon, Bornschlegel et al. 2013).

By contrast, 80% of a population-based sample had seen a clinician in a secondary survey of NHANES participants (Denniston, Klevens et al. 2012). However, among individuals receiving medical assessment, just 13% described themselves as “seeking treatment.” This finding suggests markedly lower HCV treatment willingness among rural people who use drugs relative to other prior studies, despite above-average medical follow-up rates among samples reporting active drug use. However, it is important to consider that the two most relevant

studies above were cross-sectional in nature and sampling occurred in an urban setting (Mehta, 2008, and Strathdee et al., 2005), limiting direct comparison to the patterns observed in the rural sample presented here. Nonetheless, while the proportion reporting receipt of medical follow-up in this study exceeded that in most urban drug-using samples, proportion actually seeking treatment lagged far behind. Finally, the proportion ultimately receiving treatment in this rural population (8%) was comparable to other prior studies, with reported levels between 3% and 10% (Cullen, Stanley et al. 2007; Trepka, Zhang et al. 2007; Mehta, Genberg et al. 2008) and higher uptake reported in community clinic-based (Morrill, Shrestha et al. 2005) and Australian (Grebely, Genoway et al. 2008) studies.

Several sociodemographic and behavioral factors independently predicted following up with a healthcare professional in this rural drug-using population. As with previous study of this public health problem (Stepanova, Kanwal et al. 2011; Denniston, Klevens et al. 2012), health insurance coverage was a robust predictor of healthcare system engagement in this rural drug-using population. Unfortunately, nearly 70% of this sample cohort was uninsured throughout the study period, suggesting that lack of insurance coverage and likely healthcare costs are major barriers to HCV care among rural Appalachians who use drugs. However, in light of early reports of expanding insurance coverage in the United States (Gallup Well-Being 2014; U.S. Department of Health and Human Services 2014) and Kentucky in particular (Brammer 2014) since implementation of the Affordable Care Act, there is reason for hope that the barriers erected by issues related to insurance coverage and treatment cost may diminish.

Concordant with previously reported associations between readiness to cease illicit drug use and interest in HCV treatment initiation (Strathdee, Latka et al. 2005), a lifetime history of substance abuse treatment improved the chance of receiving post-screening medical evaluation in this population. *Recent* substance abuse treatment, however, was not significantly associated with medical follow-up, and surprisingly, recent legal methadone use actually decreased the odds of seeing a healthcare professional. This negative association suggests that while past treatment for addiction issues may boost health system engagement after screening, contemporaneous substance abuse treatment and especially opioid substitution therapy do not appear conducive to HCV medical care in the rural setting. Moreover, despite the small sample of recent legal methadone recipients, the negative association of recent legal methadone use is of particular interest, implying that what few harm reduction and IDU cessation services that are available in Central Appalachia may actually deter HCV clinical assessment among seropositive

individuals. Echoing previous research (Morrill, Shrestha et al. 2005; Treloar, Newland et al. 2010; McGibbon, Bornschlegel et al. 2013; McGowan, Monis et al. 2013), there may be a potential provider- or system-lever bias against simultaneously management of opioid addiction and HCV at play. Furthermore, in terms of public health policy, this finding implies, unsurprisingly, that harm reduction, substance abuse treatment, and HCV medical management are not well integrated in the Appalachian region and may even be working antagonistically, despite evidence that the benefits of such programs are maximized if implemented with an integrated, "one-stop-shopping" approach (Grebely, Genoway et al. 2007; Grebely, Knight et al. 2010; Masson, Delucchi et al. 2013).

Two characteristics promoting HCV follow-up in this sample have not been reported in previous research. First, reporting access to the internet nearly doubled the likelihood of medical follow-up during the subsequent study interval. This association could suggest that there is a protective benefit in the ability to access information regarding the potential health consequences of CHC or to investigate current options for HCV care and treatment. In light of past research describing the potential of internet access to increase patient knowledge level, facilitate dissemination of health information, and promote "patient activism" (Stevenson, Kerr et al. 2007; Pew Internet & American Life Project 2010; Magnezi, Grosberg et al. 2014), particularly among patients with HIV (Kalichman, Weinhardt et al. 2002) and other chronic diseases such as cancer (Basch, Thaler et al. 2004), it is reasonable that similar mechanisms would be relevant to individuals testing positive for HCV. Furthermore, an innovative "telemedicine" program has leveraged the internet to improve access to HCV-related healthcare among prisoners and rural residents in New Mexico with considerable success (Arora, Thornton et al. 2007), suggesting a potential direction for interventional study of HCV management in medically underserved Central Appalachia.

