Title
Hepatitis C virus treatment, people who inject drugs, and treatment barriers in the age of direct-acting antivirals

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Hepatitis C virus treatment, people who inject drugs, and treatment barriers in the age of direct-acting antivirals

by

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DISSERTATION

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of the

WITH THANKS

To my grandmother and great-grandmother, both nurses: I am beyond proud to be a third-generation nurse and carry on the family tradition of caring for the underserved.

To my family: Thank you for your support and encouragement. I don't believe the world needs another Dr. Asher, but its been great fun to commiserate together on this journey and share such a unique experience. Mom, thank you especially for lulling me to sleep with the sounds of the dot matrix paper as you worked on your dissertation in my childhood. I am certain it was hugely influential.

Carmen, David, Kim and Carol: Thank you for your time, your support and your guidance. It is because of you that I am here today.

Carmen: Twelve years ago I walked into your office for my MEPN interview. You told me about the amazing work a Clinical Nurse Specialist can do and we both agreed it sounded fabulous. You were absolutely right and it's still my proudest badge. Thank you for the many years of support and encouragement, care and concern.

Carol: You've shown me that you can build a successful career working in substance use and helping clinicians improve the care they give. You introduced me to Paula and Kim, and helped launch my career. Thank you.

David: Thank you so much for your generosity with your time and the Diet Cokes. You pushed me, gave me goals and focused me more than I had ever been. I don't think I'd be here today if it weren't for you.

Kim: I am a smarter, more mature, more thoughtful and more careful person because of you. You helped me grow up, gave me opportunites and built my career. I can't thank you enough, or let you know how much I've felt the loss of your presence. Thank you for everything.

Abstract:

Hepatitis C virus (HCV) infection affects millions of Americans at a high public health cost. Despite the availability of a curative treatment, a significant proportion of people living with HCV are not treated. People who inject drugs (PWID), are one of the groups at highest risk of HCV transmission, and are among the least likely to get treatment. Using literature reviews to explore the evidence and a cross-sectional survey to assess what barriers providers see to treatment for PWID, this dissertation explores outcomes when PWID do receive treatment, facilitators to successful treatment outcomes, how current treatment guidelines address substance use, and how providers assess treatment candidacy in PWID. Barriers to treatment include patient-related factors such lack of engagement in healthcare and contradictions to treatment. Other barriers are provider-related, such assumptions about the ability of PWID to complete treatment, and concerns about ongoing drug use and reinfection risk. Although eradication of HCV infection through provision of this curative treatment is theoretically possible, this cannot happen until PWID are treated in large numbers. Currently, PWID face substantial barriers to treatment despite the existence of a cure. Improved provider willingness and knowledge, decreased medication costs, and interventions to address adherence and reinfection are all needed in order to facilitate increased treatment provision for PWID, and move toward eradication of HCV in the United States.

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I. Introduction

Millions of Americans are impacted by hepatitis C infection at a high public health cost [1, 2]. Injection drug use accounts for the vast majority of HCV transmissions in the United States [3], yet people who inject drugs (PWID) are among the least likely to be treated [4]. Although treatment for HCV has been available for many years, historically it was suboptimal, as the medications available had low efficacy and severe side effects. Today, as a result of significant advances in treatment medications, HCV treatment now cures in the vast majority of patients with few side effects [5]. Despite the availability of highly effective treatments for a disease associated with significant morbidity and mortality, PWID continue to face substantial barriers in treatment access. Concerns about reinfection, adherence and assumptions about PWID contribute to low rates of treatment for this population [6-8]. Despite this, research demonstrates PWID can be successfully treated [9], and that people who are treated experience lower all-cause morbidity and mortality [10]. Increasing the proportion of PWID who receive treatment may necessitate an improvment in the knowledge and practices of many providers previously not well-trained in HCV care or in caring for PWID [11-13]. In order to address the many emerging issues relating to HCV treatment for PWID in this era of highly effectively, direct-acting antiviral medications, this dissertation explores three areas: knowledge of HCV screening and treatment, substance use evaluation and management, and barriers to treatment. Understanding these areas can point to places in HCV treatment and care that need to be addressed in order to successfully extend access to this curative treatment for PWID.

Background

PWID are the group at highest risk for HCV infection, due to high risk of exposure during injection drug use [4]. Although treatment for HCV infection has been available for many

years, traditional combination therapy with interferon and ribavirin is lengthy, complicated by severe side effects and ultimately unsuccessful in as many as 50% of patients who initiate therapy [14]. The many complications and absolute contraindications related to interferon-based HCV treatment have traditionally limited the proportion of patients considered eligible for treatment. However, new direct-acting, all-oral antiviral medications have few absolute contraindications, few side effects, and shorter regimen duration, drastically changing the treatment landscape [15-17]. The clinical parameters of who may receive these new treatments is different from interferon-based treatment, and far less restrictive, but it is not clear that providers have adapted their eligibility criteria as the medications have evolved [18]. Provider knowledge, comfort with substance use, and stigma may all play a role when providers are determining treatment eligibility [7, 8, 19]. Further, the high cost of these new treatments, with a single pill costing as much as $1000, and total treatments over $100,000, may also impact access [17, 20]. Treatment guidelines, which are not standardized, do not adequately address substance use [14, 21, 22], and little is known about how providers view treatment candidacy for PWID given all-oral medications. These emerging complexities, the growing burden of HCV-related morbidity in the United States [23], and the high proportion of PWID living with HCV need to be considered in the context of the availability of highly effective, curative treatments.

Purpose

Historically, PWID have been largely excluded from HCV treatment, in part due to the significant side effects that lengthy, interferon-based medication regimens cause and the low rates of successful treatment outcomes. Barriers to treatment for PWID also include systemic health care issues including lack of access and provider reluctance, and social history of the patient [24-29]. However, when treatment is provided, outcomes have been reviewed and found

sustained virus response (SVR), the clinical indicator of treatment success, in PWID nears those of non-injecting populations in most cases, even in interferon-based regimens [9]. Further, successful HCV treatment has been shown to lower all-cause mortality [30], improve quality of life [23], and there is some evidence it may help PWID decrease or cease injection drug use [24].

Direct-acting HCV treatment regimens have reported near 100% cure with few side effects and short treatment duration. The impact of these new medications on treatment eligibility for PWID has not yet been examined, although several of clinical trials testing the medication's safety and efficacy did not summarily exclude drug users [31-33]. Despite this, it is likely that due to the high cost of medications and historical exclusion and unconscious provider bias, PWID may face continued barriers to treatment. This body of work seeks to describe what evidence is necessary for provider's to understand about HCV and PWID, how to manage substance use before and during treatment, and what barriers may need to be addressed before widespread treatment of HCV among PWID is possible.

Significance

HCV impacts as many as 5.2 million Americans [34], and after a period of stabilization from an all-time high in the 1990s, infections are again on the rise [1]. Complications include cirrhosis and hepatocellular carcinoma, and people living with HCV experience higher all-cause mortality than those without [30]. HCV infection is difficult to prevent among PWID due to the viremic nature of the virus, coupled with risks taken during the injection process. The relatively limited success of current HCV prevention practices for active PWID such as risk reduction counseling suggests that one way to successfully achieve reductions in HCV incidence and decrease the sequelae of long-term HCV infection is through increased HCV treatment coverage [35]. Though the National Institute of Health (NIH; [36] and other updated practice guidelines

[37, 38] recommend evaluation of PWID for HCV treatment, and research has demonstrated successful outcomes for PWID when treated for HCV [9], less than four percent of PWID currently receive treatment [4]. However, the data on HCV treatment in this population is largely limited to interferon-based treatments, and little has been published on outcomes with all-oral regimens in this population. Three areas in particular need more attention: provider knowledge of HCV treatment for PWID, the evaluation and management of substance use in HCV treatment, and understanding

The efficacy of interferon-based treatment for chronic HCV infection depends on a variety of factors, including genotype, time since infection, age of patient and host genetics, and results in a cure approximately 50-80% of the time [14, 39-42]. Effectiveness of interferon-based treatment has also been associated with tolerance to many of the negative, sometimes debilitating side effects related to treatment. Depression, irritability, rashes, and difficulty concentrating are among the more common side effects associated with interferon-based HCV treatment [14]. Many patients who initiate antiviral treatment utilizing interferon are unable to adhere to the treatment schedule or dosing as a result of these side effects, decreasing their ability to achieve SVR [43]. PWID are often considered especially vulnerable, although the evidence suggests little difference from people who do not report injection drug use [9, 44].

The new, direct-acting HCV treatment medications are being hailed as 'game changers' in the fight against HCV infection [45]. Despite the efficacy of these medications, it's not clear if their availability will impact the proportion of PWID who are currently considered eligible to receive HCV treatment. Evidence from HCV and HIV literature suggests that co-occurring disorders including substance use impact treatment provision. The history of poor access to therapies such as antiretrovirals for HIV infection and current treatments for HCV infection for

PWID serves as a cautionary note for roll-out of these new and highly promising medications. The proportion of patients clinically eligible for HCV treatment has increased given the availability of these medications. Despite this, issues such as illicit drug use, and concerns about adherence and reinfection will continue to be barriers to treatment candidacy.

Literature Review and Conceptual Framework

Theoretical framework

Knowledge, Attitude and Practice (KAP) surveys measure changes in human knowledge, attitudes and practices. KAP surveys gather data on what people know about a particular disease, their attitudes toward people with the disease, and what they do in regards to care of people with the disease [46]. Such surveys can serve to identify gaps in training and areas to address to improve practice. Assessing KAP is essential to identify gaps in care, and to determine barriers to reductions in morbidity, mortality and costs associated with non-treatment. The high costs of the long-term sequelea of HCV infection can be prevented if more HCV treatment is provided to the population most impacted by the virus. History, however, shows this to be a significant barrier. Even in HIV care, where mortality can be directly linked to access to treatment, providers are reluctant to treat patients who report active drug use. A 2012 study of over 600 providers in North America found that over 50% of providers surveyed would defer ART if they believed their patient injected drugs daily, and almost 25% would do so even if the CD4 count was under 200 cells/mm [8].

In HCV care, barriers to treatment have been shown to occur at both the patient and provider level. Provider barriers include lack of experience and knowledge of PWID and an emphasis on purported contraindications to treatment that is unsupported in much of the research literature [7, 19, 47, 48]. Addictophobia, or discrimination of drug users, may play a role [49], as

may lack of knowledge of the benefits of treatment [13]. Patient-related barriers include ongoing injection drug use, alcohol use and lack of knowledge about the curative properties of HCV treatment [7, 50, 51]. The United States currently spend over two billion dollars annually on HCV [2] and those costs are projected to rise substantially [52]. Increased HCV treatment provision to PWID may result in lower HCV transmission rates [35] and improved morbidity and mortality [30], as well as decrease the overall costs associated with HCV [23, 53]. Understanding the attitudes and practices of clinicians towards the care of a population with a high burden of HCV is important to understand how the availability of new medications affects the public health burden of HCV infection.

Research questions

The overarching goal of this dissertation is to examine factors that may influence access to treatment for PWID. Three papers examine different aspects of this line of inquiry:

1. What is known about HCV treatment in PWID and what do nurses need to know in order to support successful treatment outcomes?
2. What are methods used to evaluate and manage substance use during the HCV treatment process?
3. How does injection drug use impact provider's determination of treatment candidacy and what are barriers to treatment for PWID in this era of all-oral treatment medications?

Methodology

In order to address the fundamental questions posed by this work, several methodologies were undertaken. Due to the lack of HCV education reported by nurses, the largest cadre of healthcare professionals, a literature review of HCV screening and treatment provides an overview of the important issues today. This basic overview is necessary, as publically available

guidelines on HCV treatment can be vague when it comes to discussing HCV treatment candidacy, especially for PWID. This subject is explored in a second manuscript, which discusses what guidance is provided, what the evidence shows, and methods for managing substance use during treatment. A third paper describes the results of a cross-sectional study of HCV treatment providers and their assessments of treatment candidacy for PWID, outlying barriers to treatment given all-oral and interferon-based regimens.

Data for the first two papers were drawn from existing literature in PubMed on related topics and selected papers that fit key terms such as "hepatitis C and people who inject drugs", "hepatitis C and nursing" "hepatitis C treatment". More emphasis was given to papers published after 2012, as evidence about the effectiveness of direct-acting antivirals began to get published.

In order to understand changes in eligibility for HCV treatment in PWID given the availability of all-oral regimens, and barriers to treatment, a cross-sectional study of HCV treatment providers attending the American Association for the Study of Liver Disease (AASLD) Conference (the Liver Meeting®) was conducted. After demographic information was collected, participants were asked about their assessment of the patient's HCV treatment candidacy given interferon-containing and all-oral medications, and recency of the patient's injection drug use. Providers were asked to rank the most pressing issues for them to consider when assessing treatment candidacy, including social support, insurance coverage, substance use and mental illness. Analyses assessed differences between provider willingness to treat given interferon-based or all-oral medication regimens and time since the patient's last injection drug use.

Summary

In the United States, PWID are disproportionately impact by HCV, yet experience significant barriers to treatment access. The availability of a highly effective cure brings the

status quo for this population into question, but many issues need addressing for change to occur. HCV eradication in the United Sates is plausible, given the availability of direct-acting antiviral medications. Significant barriers must be addressed in order to facilitate improved treatment uptake for PWID. More research is needed to understand how to achieve the best treatment outcomes in this population using direct-acting antivirals. The following summarizes what is known about HCV treatment, evidence-based facilitators of good treatment outcomes, and what barriers to treatment exist for PWID in this age of direct-acting antivirals.