Another unexpected positive association was observed among recent marijuana users in this rural cohort, who were nearly twice as likely to obtain medical follow-up following an HCV-positive test and counseling. As one might expect, few studies have examined the impact of recent cannabis use on outcomes related to HCV treatment uptake, although a major study from the interferon/ribavirin era reported significant improvements in both treatment retention and efficacy among patients reporting recent use of marijuana (Sylvestre 2002; Sylvestre, Clements et al. 2006). However, no other studies have reported other "protective" associations with regard to marijuana use and uptake of medical care or related outcomes. One hypothesis

would be that rural PWID with high interest in quitting IDU but poor access to addiction treatment options might substitute marijuana for prescription opioids and other preferred drugs of injection, but in lieu of related research, further investigation of marijuana's influence on healthcare decisions among rural HCV-seropositive PWID is necessary. Regardless, in light of daily cannabis smoking being a potential risk factor for accelerated disease progression among individuals with CHC (Hezode, Zafrani et al. 2008; Mallat, Hezode et al. 2008) and the scarcity of other mechanisms promoting HCV-related care in Central Appalachia, this tendency among recent marijuana users is fortuitous at worst.

Finally, the two psychiatric measures independently associated with medical follow-up are of particular interest given the central role of psychiatric comorbidity in the determining HCV treatment eligibility (American Association for the Study of Liver Diseases 2014) and high prevalence of psychosocial impairment among CHC patients (Fireman, Indest et al. 2005; Modabbernia, Poustchi et al. 2013). In addition to being a major contraindication to treatment, unmanaged depression and related social isolation is a common barriers to healthcare engagement among individuals with CHC in particular (Nguyen, Dore et al. 2007; Treloar, Newland et al. 2010). Moreover, depression is frequently comorbid with HCV, and depressed individuals are more likely to report symptoms, fatigue, and other adverse impacts on lifestyle resulting from chronic infection (Dwight, Kowdley et al. 2000; Golden, O'Dwyer et al. 2005). Interestingly, individuals meeting the DSM-IV criteria for generalized anxiety disorder (GAD) displayed a strong positive association with obtaining medical care, suggesting that individuals more likely to experience anxiety after HCV status disclosure and counseling are also more inclined to seek medical care. In one of the few prior studies to investigate anxiety and HCV, no differences in adverse impacts of illness were reported among patients with CHC (Golden, O'Dwyer et al. 2005), despite frequent associations between anxiety disorders and chronic hepatitis C (el-Serag, Kunik et al. 2002). While no previous studies have reported associations between GAD and care initiation or uptake of treatment for HCV, the notion that a predisposition for anxiety might promote initiation of medical care for a potentially fatal infection is reasonable from an intuitive standpoint.

While this study provides important insight into factors impacting the initiation of HCV medical management in a vulnerable population, there are some limitations to consider. First, due to practical limitations on size of the study survey instrument, some variables were reported only at baseline and thus analyzed as time-invariant measures, although they may

have in fact changed over time. This includes the DSM-IV psychiatric measures, income, and access to transportation and possession of a driver's license. Next, a common predictor of HCV care engagement and treatment uptake is having a regular physician, but this characteristic was not assessed in the study questionnaire. However, several time-varying proxy measures for health management status were considered in analysis, including having a chronic medical condition and regularly taking legally prescribed medication. Another potential limitation is the unbalanced nature of data collection occasions, although in this analysis mean interval length between baseline, 6, 12, and 18 months was relatively homogeneous. However, there were substantial between-subject differences in interval length and "eligible" days for seeking care following HCV-positive status disclosure and the subsequent interview. Thus, the time-weighted model presented in the Appendix adjusted for this potential source of variability; likelihood-based goodness-of-fit statistics (AIC/BIC) suggested model performance after adjusting for heterogeneous interval length, so the final model was fit assuming uniform interval length (bin width) between and within participants. Finally, as with results presented in chapter 3, these analyses relied on self-reported data, which can be subject to social desirability and recall biases. Again, recall bias is expected to be minimized by the primary use of time-variant measures pertaining to the last 6 months or less, and previous studies have suggested self-reported data from people who use and inject drugs to be reliable (Kokkevi, Richardson et al. 1997; Darke 1998).

In this sample of rural PWID, the proportion obtaining medical follow-up after positive serotesting and counseling was above average, self-reported "treatment seeking" behavior was low, and HCV treatment uptake over the 18-month study period was average to above average relative to other observational studies of drug-using populations. This pattern seems to suggest that barriers on the individual level may be more significant than those among physicians, given that 21 of the 35 (60%) participants who reported seeking treatment from a healthcare provider also reported receiving treatment for HCV. Along with typical measures promoting healthcare engagement such as having health insurance coverage and a history of substance abuse treatment, there were some unexpected associations such as generalized anxiety disorder, internet access, and recent marijuana use. Surprisingly, lower income level, recent IDU, and other illicit drug use measures did not seem to inhibit medical follow-up as reported in other studies. The characteristics associated with decreased likelihood of medical follow-up, including legal or illicit methadone use and major depression, indicate substantial but potentially

modifiable barriers to the initiation of care for HCV. Furthermore, these inhibitory factors suggest a need to couple mental health services, substance abuse treatment, and opioid substitution therapy with more accessible HCV medical care services in this high-prevalence population. This is especially true with regard to methadone recipients, who have an opportunity to be linked with medical care at what may be one of the few points of health system contact rural PWID with HCV may experience. Integrated programs combining HCV management with other services such as psychiatric care, peer support and counseling, and substance abuse treatment have been demonstrated to be effective with regard to promotion of primary (Sacks-Davis, Horyniak et al. 2012) as well as secondary (Birkhead, Klein et al. 2007) prevention of HCV. Multidisciplinary HCV and addiction services targeted to PWID in the Netherlands, for example, reported secondary medical assessment among 76% of study participants, and 33% initiated treatment (Lindenburg, Lambers et al. 2011), proportions comparable to clinic- and population-based studies. Such findings reinforce the effectiveness of integrated approaches to address both IDU and HCV simultaneously among people with a history of injecting drugs. Interventional research targeted to rural individuals least likely to seek care for HCV would be of considerable value, particularly programs offering combined care for psychiatric, substance abuse, and infectious disease comorbidity.