Hepatitis C Virus Treatment in People who Inject Drugs: An Update for Nurses

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Abstract:

Aim: To discuss new and emerging hepatitis c virus (HCV) treatment regimens and clinical considerations of treatment eligibility among people who inject drugs (PWID)

Background: Hepatitis C virus (HCV) infection is a major health concern affecting millions of Americans at a high public health cost. Treatment has been available, but suboptimal due to low efficacy and severe side effects. People who inject drugs (PWID), the group most significantly impacted by HCV, are among those who have had limited HCV treatment access. Clinical contraindications, patient readiness and provider willingness have all been shown to be barriers to HCV treatment. The HCV treatment landscape is rapidly evolving, and new and emerging medications have reported near 100% cure rates with fewer clinical contraindications, side effects and shorter treatment duration. Many groups historically not considered for HCV treatment may be more successful in this new treatment paradigm. Nurses are an important facilitator of successful treatment, but often lack specialized training on HCV. This paper provides an update to the recent advances in HCV treatment and discusses the implications for nursing practice.

Design: This is a clinical application paper

Data Sources: A PubMed search of works from 2004-2014 using the terms 'hepatitis C' 'treatment' 'people who inject drugs' 'hepatitis C treatment and nursing'

Implications for Nursing: As new HCV therapies become available, treatment will increasingly be provided in the community setting, and nurses will increasingly become an essential part of HCV treatment and care. All nurses should be well-poised to provide it.

Conclusion: The new generation of safe and effective oral medications for HCV treatment necessitates ongoing education. Emerging treatments for HCV infection can play a role in the reduction of HCV-related morbidity and mortality, and nurses will increasingly play a significant role in treatment and treatment outcomes.

Word count: 4873

Key words: Adult Nursing, Viral hepatitis, Substance Abuse

Introduction

Hepatitis C virus (HCV) infection is a major public health concern, affecting approximately 3.2 million Americans [54] at a cost of over two billion dollars annually [30]. Treatment has been available, but suboptimal due to the low efficacy and severe side effects associated with traditional interferon (IFN) and ribavirin (RBV) combination therapy. People who inject drugs (PWID), the group most significantly impacted by HCV, are among those who have had difficulty with HCV treatment access in the past. Clinical contraindications to treatment medications, patient readiness, and provider willingness to treat have all been shown to be barriers to HCV treatment [4, 28, 48, 55]. The HCV treatment landscape is rapidly evolving, and interferon-based therapies are rapidly being replaced by all-oral treatments that have reported near 100% cure rates with fewer contraindications, lesser side effects and shorter treatment duration [17]. These medications may provide much-needed opportunities to improve access to HCV treatment for many populations previously excluded. The implementation of the Affordable Healthcare Act, coupled with improvements in HCV treatment, will likely increasingly place HCV treatment in the primary care setting, significantly elevating the need for nurses to be well-versed in HCV care and treatment. Many groups historically not considered for HCV treatment may be more likely to be successful in this new treatment paradigm. All nurses, particularly advanced practice nurses, should be well-poised to provide comprehensive, informed HCV care. This paper will examine what nurses need to know about HCV treatment regimens and considerations for HCV treatment candidacy in all populations, including PWID.

Background

HCV infection disproportionately affects PWID. Since screening for HCV infection in blood products was introduced in 1992, HCV is most efficiently transmitted though

equipment used to inject drugs, with 25% of PWID becoming infected within two years of initiation of injection [56], and 50-80% of PWID becoming infected within five years [57]. Unlike HIV transmission which has decreased significantly among PWID through increasing utilization of syringe exchange programs (SEPs), HCV incidence in this population remains high [58, 59]. HCV is particularly viremic and transmissible; although HIV is primarily transmitted through syringes used in the injecting process, HCV can be transmitted through syringes, cookers, tourniquets, water and alcohol wipes [60]. The United States expends upwards of $3 billion annually on HCV-associated illness and those costs are projected to rise substantially over the next twenty years [2].

To date, HCV prevention efforts have focused on reducing transmission risk via behavioral interventions [61]. Despite this, the burden of HCV remains high. There is currently no vaccine to protect against HCV [62]. Highly effective treatments for HCV infection may prove to be more efficient in the global fight against HCV than transmission interventions alone [61, 63]. 'Cure as prevention', an approach that works to decrease viral transmission though treatment, is plausible because HCV treatment is now highly effective, of finite duration and leads to a true cure [61]. Today, the vast majority of genotypes and degrees of disease progression can be treated, improving quality of life and decreasing all-cause mortality [30, 64]. Eradication of HCV infection may be possible, but a scaled, response is necessary, and PWID must be at the center of those getting treated. As nurses are the largest cadre of health care providers, it is essential that nurses are well trained in HCV identification and care.

Data Sources

This is a clinical application paper. Data is drawn from a review of literature on HCV screening and treatment as it pertains to PWID. Data for this manuscript was retrieved

performing a PubMed search of works from 2008-2014 using the terms 'hepatitis C virus' 'hepatitis C treatment' 'hepatitis C treatment and people who inject drugs' and 'hepatitis C and nurses'. Articles which addressed hepatitis C screening, treatment medications, people who inject drugs and nursing care were considered relevant to this work and evaluated for inclusion. The time period was chosen to reflect the most recent trends in HCV research. Special focus was given to articles published in 2013-2014, as most evidence related to the most effective treatments were published in these years. A nursing-specific electronic database, CINHAL was also checked but did not yield any additional articles.

HCV screening

In the Unites States, less than 50% of those infected with HCV are aware of their status [65]. Because PWID experience ongoing risk throughout their injection career, they require frequent screening for HCV infection [66].Complicating HCV identification efforts are spontaneous clearance and reinfection. Twenty- to twenty-five percent of people with HCV spontaneously clear the virus within six months [67, 68]. While the exact mechanisms are not well characterized, a variety of factors have been shown to be associated with clearance. They include female gender [68], the presence of the *interleuken (IL) 28B* CC (versus non-CC) genotype [69], and other host genetic factors [70-72]. Though almost one-quarter of all people with HCV demonstrate spontaneous clearance, reinfection is possible [73]. Some evidence suggests that previous spontaneous clearance predicts subsequent clearance [74, 75], however, many individuals who have spontaneously cleared their HCV infection do develop chronic infection with secondary infections.

Antibodies to HCV infection (anti-HCV) remain detectable in blood after spontaneous resolution, although they may wane over time [76] and in association with HIV infection or

immunocompromization [77]. In order to correctly identify HCV infection, patients must be tested for HCV RNA as well as anti-HCV [14]. Anti-HCV tests are relatively inexpensive and, with the recent introduction of point-of-care rapid tests, results can be available in twenty minutes. Despite clear algorithms, over 50% of people in the Unites States testing positive for HCV antibody do not get appropriate follow up testing to confirm infection status [78].

HCV treatment medications

Interferon and ribavirin combination treatment

Until recently, all HCV treatment was provided by a combination of interferon and ribavirin, which have many clinical contraindications and effectively cure HCV only 45-80% of the time, depending on many factors. Because some new treatment regimens still contain interferon and most still utilize ribavirin, it is important to understand these medications. Additionally, many patients, and clinicians, may hold preconceived notions about HCV treatment due to these medications. Education is necessary to differentiate historical issues from current ones. It will be important for all clinicians to understand these medications as much as newer regimens.

The majority of people taking interferon experience at least one side effect related to the medication [14], and as many as 15% must discontinue treatment due to the severity of these effects [79]. Common side effects related to IFN are fatigue, fever, chills, myalgias, arthralgias, backache, headache, anorexia, nausea, diarrhea, depression, impaired concentration, difficulty sleeping, weight loss, decreased libido, hair loss, and bone marrow suppression. Taken alone, ribavirin has no affect on HCV; however, when taken with IFN, triples the likelihood of achieving SVR. Approximately two-thirds of patients taking ribavirin develop anemia in

response to the medication [79], and in 15% of patients, this anemia is severe enough to stop treatment or dose-reduce [80].

Newer agents to fight HCV infection have recently been introduced. In 2013, simprevir entered the market for the treatment of genotype 1 [81], and the first all-oral, interferon-free regimen for genotypes 2 and 3 HCV infection, sofosbuvir (as a part of dual-therapy with ribavirin) also became available [82]. Sofosbuvir can also be used as a part of a triple combination therapy for genotype 1 infection. The introduction of these medications into the HCV treatment landscape has the potential to serve as 'game-changers'. Not only have these medications shown enhanced efficacy, demonstrating SVR in 85-89% of patients living with genotype 1, and up to 98% of patients with genotypes 2 and 3 HCV infection, but treatment duration is as short as twelve weeks [82, 83]. Adverse events have been minimal. These medications are recommended as 'first line' treatments in 2014 guidelines [84, 85]. These medications are also expected to be expensive , with a single treatment likely to exceed $100,000 dollars [86].

Multi-class combination drugs

In 2014 three multi-class combination drugs were submitted for regulatory approval that could potentially take HCV treatment to a once daily, all-oral regimen with minimal side effects and high rates of SVR [87-89]. These combinations, ABT-267/ABT-450, sofosbuvir/ledipasvir, and asunaprevir/daclatasivir, have been shown to be highly effective in the treatment of genotype 1 HCV infection, and are among the first medications for HCV treatment that do not rely on interferon or ribavirin. These highly effective, short regimens obviate many of the existing barriers to HCV treatment, including regimen toxicity, duration, and dosing complexity [4].

There is a high likelihood their availability will yet again change the HCV treatment landscape and push the barriers for treatment access.

Clinical contraindications

Historically, clinical contraindications and concerns about adverse events were among the most compelling reasons to deny or delay treatment [4, 90]. Interferon-based regimens have many contraindications, including hepatic decompensation, uncontrolled severe psychiatric disease, autoimmune disease, uncontrolled cardiac disease, uncontrolled diabetes, pregnancy, and non-liver solid organ transplantation. However, many of these contraindications can be managed and should be re-evaluated over time [13].

While many available regimens continue to rely on interferon to achieve high rates of SVR, for the most part, all oral regimens have far fewer absolute contraindications. Currently, no HCV treatment medications have been shown to be safe for use in pregnancy or in people whose partners intend to become pregnant. Drug-drug interactions may be present with many medications. It is important to have a clear understanding of any warnings and contraindications to ensure

Adverse events

As noted, adverse events related to IFN and RBV can be quite significant, and at least one is expected in most people undergoing HCV treatment using medication regimens that contain these drugs, and as many as 15% of people undergoing treatment using these medications must stop due to these events [79]. Teleprivir and boceprevir, are also associated with significant side effects that are compounded by IFN and RBV, most notably a rash, which occurs in approximately 16% of patients taking boceprivir and over 50% of patients on teleprivir [91]. The significant impact of side effects has been shown to reduce HCV treatment uptake [4,

25, 92], and it is important to help patients understand that the newest treatments, which are shorter in duration, and may not contain IFN, are associated with fewer and less severe adverse events. Simeprevir and sofosbuvir, and the non-IFN and non-RBV combination medications are not associated with neuropsychiatric effects, flu-like symptoms or rash. Fatigue, headache and nausea, however, are experienced in about 30% of patients using these medications [81, 82, 87-89].

Despite approximately one-third of patients taking even the newest, most effective HCV medications still experiencing side effects, it is possible to manage these effects. Counseling patients on what to expect before initiating treatment is important, and can help patients feel prepared as they begin medications [93]. Nausea can often be mitigated by counseling patients to eat small meals more frequently, or treated with antiemetics. Patients may also use over-the-counter antacids to effectively combat nausea. Over the counter medications may also help manage headaches, and naps, light exercise and good nutrition may help reduce fatigue. Treatment regimens that contain RBV still carry a risk of severe anemia. In some cases, use of erythropoietin may be necessary.

Patient-related barriers to treatment

Many other patient-related barriers still present challenges to HCV treatment provision, including illicit substance use, alcohol use, and mental illness. The evidence suggests that some of these barriers should not impact HCV treatment provision decisions, but others need management before and during treatment. This next section explores some of the prevalent patient-related barriers to HCV treatment.

Illicit substance use

Concurrent illicit drug use is a major concern for most providers of HCV treatment, and complicating treatment eligibility assessments is the possibility of HCV reinfection in this population. Since 2002, the National Institutes for Health released a Consensus Statement recommending the treatment of active drug users on a case-by-case basis [22], people who use drugs have undergone HCV treatment. Although reinfection is a primary concern, and while relateively few PWID have been treated, overall, evidence of reinfection following SVR is low [94, 95], and should not be a limiting factor in HCV treatment uptake. Despite this, HCV treatment can be extremely costly, so providers may be reluctant to treat PWID, however low the risk of reinfection. It is important to be aware that the evidence around SVR rates and reinfection demonstrate concurrent drug use should not necessarily be an exclusionary criterion to HCV treatment.

Some concurrent drug use may not interfere with HCV treatment outcomes and many patients may be willing to undergo substance use treatment as a part of their HCV treatment regimen. Most trials looking at HCV treatment outcomes among PWID have utilized methadone or suboxone as a part of the treatment regimen [44, 96, 97]. There is some evidence that suggests that for some PWID, the process of establishing candidacy for HCV treatment has a positive impact on a decreasing substance use, regardless of whether or not treatment is initiated [24]. Previous studies have shown that complete abstinence is not necessary for successful HCV treatment [9], but regular and daily drug use are associated with treatment drop-out, non-adherence and failure to achieve SVR [98]. This research was based on interferon-containing regimens which require that patients need to be about 80% adherent to IFN/RBV [99]. All oral regimens may need adherence rates above 90% for effectiveness [100], suggesting that the impact of substance use on adherence may be necessary to consider in order to achieve treatment

success in PWID. There is a significant body of research which demonstrates that patients who initiate opiate replacement therapy before HCV therapy have HCV treatment outcomes similar to non-injecting populations [44, 96, 97, 101-103].

There is currently no research that specifically investigates the impact of injection drug use on all-oral regimens, but some recent clinical trials for these new therapies did not summarily exclude PWID [31-33], although others did [104]. Following NIH and other governing bodies guidelines, clinicians should assess appropriateness for PWID to receive HCV treatment on a case-by-case basis [21, 22, 105, 106]. This is especially important as non-treatment and unsuccessful treatment are both predictors of morbidity and mortality among those living with HCV [30, 107].