5.5 Conclusions

These findings offer valuable insight into the potential public health impact of screening on primary and secondary prevention of HCV among rural Appalachian people who use and inject drugs. Despite overall declines in IDU and IDU sharing and some indication of transient positive effects on risk behavior, the longitudinal patterns observed over two years of study are generally in agreement with previous studies indicating that HCV screening and counseling alone are not sufficient to make meaningful impact on HCV transmission risk in most high-risk populations. In this cohort, apparent preventive benefit was observed simply from being enrolled in a structured longitudinal study and receiving health-related informational materials among all PWID regardless of serostatus. Substantial declines in reported IDU frequency and sharing of IDU paraphernalia were observed over time in the overall sample, particularly in the first 18 months of the study. However, with some exceptions, this protective trend occurred mostly independent of serotest results and post-test counseling, and there were indications of

leveling off and even potential increases in IDU sharing reported at the final study visit after more than 24 months.

On balance, this trajectory concurs with the conclusions of Page (2007) and other researchers (Aspinall, Weir et al. 2014) that screening and counseling along are not sufficient to effect lasting gains with regard to the primary prevention of HCV, and integrated multidisciplinary approaches are required to make meaningful impact on HCV incidence in high-prevalence populations (Hagan and Schinazi 2013; Grebely and Dore 2014). However, it is worth noting that the modest preventive gains discussed in Chapter 2 indicate that PWID in resource-deprived rural areas may in fact be somewhat more responsive to HCV screening and counseling than has generally been reported among their urban counterparts. This may be particularly true among women with regard to reducing the frequency of sharing syringes and other equipment used during IDU. However, much of this gender-specific benefit is apparently offset by engaging in risky sexual relationships with other PWID, a characteristic emerging as a major deterrent to primary prevention across several measures of IDU risk. In addition, affirming prior findings in this study cohort (Havens, Lofwall et al. 2013), frequent injection of prescription opioids was a robust predictor of elevated IDU risk in multiple models. In light of dense risk network structure and its value in predicting HIV risk behavior in rural Appalachia (Havens, Oser et al. 2010), these consistent associations indicate that network-oriented analysis of the interplay between IDU risk and the characteristics of sexual dyads is likely to be a productive avenue of research with regard to preventing the transmission of bloodborne viruses such as HCV and HIV in this population.

As for secondary prevention modalities after positive serotesting, descriptive proportions in this study sample reflect encouraging levels of medical follow-up and treatment uptake, but a far less treatment-seeking behavior relative to other studies. While this could reflect differences in question format related to the semantics of “treatment willingness” versus “treatment seeking,” it is also possible that seeking HCV treatment is simply not normative behavior among PWID in rural Appalachia. Negative perceptions and peer anecdotes regarding HCV treatment have been reported in previous studies (Swan, Long et al. 2010; Treloar, Newland et al. 2010), and qualitative study of attitudes towards HCV treatment in a social network context would shed fascinating light on individual and community-level barriers to care in this cohort. As for the significant predictors of healthcare engagement, possession of health insurance stands out. In light of dramatic increases in access to care and sweeping system-level

changes to American healthcare under the Affordable Care Act, expansion of health insurance coverage likely offers the greatest potential to impact uptake of care and treatment for HCV in the immediate future. In addition, in the resource-deprived context of Central Appalachia, the gradual expansion of internet access in rural Eastern Kentucky (Cheves 2014) and the potential of scaled-up substance abuse treatment services could also have substantial impact on the hepatitis C landscape in the recently diagnosed drug-using population.

Finally, widespread treatment of active PWID was modeled to be cost-effective in populations with "moderate" HCV prevalence, or approximately 40% (Martin, Vickerman et al. 2012). Based on the implications of this model, the cost-benefit ratio with regard to population-level primary prevention via HCV treatment may have substantially deteriorated in this cohort during the course of data collection. Sample HCV prevalence was 54% among PWID at baseline (Havens, Lofwall et al. 2013), but after 6 months it exceeded 60% and had surpassed 65% by 24 months. Unfortunately, this suggests the window of opportunity to leverage the HCV "treatment-as-prevention" approach (Hagan, Wolpe et al. 2013) may be distressingly narrow in rural Appalachia, and it may have been abruptly shut by potentially high seroincidence in this cohort. Regardless, beyond cost-effectiveness arguments, secondary prevention of CHC disease manifestations carries substantial value in terms of both long-term public health benefit and bioethical considerations concerning allocation of care (Edlin, Seal et al. 2001). Moreover, recent clinical trial data indicate that imminently available drug treatment agents may be even more efficacious and less toxic than previously predicted (Doyle, Aspinall et al. 2013; Afdhal, Reddy et al. 2014; Afdhal, Zeuzem et al. 2014). Such a trend will no doubt necessitate reevaluation of previous cost-effectiveness estimates, particularly once the cost of HCV treatment begins to decline. At the present time, it appears clinical factors such as middling efficacy and high toxicity will soon fade as prohibitive concerns with regard to the initiation of HCV treatment. In the immediate future, however, the astronomical price tag will undoubtedly restrict many eligible patients from receiving curative treatment, raising new, difficult questions with regard to the allocation of care for chronic hepatitis C worldwide.