Alcohol use

Alcohol use has been shown to impact the response to IFN therapy [108]. This is a complicated issue: alcohol use exacerbates liver disease and speeds rates of cirrhosis in people living with HCV infection, but also can impair medication adherence. Many PWID have co-morbid alcohol dependence [109-111]. People with a history of alcohol abuse are most likely to experience the severe sequelae of HCV such as cirrhosis, hepatocellular carcinoma or end-stage liver disease [67, 112]. Despite being at the highest risk for negative outcomes related to HCV infection, people who drink alcohol are frequently excluded from HCV treatment [113] although practice guidelines do not limit treatment to non-drinkers [22]. Research, however, suggests that there is little evidence to support this exclusionary criterion. A systematic review of predictors of HCV treatment outcomes found that the amount of alcohol consumed may be an important factor when assessing treatment candidacy [113]. Patients who drank less than 30 grams of alcohol daily had SVR rates comparable to non-drinkers, but heavier daily alcohol consumption (>70

grams/day) had an adverse impact on a patient's ability to achieve SVR, with treatment drop-out rates up to 44%. A retrospective case-control study of 69 HCV-infected heavy drinkers and 69 matched HCV-infected light drinkers found that although heavy drinkers (defined as >60 grams/day) were less likely to be considered candidates for HCV treatment, if treatment was initiated in this group, rates of SVR were similar to non-drinkers (25.8% vs 33.2%, p=0.58) [114]. Alcohol use needs to be monitored during HCV treatment, but should not necessarily be considered an exclusionary criterion.

Less is understood about the impact of alcohol on all-oral regimens. Many recent trials have excluded people who consume large amounts of alcohol. There are currently no known interactions between HCV treatment medications and alcohol [115, 116]. Similar to regular drug use, it is likely heavy consumption can impact adherence, thus SVR, and should be managed before initiating treatment.

Mental illness

Given the sometimes severe psychiatric effects related to IFN, uncontrolled mental illness has long been a barrier to HCV treatment. Neuropsychiatric effects and preexisting mental illness are among the most common reasons providers cite in their decision not to provide HCV treatment [13]. The significant depression associated with interferon can be dramatic, debilitating and even dangerous, and is classified as a major substance-induced mood disorder [117]. Anyone undergoing interferon-based HCV treatment is at risk regardless of medical history, affecting approximately 80% of all patients [118]. Those with a history of mental illness may especially be at risk [119], and there is some evidence that PWID have higher rates of suicidality during HCV treatment than non-PWID [120]. However, it has been shown that the depressive effects of IFN can be successfully challenged with the use of anti-depressants [120, 121].

Overall, studies suggest no difference in HCV outcome between those with prior mental illness and those without [121]. It is evident that even people with severe mental illness can be successfully treated for HCV infection [120, 122]. Many of the neuropsychiatric effects can be mitigated by use of antidepressants before and during HCV treatment. Preexisting mental illness or concerns about the possibility of mental illness during treatment are not just causes to summarily exclude anyone, including PWID, from receiving HCV treatment.

All-oral regimens have shown no significant neuropsychiatric effects. Uncontrolled mental illness is not an absolute contraindication to providing HCV treatment to anyone using these regimens. However, as adherence is important, it is essential that any patient undergoing HCV treatment can adhere to medications as prescribed.

Adherence

Adherence for interferon/ribavirin therapy needs to be at least 80% to achieve SVR. For newer regimens, adherence will need to reach at least 90% [100]. Issues such as ongoing drug use, alcohol consumption and mental illness have historically been major barriers to treatment, but in fact adherence may be the most important factor in achieving SVR. PWID are not necessarily non-adherent. The evidence demonstrating SVR outcomes among PWID nearly equivalent to those who do not report drug use shows that drug use cannot serve as a measurement of adherence. Further, the increasingly shorter duration of HCV treatment has the potential to improve adherence rates over time. While there are few studies of interventions for adherence in HCV treatment, cognitive behavioral interventions have been shown to be effective to enhance antiretroviral therapy in substance users in HIV treatment research [123, 124]. Adherence counseling must be an important facet of HCV treatment and care.

Willingness and perceived need

Even when providers are willing to treat patients for their HCV infection, many patients frequently elect not to pursue treatment [4, 125]. It is important for the clinician to effectively educate patients on recent improvements in HCV treatment, and the risks related to non-treatment. A German study of 7658 untreated patients with chronic HCV found that although 50% of patients with a history of drug use refused treatment, those with a history of use were more likely to want treatment than those without a history of drug use, yet were less likely to receive it [126]. In this study, physicians most often cited history of substance use as the primary reason not to treat. The most frequent reason cited by patients when choosing not to undergo treatment was belief that treatment was unnecessary. An American cross-sectional study of 216 young PWID found 81.5% expressed interest in receiving HCV treatment, but only 27.3% reported receiving follow up care from a health care provider after testing HCV positive [125]. 17% had ever been offered HCV treatment. No interest in treatment was associated with lack of regular health care, alcohol dependence and lower readiness to quit drug use scores on validated instruments. Being told about the risks of HCV-related sequelea by a medical provider significantly increased interest in HCV treatment. Another cross-sectional study of 597 PWID showed similar results [4]. Although 70% of participants were aware that HCV treatment was available, only 22% understood that treatment could cure HCV, and only 21% had discussed treatment with a medical provider. The most common reason participants cited for not wanting HCV treatment or for deferring it was fear of treatment or related side effects, followed by the belief that treatment was not needed. Although concerns about treatment-related adverse events are warranted, medical providers must be aware of the importance of patient education and the impact it has on treatment uptake.

Implications for nursing

Nurse-led programs have been especially effective for successful HCV treatment in PWID [127-129]. In addition to improved opportunities for patient education and communication, Advanced Practice Nurses may be particularly well-poised to manage the complex needs of PWID, with training in patient education and counseling as well as in medical management [130]. A prospective cohort study comparing effectiveness of HCV treatment provision through specialty care to a nurse-led program found better adherence to treatment and an increased proportion of patients achieving SVR in the nurse-led group compared to the Specialists [129]. An observational cohort study of an HCV treatment program provided to incarcerated patients in Australia showed enhance treatment uptake and successful treatment outcomes when management was provided by trained nurses [128]. A retrospective study examining the impact of directly observed therapy (DOT) on HCV treatment used nurse practitioners to treat patients and found outcomes comparable to treatment provided by specialists [127]. The data, however, may be skewed, as programs that incorporate nursing tend to be comprehensive, interdisciplinary and incorporate many specialty roles including mental health and social work as well. Although it is difficult to separate the effect of the utilization of the nurse from the effect of other attributes of these programs, the trends suggest that including nurses in HCV treatment programs is effective and contributes to better outcomes. This is especially notable as increasing the pool of providers is essential if HCV treatment uptake is to improve. Providing treatment to PWID may be especially complex, but research has demonstrated the effectiveness of including nurses in HCV treatment and management, with successful outcomes in PWID. This has been especially notable in primary care [11, 131]. HCV treatment will increasingly move to the purview of primary

care as treatment regimens simplify, and nurses will be an essential piece of success in this transition.