Table A3.1

Predictors of decreased IDU sharing among recent PWID (n=203): Autoregressive covariance

Characteristic	Adjusted Odds Ratio	95% CI	p-value
Male	0.32	0.15 – 0.67	0.002
Number of dependents (per individual)	0.67	0.50 – 0.90	0.008
Any religious affiliation reported	2.54	1.24 – 5.21	0.011
HCV+ test & counseling: 3 study intervals previously	1.20	0.99 – 1.43	0.068
Unprotected sex (last 30 days)	0.74	0.60 – 0.92	0.007
Prescription opioid IDU (last 6 months)	0.79	0.63 – 0.98	0.031

[1] Population-averaged GEE estimates adjusted for RDS

Table A3.2

Description of sample and population-averaged bivariate associations with increased IDU sharing among recent PWID with no previous HCV+ test (n=283)[1]

Characteristic		Sample total	Odds Ratio	95% CI	p-value
Time-invariant					
Received HCV+ test prior to study		63 (22.3)	1.10	0.39 – 3.08	0.853
Male		167 (59.0)	0.72	0.34 – 1.52	0.389
White		265 (93.6)	4.11	0.56 – 30.13	0.164
Age (per year) - mean (SD)		32.7 (7.9)	0.96	0.92 – 1.00	0.031
Any religious affiliation reported		81 (28.6)	1.05	0.52 – 2.14	0.890
Married		68 (24.0)	1.40	0.61 – 3.18	0.426
Bisexual or homosexual		27 (9.5)	1.24	0.60 – 2.54	0.561
Number of dependents - mean (SD)		1.0 (1.4)	0.95	0.81 – 1.12	0.507
Education (per year)		11.7 (2.4)	0.91	0.81 – 1.03	0.120
Monthly income (per $100 US) - mean (SD)		1340.5 (2014.0)	0.98	0.95 – 1.00	0.092
Most often unemployed (last 3 years)		84 (29.7)	2.18	1.01 – 4.68	0.046
Driver's license and vehicle		93 (32.9)	0.73	0.36 – 1.48	0.379
Major Depressive Disorder		77 (27.2)	0.95	0.47 – 1.91	0.886
Generalized Anxiety Disorder		84 (29.0)	0.58	0.27– 1.23	0.156
Antisocial Personality Disorder		97 (34.3)	0.93	0.44 – 1.96	0.839
Post-Traumatic Stress Disorder		39 (13.8)	0.33	0.10 – 1.13	0.077
≥5 of 6 general HCV questions correct		257 (90.8)	2.83	0.79 – 10.21	0.111
3 of 3 HCV transmission questions correct		271 (95.8)	2.98	0.43 – 20.69	0.269
Time-varying					
HCV+ T&C at any study visit (0-18m)		192 (67.8)	1.73	0.79 – 3.76	0.169
Study occasions since HCV+ T&C:	1	151 (53.4)	2.15	1.33 – 3.47	0.002
	2	177 (62.5)	0.93	0.54 – 1.60	0.782
	3	186 (65.7)	0.48	0.20 – 1.18	0.109
	4	192 (67.8)	0.97	0.42 – 2.20	0.934
Followed up with clinician after HCV+ test		116 (41.0)	1.47	0.75 – 2.90	0.260
Sought treatment after HCV+ test		28 (9.9)	2.66	0.89 – 7.99	0.081
Received HCV treatment after HCV+ test		17 (6.0)	3.33	0.89 – 12.48	0.074