Summary discussion

Recent developments in HCV treatment have striking implications for reducing overall HCV prevalence, morbidity and mortality. However, many of the groups most at risk for HCV infection may not have access to these treatments, due to ongoing biases based on historical data and concurrent drug use. Although this area of research has not been developed, ongoing substance use does not mitigate treatment for other chronic illnesses such as asthma or diabetes [132]. The US Department of Health and Human Services wrote a set of guidelines for the management of substance users living with HIV in which providers are reminded of a 'duty to treat', especially the most marginalized patients, while balancing the principles of beneficence and nonmalficence [133]. HCV treatment providers must adhere to these same principles. Though HCV treatment non-response has been implicated in the development of cirrhosis [134], failure to attain SVR has been more often linked to intolerable side effects than substance use itself [98, 122]. Research shows significantly better health outcomes for people who have been successfully treated than those who have not, including a 75% reduction in hepatocellular carcinoma incidence [135], and an overall reduction in all-cause mortality [136].

Clear guidelines for which regimens should be used in specific populations are needed to provide a map for successful treatment [84]. Less clear is how to treat the lifestyle factors that may or may not have an impact on treatment outcomes. Historically many groups have been excluded from treatment, but the high public health impact of HCV infection, coupled with transformations in treatment point to the need for proactively addressing HCV infection in these groups. Models suggest that in addition to current prevention approaches, successful reductions

in HCV prevalence could be achieved through increased HCV treatment coverage [35]. Increased access to substance use and mental health programs are also needed to improve prevention, and treatment outcomes. Thus far there has been low uptake of HCV treatment among PWID for clinical and behavioral reasons, and due to clinician level of comfort. With the new generation of safe, effective oral medications, it will be important to educate and monitor how these medications are ordered, accepted and continued.

The side effects and poor outcomes related to length IFN/RBV combination therapy should no longer be of great concern in this era of HCV treatment. More significant concerns today are related to adherence, but the shorter duration of treatments, coupled with the higher tolerability of the drugs, should do much to overcome these barriers. The improvements in HCV treatment will not result in a significant reduction in HCV-related morbidity until the historical biases impacting treatment provision and patient uptake are also addressed. In order for these medications to reach their full potential, a strong understanding of current HCV therapies, and the management of patient-related factors impacting treatment eligibility and outcomes, is essential. Patient education is also important. The evidence demonstrates the importance of the nurse in creating a therapeutic relationship, improving patient-provider communication and improving adherence. Nurses are well-poised as critical members of the HCV treatment team to help improve HCV care for all populations.

Conclusion

Rapidly improving HCV treatment medications, healthcare reorganization through the ACA and the increasing burden of HCV disease all point to an expanding role for nurses in HCV care and treatment. Understanding which populations can be successfully treated, how treatment can be managed and under which conditions is essential in improving the lives of people living

with HCV. As IDU is the primary transmission factor of HCV infection, a thorough understanding of the unique challenges in treating PWID is also essential in overcoming the significant morbidity and mortality of HCV, and reducing the barriers to treatment historically faced by this population. Nurses can and should play an important role in improving access to HCV treatments and working with patients to facilitate positive outcomes.

References

Abbievie. (2014). Abbievie submits new drug application to U.S. FDA for its investigational, all-oral, interferfon-free therapy for the treatment of hepaititis C Retrieved 5/19/14, 2014, from http://abbvie.mediaroom.com/2014-04-22-AbbVie-Submits-New-Drug-Application-to-U-S-FDA-for-its-Investigational-All-Oral-Interferon-Free-Therapy-for-the-Treatment-of-Hepatitis-C

American Association for the Study of Liver Disease, & Infectious Diseases Society of America. (2014). Recommendations for testing, managing and treating hepatitis C Retrieved 5/20/14, 2014, from http://www.hcvguidelines.org/full-report-view

American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th ed., text rev.) doi:doi:10.1176/appi.books.9780890423349.

Anand, B. S., Currie, S., Dieperink, E., Bini, E. J., Shen, H., Ho, S. B., & Wright, T. (2006). Alcohol use and treatment of hepatitis C virus: results of a national multicenter study. *Gastroenterology, 130*(6), 1607-1616. doi: 10.1053/j.gastro.2006.02.023

Arasteh, K., Jarlais, D. C. D., & Perlis, T. E. (2008). Alcohol and HIV Sexual Risk Behaviors among Injection Drug Users. *Drug Alcohol Depend, 95*(1-2), 54-61. doi: 10.1016/j.drugalcdep.2007.12.008

Arora, S., Kalishman, S., Thornton, K., Dion, D., Murata, G., Deming, P., . . . Pak, W. (2010). Expanding Access to HCV Treatment - Extension for Community Healthcare Outcomes (ECHO) Project: Disruptive Innovation in Specialty Care. *Hepatology, 52*(3), 1124-1133. doi: 10.1002/hep.23802

Arora, S., Thornton, K., Murata, G., Deming, P., Kalishman, S., Dion, D., . . . Qualls, C. (2011). Outcomes of Hepatitis C Treatment by Primary Care Providers. *The New England journal of medicine, 364*(23). doi: 10.1056/NEJMoa1009370

Asher, A., Lum, P. J., & Page, K. (2012). Assessing candidacy for acute hepatitis C treatment among active young injection drug users: a case-series report. *J Assoc Nurses AIDS Care, 23*(1), 16-29. doi: 10.1016/j.jana.2011.01.006

Asselah, T., & Marcellin, P. (2013). Interferon free therapy with direct acting antivirals for HCV. *Liver international : official journal of the International Association for the Study of the Liver, 33 Suppl 1*, 93-104. doi: 10.1111/liv.12076

Bakti, S. L., & Selwyn, P. A. (2000). *Substance abuse treatment for persons with HIV/AIDS.* Rockville: Retrieved from http://radar.boisestate.edu/pdfs/TIP37.pdf.

Belfiori, B., Chiodera, A., Ciliegi, P., Tosti, A., Baldelli, F., Stagni, G., & Francisci, D. (2007). Treatment for hepatitis C virus in injection drug users on opioid replacement therapy: a prospective multicentre study. *Eur J Gastroenterol Hepatol, 19*(8), 731-732. doi: 10.1097/01.meg.0000280175.79379.04

Bryistol-Myers Squibb. (2014). Bristol-Myers Squibb submits NDAs for Daclatasvir and Asunaprevir to US FDA for the treatment of hepatitis C Retrieved 5/19/14, 2014, from http://news.bms.com/press-release/bristol-myers-squibb-submits-ndas-daclatasvir-and-asunaprevir-us-fda-treatment-hepatit

Carney, K., Dhalla, S., Aytaman, A., Tenner, C. T., & Francois, F. (2013). Association of tattooing and hepatitis C virus infection: a multicenter case-control study. *Hepatology, 57*(6), 2117-2123. doi: 10.1002/hep.26245

Centers for Disease Control and Prevention, C. (2002). Viral hepatitis and injection drug users Retrieved from http://www.cdc.gov/idu/hepatitis/viral_hep_drug_use.pdf