Health insurance coverage	140 (49.5)	0.65	0.34 – 1.24	0.194
"Poor" to "fair" health status	168 (59.4)	1.44	0.96 – 2.18	0.080
Days with health problems[2] - mean (SD)	5.0 (7.6)	0.96	0.93 – 1.00	0.025
Reported chronic medical condition	141 (49.8)	0.53	0.28 – 1.01	0.053
Taking legally prescribed medication	139 (49.1)	0.52	0.27 – 1.01	0.053
Receiving physical disability pension	64 (22.6)	0.32	0.15 – 0.67	0.002
Substance use treatment (last 6m)	87 (30.7)	0.39	0.15 – 1.01	0.052
Legal methadone use (last 6m)	32(11.3)	0.40	0.04 – 3.83	0.424
Legal buprenorphine use (last 6m)	48 (17.0)	2.09	1.06 – 4.15	0.034
Incarceration[2]	121 (42.8)	0.28	0.10 – 0.79	0.015
Lifetime behavior				
Incarceration	241 (85.2)	0.58	0.19 – 1.79	0.344
Substance abuse treatment	186 (65.7)	1.61	0.70 – 3.71	0.260
Drug overdose	104 (36.8)	0.86	0.42 – 1.72	0.662
Years of IDU - mean (SD)	8.0 (7.0)	0.93	0.88 – 1.00	0.034
Heroin use	123 (43.5)	0.78	0.37 – 1.62	0.504
Illicit methadone use	261 (92.2)	0.62	0.23 – 1.69	0.352
Legal methadone use	45 (15.9)	1.35	0.60 – 3.04	0.463
Illicit buprenophine use	201 (71.0)	1.64	0.76 – 3.54	0.208
Legal buprenorphine use	41 (14.5)	1.81	0.52 – 6.35	0.354
Illicit OxyContin® use	272 (96.1)	3.86	0.51 – 29.14	0.191
Other illicit oxycodone use	273 (96.5)	0.36	0.10 – 1.34	0.128
Any other prescription opioid use	231 (81.6)	1.36	0.58 – 3.20	0.481
Sedative, hypnotic, or tranquilizer use	246 (86.9)	0.70	0.30 – 1.64	0.408
Barbiturate use	31 (11.0)	0.59	0.23 – 1.50	0.268
Crack use	212 (74.9)	0.72	0.27 – 1.91	0.511
Cocaine use	267 (94.4)	2.66	0.62 – 11.49	0.190
Methamphetamine use	128 (45.2)	0.97	0.48 – 1.94	0.928
Prescription stimulant use	110 (38.9)	0.78	0.40 – 1.54	0.476
Marijuana use	276 (97.5)	0.14	0.02 – 0.84	0.031
Hallucinogen use	142 (50.2)	1.03	0.48 – 2.20	0.938
Inhalant use	59 (20.9)	0.52	0.23 – 1.16	0.110
Multiple substance use	264 (93.3)	9.89	1.39 – 70.09	0.022
Recent risk behavior (last 6m unless indicated)				
Recent unprotected sex[2]	252 (89.1)	5.67	2.85 – 11.25	<0.0001
Recent unprotected sex with PWID[2]	110 (38.9)	10.80	5.96 – 19.58	<0.0001
Recent unprotected transactional sex[2]	10 (3.5)	1.20	0.17 – 8.64	0.858
Drug overdose	18 (6.4)	1.87	0.57 – 6.13	0.303
Alcohol use to intoxication	174 (61.5)	1.48	0.83 – 2.65	0.192
Daily or greater IDU frequency	144 (50.9)	7.84	4.16 – 14.78	<0.0001
Days of IDU[2] - mean (SD)	11.9 (10.3)	1.10	1.08 – 1.13	<0.0001
Heroin use	39 (13.8)	2.03	0.63 – 6.61	0.238
Heroin IDU	25 (8.8)	3.30	0.93 – 11.75	0.065
Illicit methadone use	214 (75.6)	1.29	0.81 – 2.05	0.286
Illicit buprenorphine use	208 (73.5)	1.95	0.99 – 3.86	0.055
OxyContin® use[3]	248 (87.6)	2.04	1.13 – 3.66	0.017
Any other oxycodone use	270 (95.4)	4.04	1.86 – 8.76	<0.0001
Any other prescription opioid use	252 (89.1)	2.13	1.28 – 3.54	0.003
Any prescription opioid IDU[4]	219 (77.4)	n/a	n/a	<0.0001
Days of Rx opioid IDU[2] - mean (SD)	7.2 (8.8)	1.10	1.08 – 1.13	<0.0001
Sedative, hypnotic or tranquilizer use	246 (86.9)	2.25	1.25 – 4.07	0.007
Sedative, hypnotic or tranquilizer IDU	6 (2.1)	1.87	0.11 – 31.14	0.662
Barbiturate use	23 (8.1)	1.51	0.52 – 4.38	0.444

Crack use	70 (24.7)	1.06	0.49 – 2.29	0.875
Cocaine use	135 (47.7)	2.23	1.08 – 4.57	0.030
Cocaine IDU	76 (26.9)	0.57	0.26 – 1.23	0.152
Methamphetamine use	49 (17.3)	0.71	0.19 – 2.66	0.608
Methamphetamine IDU	14 (5.0)	1.88	0.39 – 9.14	0.436
Prescription stimulant use	79 (27.9)	2.35	1.25 – 4.43	0.008
Prescription stimulant IDU	5 (1.8)	8.05	1.46 – 44.31	0.017
Marijuana use	223 (78.8)	1.30	0.72 – 2.37	0.386
Hallucinogen use	18 (6.4	0.47	0.21 – 1.05	0.067
Multiple substance use	263 (92.9)	1.11	0.70 – 1.76	0.665

[1] GEE population-averaged estimates adjusted for RDS
[2] Last 30 days
[3] Includes original and abuse-deterrent formulations of OxyContin®
[4] GEE did not converge; 100% of participants with any increased IDU sharing also reported recent prescription
opioid IDU (p-value via Fisher's exact test)

Table A3.3
Predictors of increased IDU sharing among recent PWID (n=264)[1]: Autoregressive covariance