Charlebois, A., Lee, L., Cooper, E., Mason, K., & Powis, J. (2012). Factors associated with HCV antiviral treatment uptake among participants of a community-based HCV programme for marginalized patients. *J Viral Hepat, 19*(12), 836-842. doi: 10.1111/j.1365-2893.2012.01648.x

Cioe, P. A., Stein, M. D., Promrat, K., & Friedmann, P. D. (2013). A Comparison of Modified Directly Observed Therapy to Standard Care for Chronic Hepatitis C. *J Community Health*. doi: 10.1007/s10900-013-9663-3

Clark, R. E., Weir, S., Ouellette, R. A., Zhang, J., & Baxter, J. D. (2009). Beyond health plans: behavioral health disorders and quality of diabetes and asthma care for Medicaid beneficiaries. *Med Care, 47*(5), 545-552. doi: 10.1097/MLR.0b013e318190db45

Costentin, C. E., Trabut, J. B., Mallet, V., Darbeda, S., Thepot, V., Nalpas, B., . . . Pol, S. (2013). Management of Hepatitis C Virus Infection in Heavy Drinkers. *Alcohol Alcohol*. doi: 10.1093/alcalc/agt020

Cozen, M. L., Ryan, J. C., Shen, H., Lerrigo, R., Yee, R. M., Sheen, E., . . . Monto, A. (2013). Nonresponse to interferon-alpha based treatment for chronic hepatitis C infection is associated with increased hazard of cirrhosis. *PloS one, 8*(4), e61568. doi: 10.1371/journal.pone.0061568

Cribier, B., Rey, D., Schmitt, C., Lang, J. M., Kirn, A., & Stoll-Keller, F. (1995). High hepatitis C viraemia and impaired antibody response in patients coinfected with HIV. *AIDS, 9*(10), 1131-1136.

Daughters, S. B., Magidson, J. F., Schuster, R. M., & Safren, S. A. (2010). ACT HEALTHY: A Combined Cognitive-Behavioral Depression and Medication Adherence Treatment for HIV-Infected Substance Users. *Cogn Behav Pract, 17*(3), 309-321.

Department of Veterans Affairs. (2007). Managing side effects of hepatitis C treatment Retrieved from http://www.hepatitis.va.gov/pdf/treatment-side-effects.pdf

Department of Veterans Affairs. (2013). *Hepatitis C: Guidelines and best practices*. Washington DC: Retrieved from http://www.hepatitis.va.gov/provider/guidelines/.

Doerrbecker, J., Friesland, M., Ciesek, S., Erichsen, T. J., Mateu-Gelabert, P., Steinmann, J., . . . Steinmann, E. (2011). Inactivation and survival of hepatitis C virus on inanimate surfaces. *J Infect Dis, 204*(12), 1830-1838. doi: 10.1093/infdis/jir535

Edlin, B. R., Kresina, T. F., Raymond, D. B., Carden, M. R., Gourevitch, M. N., Rich, J. D., . . . Cargill, V. A. (2005). Overcoming barriers to prevention, care, and treatment of hepatitis C in illicit drug users. *Clin Infect Dis, 40 Suppl 5*, S276-285. doi: 10.1086/427441

El-Kamary, S. S., Jhaveri, R., & Shardell, M. D. (2011). All-cause, liver-related, and non-liver-related mortality among HCV-infected individuals in the general US population. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 53*(2), 150-157. doi: 10.1093/cid/cir306

El Khoury, A. C., Klimack, W. K., Wallace, C., & Razavi, H. (2012). Economic burden of hepatitis C-associated diseases in the United States. *J Viral Hepat, 19*(3), 153-160. doi: 10.1111/j.1365-2893.2011.01563.x

European Association for the Study of the Liver. (2011). EASL clinical practice guidelines: Management of hepatitis C virus infection. *J Hepatology, 55*, 245-264.

Fellay, J., Thompson, A. J., Ge, D., Gumbs, C. E., Urban, T. J., Shianna, K. V., . . . Goldstein, D. B. (2010). ITPA gene variants protect against anaemia in patients treated for chronic hepatitis C. *Nature, 464*(7287), 405-408. doi: 10.1038/nature08825

Gara, N., & Ghany, M. G. (2013). What the Infectious Disease Physician Needs to Know About Peginterferon and Ribavirin. *Clin Infect Dis*. doi: 10.1093/cid/cit074

Ghany, M. G., Strader, D. B., Thomas, D. L., & Seeff, L. B. (2009). Diagnosis, management, and treatment of hepatitis C: an update. [Practice Guideline]. *Hepatology, 49*(4), 1335-1374. doi: 10.1002/hep.22759

Gidding, H. F., Law, M. G., Amin, J., Macdonald, G. A., Sasadeusz, J. J., Jones, T. L., . . . Dore, G. J. (2011). Predictors of deferral of treatment for hepatitis C infection in Australian clinics. *Med J Aust, 194*(8), 398-402.

Gilead. (2013). Sovaldi prescribing information *Package insert*.

Gilead. (2014). Gilead announced U.S. FDA priority review for designation for ledipasvir/sofosbuvir fixed-dose combination tablet for chronic hepatitis C genotype 1 infection Retrieved 5/19/14, 2014, from http://www.gilead.com/news/press-releases/2014/4/gilead-announces-us-fda-priority-review-designation-for-ledipasvirsofosbuvir-fixeddose-combination-tablet-for-chronic-hepatitis-c-genotype-1-infection

Grady, B. P., Vanhommerig, J. W., Schinkel, J., Weegink, C. J., Bruisten, S. M., Lindenburg, C. E., & Prins, M. (2012). Low incidence of reinfection with the hepatitis C virus following treatment in active drug users in Amsterdam. *Eur J Gastroenterol Hepatol, 24*(11), 1302-1307. doi: 10.1097/MEG.0b013e32835702a8

Grebely, J., Conway, B., Raffa, J. D., Lai, C., Krajden, M., & Tyndall, M. W. (2006). Hepatitis C virus reinfection in injection drug users. *Hepatology, 44*(5), 1139-1145. doi: 10.1002/hep.21376

Grebely, J., Knight, E., Ngai, T., Genoway, K. A., Raffa, J. D., Storms, M., . . . Conway, B. (2010). Reinfection with hepatitis C virus following sustained virological response in injection drug users. *J Gastroenterol Hepatol, 25*(7), 1281-1284. doi: 10.1111/j.1440-1746.2010.06238.x

Grebely, J., Petoumenos, K., Matthews, G. V., Haber, P., Marks, P., Lloyd, A. R., . . . Hellard, M. (2010). Factors associated with uptake of treatment for recent hepatitis C virus infection in a predominantly injecting drug user cohort: The ATAHC Study. *Drug Alcohol Depend, 107*(2-3), 244-249. doi: 10.1016/j.drugalcdep.2009.09.015

Hagan, H., Latka, M. H., Campbell, J. V., Golub, E. T., Garfein, R. S., Thomas, D. A., . . . Strathdee, S. A. (2006). Eligibility for treatment of hepatitis C virus infection among young injection drug users in 3 US cities. *Clin Infect Dis, 42*(5), 669-672. doi: 10.1086/499951