Characteristic		**Adjusted Odds Ratio**	**95% CI**	**p-value**
Time elapsed since study enrollment (per month)		1.04	1.01 – 1.07	0.013
Monthly income (per $100)		0.97	0.95 – 1.00	0.029
Study intervals since HCV+ test & counseling:	1	1.36	0.54 – 3.39	0.515
	2	1.05	0.43 – 2.54	0.918
	3	0.42	0.16 – 1.10	0.078
	4	0.30	0.08 – 1.10	0.070
Unprotected sex with PWID (last 30 days)		5.77	3.05 – 10.91	<0.0001
Ever used marijuana (lifetime)		0.34	0.17 – 0.65	0.001
Prescription stimulant use (last 6m)		3.18	1.28 – 7.87	0.012
Days of prescription opioid IDU in last 30d (per day)		1.09	1.06 – 1.11	<0.0001

[1] GEE population-averaged estimates adjusted for RDS

Table A3.4

Bivariate population-averaged associations with IDU cessation in the last 6 months (n=220)[1]

Characteristic		Sample total	Odds Ratio	95% CI	p-value
Time-invariant					
Received HCV+ test prior to study[2]		63 (22.3)	0.54	0.33 – 0.88	0.014
Male		134 (60.9)	0.65	0.41 – 1.03	0.066
White		205 (93.2)	0.48	0.20 – 1.13	0.094
Age (per year) - mean (SD)		32.5 (8.2)	1.03	1.00 – 1.06	0.031
Any religious affiliation reported		55 (25.0)	1.22	0.77 – 1.95	0.393
Married		74 (25.4)	0.95	0.58 – 1.58	0.853
Bisexual or homosexual		20 (9.1)	1.33	0.74 – 2.39	0.343
Number of dependents - mean (SD)		0.9 (1.3)	1.26	1.04 – 1.53	0.021
Education (per year) - mean (SD)		11.7 (2.5)	1.08	0.98 – 1.19	0.109
Monthly income (per $100 US) - mean (SD)		1250.4 (1832.9)	0.99	0.98 – 1.01	0.306
Most often unemployed (last 3 years)		63 (28.6)	0.80	0.50 – 1.29	0.364
Driver's license and vehicle		70 (31.8)	1.06	0.64 – 1.74	0.826
Major Depressive Disorder		57 (25.9)	0.89	0.55 – 1.46	0.650
Generalized Anxiety Disorder		57 (25.9)	1.08	0.63 – 1.83	0.781
Antisocial Personality Disorder		78 (35.5)	0.74	0.45 – 1.21	0.228
Post-Traumatic Stress Disorder		33 (15.0)	1.46	0.82 – 2.61	0.195
≥5 of 6 general HCV questions correct		196 (89.1)	0.54	0.27 – 1.08	0.080
3 of 3 HCV transmission questions correct		209 (95.0)	0.47	0.13 – 1.71	0.250
Time-varying					
HCV+ T&C at any study visit (0-18m)		134 (60.9)	0.49	0.32 – 0.75	0.001
Study occasions since HCV+ T&C:	1	107 (48.6)	0.37	0.25 – 0.54	<0.0001
	2	120 (54.6)	1.28	0.96 – 1.69	0.088
	3	128 (58.2)	1.08	0.79 – 1.48	0.624
	4	134 (60.9)	1.21	0.86 – 1.70	0.265
Followed up with clinician after HCV+ test		74 (33.6)	0.87	0.59 – 1.29	0.491
Sought treatment after HCV+ test		11 (5.0)	1.02	0.55 – 1.90	0.957
Received HCV treatment after HCV+ test		8 (3.6)	1.06	0.51 – 2.20	0.868
Health insurance coverage		109 (49.6)	1.30	0.91 – 1.87	0.155
"Poor" to "fair" health status		127 (57.7)	0.87	0.66 – 1.13	0.295
Days with health problems[3] - mean (SD)		5.1 (7.9)	1.01	0.99 – 1.02	0.246
Reported chronic medical condition		109 (49.6)	1.24	0.89 – 1.71	0.202
Taking legally prescribed medication		104 (47.3)	1.58	1.11 – 2.26	0.012
Receiving physical disability pension		59 (26.8)	2.01	1.31 – 3.07	0.001
Substance use treatment (last 6m)		64 (29.1)	1.75	1.06 – 2.88	0.029
Legal methadone use (last 6m)		24 (10.9)	1.68	0.90 – 3.10	0.101
Legal buprenorphine use (last 6m)		31 (14.1)	0.67	0.35 – 1.30	0.239
Incarceration[3]		87 (39.6)	1.06	0.71 – 1.59	0.764
Lifetime behavior					
Incarceration		184 (83.6)	0.37	0.20 – 0.67	0.001
Substance abuse treatment		141 (64.1)	0.72	0.44 – 1.19	0.200
Drug overdose		73 (33.2)	0.89	0.54 – 1.46	0.644
Years of IDU - mean (SD)		7.6 (7.0)	1.00	0.97 – 1.03	0.872
Heroin use		89 (40.5)	0.58	0.37 – 0.93	0.023
Illicit methadone use		201 (91.3)	1.17	0.55 – 2.48	0.685
Legal methadone use		32 (14.6)	1.42	0.77 – 2.62	0.261
Illicit buprenophine use		153 (69.6)	0.88	0.53 – 1.45	0.608
Legal buprenorphine use		25 (11.4)	0.53	0.27 – 1.04	0.064

Illicit OxyContin® use	209 (95.0)	0.17	0.06 – 0.50	0.001
Other illicit oxycodone use	211 (95.9)	6.01	1.16 – 31.22	0.033
Any other prescription opioid use	180 (81.8)	0.78	0.42 – 1.43	0.419
Sedative, hypnotic, or tranquilizer use	187 (85.0)	1.81	0.93 – 3.53	0.080
Barbiturate use	21(9.6)	1.56	0.77 – 3.15	0.220
Crack use	159 (72.3)	0.89	0.55 – 1.44	0.641
Cocaine use	205 (93.2)	0.86	0.39 – 1.91	0.713
Methamphetamine use	93 (42.3)	0.60	0.38 – 0.94	0.027
Prescription stimulant use	85 (38.6)	0.97	0.59 – 1.57	0.891
Marijuana use	215 (97.7)	0.14	0.03 – 0.49	0.003
Hallucinogen use	110 (50.0)	0.90	0.57 – 1.41	0.637
Inhalant use	47 (21.4)	1.21	0.73 – 1.99	0.462
Multiple substance use	202 (91.8)	0.59	0.27 – 1.28	0.184
Recent risk behavior (last 6m unless indicated)				
Recent unprotected sex[3]	200 (90.9)	0.86	0.64 – 1.16	0.323
Recent unprotected sex with PWID[3]	82 (37.3)	0.21	0.13 – 0.35	<0.0001
Recent unprotected transactional sex[3]	7 (3.2)	0.85	0.22 – 3.36	0.825
Drug overdose	14 (6.4)	0.57	0.28 – 1.15	0.117
Alcohol use to intoxication	142 (64.6)	0.64	0.47 – 0.87	0.005
Daily or greater IDU frequency[5]	69 (31.4)	0.38	0.24 – 0.63	<0.0001
Heroin use	25 (11.4)	0.48	0.20 – 1.13	0.093
Heroin IDU[5]	28 (12.7)	1.07	0.51 – 2.24	0.852
Illicit methadone use	172 (78.2)	0.71	0.52 – 0.99	0.043
Illicit buprenorphine use	159 (72.3)	0.61	0.45 – 0.84	0.002
OxyContin® use[4]	189 (85.9)	0.27	0.19 – 0.38	<0.0001
Any other oxycodone use	208 (94.6)	0.32	0.21 – 0.50	<0.0001
Any other prescription opioid use	192 (87.3)	0.68	0.52 – 0.88	0.003
Any prescription opioid IDU[5]	202 (91.8)	0.36	0.19 – 0.71	0.003
Days of opioid IDU[3,5] - mean (SD)	10.8 (11.5)	0.93	0.91 – 0.95	<0.0001
Sedative, hypnotic or tranquilizer use	187 (85.0)	0.53	0.39 – 0.72	<0.0001
Sedative, hypnotic or tranquilizer IDU[5]	12 (5.5)	1.89	0.80 – 4.48	0.146
Barbiturate use	19 (8.6)	0.81	0.38 – 1.69	0.568
Crack use	57 (25.9)	0.50	0.29 – 0.87	0.014
Cocaine use	107 (48.6)	0.40	0.27 – 0.60	<0.0001
Cocaine IDU[5]	88 (40.0)	1.19	0.75 – 1.90	0.453
Methamphetamine use	36 (16.4)	0.50	0.29 – 0.87	0.014
Methamphetamine IDU[5]	7 (3.2)	3.42	1.11 – 10.53	0.032
Prescription stimulant use	67 (30.5)	0.65	0.43 – 1.00	0.050
Prescription stimulant IDU[5]	9 (4.1)	0.56	0.21 – 1.48	0.244
Marijuana use	181 (82.3)	0.66	0.49 – 0.89	0.006
Hallucinogen use	16 (7.7)	1.47	0.62 – 3.47	0.377
Multiple substance use	203 (92.3)	0.57	0.43 – 0.75	<0.0001

[1] GEE population-averaged estimates adjusted for RDS

[2] n=283 (participants who reported IDU in the 6 months preceding baseline and returned after 6 months

[3] Last 30 days

[4] Includes original and abuse-deterrent formulations of OxyContin®

[5] Reported at baseline

Table A3.5

Predictors of IDU cessation among recent PWID, excluding recent illicit drug use measures (n=203)[1]: Autoregressive covariance

Characteristic		Adjusted Odds Ratio	95% CI	p-value
Study intervals since HCV+ test & counseling:	1	0.53	0.29 – 0.95	0.034
	2	1.62	0.89 – 2.97	0.114
	3	1.47	0.79 – 2.73	0.221
	4	2.11	0.91 – 4.88	0.082
Number of dependents (per individual)		1.26	1.06 – 1.51	0.010
Lifetime history of incarceration		0.23	0.09 – 0.48	<0.0001
Currently receiving disability pension		2.72	1.52 – 4.87	0.001
Substance abuse treatment (last 6m)		2.41	1.32 – 4.42	0.004
Unprotected sex with PWID (last 30d)		0.16	0.08 – 0.32	<0.0001
Ever used illicit OxyContin® (lifetime)		0.21	0.09 – 0.48	<0.0001
Days of Rx opioid IDU in last 30d (per day)[2]		0.94	0.91 – 0.96	<0.0001

[1] GEE population-averaged estimates adjusted for RDS

[2] At baseline

Table A3.6

Predictors of IDU cessation among recent PWID, with recent illicit drug use measures (n=203)[1]: Autoregressive covariance

Characteristic		Adjusted Odds Ratio	95% CI	p-value
Time since study enrollment (per month)		0.97	0.95 – 1.00	0.056
Study intervals since HCV+ test & counseling:	1	0.36	0.18 – 0.70	0.003
	2	1.07	0.56 – 2.04	0.832
	3	1.08	0.54 – 2.19	0.833
	4	1.20	0.53 – 2.76	0.660
Number of dependents (per individual)		1.25	1.02 – 1.53	0.031
Lifetime history of incarceration		0.21	0.10 – 0.46	<0.0001
Currently receiving disability pension		2.52	1.37 – 4.63	0.003
Unprotected sex with PWID (last 30d)		0.20	0.10 – 0.40	<0.0001
Days of Rx opioid IDU in last 30d (per day)[2]		0.93	0.91 – 0.95	<0.0001
Illicit OxyContin® use (last 6m)		0.23	0.13 – 0.42	<0.0001
Other oxycodone use (last 6m)		0.34	0.21 – 0.56	<0.0001
Cocaine use (last 6m)		0.52	0.30 – 0.88	0.016

[1] GEE population-averaged estimates adjusted for RDS

[2] At baseline

Table A5.1

Goodness-of-fit statistics for various parameterizations of time

Time Model	DF	Deviance	ΔDeviance[1]	p-value	ΔDeviance[2]	p-value	AIC	BIC
Discrete	3	552.01	-	-	-	-	558.01	570.56
Adj. discrete[3]	3	566.30	-	-	14.29 (0)	-	572.30	584.85
Constant	1	569.29	-	-	17.28 (2)	0.0002	571.29	575.48
Adj. linear[3]	2	557.98	11.31 (1)	0.0008	5.97 (1)	0.015	561.98	570.35
Linear	**2**	**554.00**	**15.29 (1)**	**<0.0001**	**1.99 (1)**	**0.158**	**558.00**	**566.37**
Quadratic	3	553.05	0.95 (1)	0.331	1.04 (0)	-	559.05	571.61

[1] Versus preceding model with fewer parameters

[2] Versus fully discrete time specification

[3] Weighted to adjust for interval length

Table A5.2

Predictors of medical follow-up after HCV-positive T&C: Interval-weighted linear time model[1]

Variable	Adjusted Odds Ratio	95% CI	p-value
Time (per study interval)	0.64	0.47 – 0.89	0.007
Aware of HCV+ status at time of serotest	1.73	0.94 – 3.16	0.076
Ever received substance abuse treatment	1.64	1.01 – 2.75	0.045
Percent of income legal	0.99	0.97 – 1.00	0.063
Health insurance	2.04	1.18 – 3.53	0.010
Access to internet	1.82	1.14 – 2.90	0.012
Major depressive disorder	0.46	0.22 – 0.96	0.038
Generalized anxiety disorder	2.68	1.34 – 5.35	0.005
Ever used illicit methadone	0.32	0.13 – 0.79	0.014
Legal methadone use (past 6 months)	0.20	0.05 – 0.91	0.037
Marijuana use (past 6 months)	1.77	1.09 – 2.87	0.021

[1] Discrete-time survival analysis adjusted for RDS

Table A5.3

Predictors of medical follow-up after HCV-positive test and counseling: Discrete-time model[1]

Variable	Adjusted Odds Ratio	95% CI	p-value
Aware of HCV+ status at time of serotest	1.69	0.93 – 3.08	0.084
Ever received substance abuse treatment	1.66	1.01 – 2.73	0.047
Percent of income legal	0.99	0.97 – 1.00	0.069
Health insurance	2.07	1.21 – 3.56	0.008
Access to internet	1.82	1.14 – 2.90	0.012
Major depressive disorder	0.48	0.23 – 0.97	0.040
Generalized anxiety disorder	2.64	1.34 – 5.20	0.005
Ever used illicit methadone	0.32	0.13 – 0.79	0.013
Legal methadone use (past 6 months)	0.21	0.05 – 0.90	0.036
Marijuana use (past 6 months)	1.73	1.07 – 2.79	0.026

[1] Discrete-time survival analysis adjusted for RDS

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Publications

- Stephens DB and Havens JR. Predictors of alcohol use among rural drug users after disclosure of hepatitis C virus status. *Journal of Studies on Alcohol and Drugs* 74 (2013): 386-95.

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- Young AM, Stephens DB, Abdulghafoor H, Havens JR. Hepatitis C vaccine clinical trials among people who use drugs: potential for participation and involvement in recruitment