Hagan, H., Pouget, E. R., Des Jarlais, D. C., & Lelutiu-Weinberger, C. (2008). Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. *Am J Epidemiol, 168*(10), 1099-1109. doi: 10.1093/aje/kwn237

Hagan, L. M., Wolpe, P. R., & Schinazi, R. F. (2013). Treatment as prevention and cure towards global eradication of hepatitis C virus. *Trends Microbiol, 21*(12), 625-633. doi: 10.1016/j.tim.2013.09.008

Halliday, J., Klenerman, P., & Barnes, E. (2011). Vaccination for hepatitis C virus: closing in on an evasive target. *Expert Rev Vaccines, 10*(5), 659-672. doi: 10.1586/erv.11.55

Harris, K. A., Jr., Arnsten, J. H., & Litwin, A. H. (2010). Successful integration of hepatitis C evaluation and treatment services with methadone maintenance. *J Addict Med, 4*(1), 20-26. doi: 10.1097/ADM.0b013e3181add3de

Hellard, M., Sacks-Davis, R., & Gold, J. (2009). Hepatitis C treatment for injection drug users: a review of the available evidence. *Clin Infect Dis, 49*(4), 561-573. doi: 10.1086/600304

Holmberg, S. D., Spradling, P. R., & Moorman, A. C. (2013). Hepatitis C in the United States. *The New England journal of medicine, 368*(20), 1857-1859. doi: 10.1056/NEJMp1303819

Janssen and Medivir AB. (2013). Olysio full prescribing information.

Kim, A. Y., Kuntzen, T., Timm, J., Nolan, B. E., Baca, M. A., Reyor, L. L., . . . Lauer, G. M. (2011). Spontaneous control of HCV is associated with expression of HLA-B 57 and preservation of targeted epitopes. *Gastroenterology, 140*(2), 686-696 e681. doi: 10.1053/j.gastro.2010.09.042

Kowdley, K. V., Lawitz, E., Crespo, I., Hassanein, T., Davis, M. N., DeMicco, M., . . . Jacobson, I. M. (2013). Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. *Lancet, 381*(9883), 2100-2107. doi: 10.1016/s0140-6736(13)60247-0

Lange, C. M., & Zeuzem, S. (2013). Perspectives and challenges of interferon-free therapy for chronic hepatitis C. [Review]. *Journal of hepatology, 58*(3), 583-592. doi: 10.1016/j.jhep.2012.10.019

Larrey, D., Salse, A., Ribard, D., Boutet, O., Hyrailles-Blanc, V., Niang, B., . . . Daures, J. P. (2011). Education by a nurse increases response of patients with chronic hepatitis C to therapy with peginterferon-alpha2a and ribavirin. *Clin Gastroenterol Hepatol, 9*(9), 781-785. doi: 10.1016/j.cgh.2011.05.022

Lauer, G. M. (2013). Immune responses to hepatitis C virus (HCV) infection and the prospects for an effective HCV vaccine or immunotherapies. *J Infect Dis, 207 Suppl 1*, S7-S12. doi: 10.1093/infdis/jis762

Lauer, G. M., Barnes, E., Lucas, M., Timm, J., Ouchi, K., Kim, A. Y., . . . Klenerman, P. (2004). High resolution analysis of cellular immune responses in resolved and persistent hepatitis C virus infection. *Gastroenterology, 127*(3), 924-936.

Lawitz, E. J. (2011). Diagnosis and management of telaprevir-associated rash. *Gastroenterol Hepatol (N Y), 7*(7), 469-471.

Lawitz, E. J., Rodriguez-Torres, M., Denning, J., Mathias, A., Mo, H., Gao, B., . . . Symonds, W. T. (2013). All-oral therapy with nucleotide inhibitors sofosbuvir and GS-0938 for 14 days in

treatment-naive genotype 1 hepatitis C (NUCLEAR). *J Viral Hepat, 20*(10), 699-707. doi: 10.1111/jvh.12091

Le Marchand, C., Evans, J., Page, K., Davidson, P. J., & Hahn, J. A. (2013). Hazardous alcohol consumption among young adult IDU and its association with high risk behaviors*. *Drug Alcohol Depend, 127*(0), 143-149. doi: 10.1016/j.drugalcdep.2012.06.024

Litwin, A. H., Harris, K. A., Jr., Nahvi, S., Zamor, P. J., Soloway, I. J., Tenore, P. L., . . . Arnsten, J. H. (2009). Successful treatment of chronic hepatitis C with pegylated interferon in combination with ribavirin in a methadone maintenance treatment program. *J Subst Abuse Treat, 37*(1), 32-40. doi: 10.1016/j.jsat.2008.09.009

Lloyd, A. R., Clegg, J., Lange, J., Stevenson, A., Post, J. J., Lloyd, D., . . . Monkley, D. (2013). Safety and Effectiveness of a Nurse-Led Outreach Program for Assessment and Treatment of Chronic Hepatitis C in the Custodial Setting. *Clin Infect Dis*. doi: 10.1093/cid/cis1202

Makuria, A. T., Raghuraman, S., Burbelo, P. D., Cantilena, C. C., Allison, R. D., Gibble, J., . . . Alter, H. J. (2012). The clinical relevance of persistent recombinant immunoblot assay-indeterminate reactions: insights into the natural history of hepatitis C virus infection and implications for donor counseling. *Transfusion, 52*(9), 1940-1948. doi: 10.1111/j.1537-2995.2011.03524.x

Martin, N. K., Vickerman, P., Foster, G. R., Hutchinson, S. J., Goldberg, D. J., & Hickman, M. (2011). Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. [Research Support, Non-U.S. Gov't]. *Journal of hepatology, 54*(6), 1137-1144. doi: 10.1016/j.jhep.2010.08.029

Martin, N. K., Vickerman, P., Grebely, J., Hellard, M., Hutchinson, S. J., Lima, V. D., . . . Hickman, M. (2013). HCV treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology*. doi: 10.1002/hep.26431

McGowan, C. E., Monis, A., Bacon, B. R., Mallolas, J., Goncales, F. L., Goulis, I., . . . Fried, M. W. (2013). A global view of hepatitis C: Physician knowledge, opinions, and perceived barriers to care. *Hepatology*. doi: 10.1002/hep.26246

McHutchison, J. G., Manns, M., Patel, K., Poynard, T., Lindsay, K. L., Trepo, C., . . . Albrecht, J. K. (2002). Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology, 123*(4), 1061-1069.

Mehta, S. H., Cox, A., Hoover, D. R., Wang, X. H., Mao, Q., Ray, S., . . . Thomas, D. L. (2002). Protection against persistence of hepatitis C. *Lancet, 359*(9316), 1478-1483. doi: 10.1016/s0140-6736(02)08435-0

Mehta, S. H., Genberg, B. L., Astemborski, J., Kavasery, R., Kirk, G. D., Vlahov, D., . . . Thomas, D. L. (2008). Limited uptake of hepatitis C treatment among injection drug users. *J Community Health, 33*(3), 126-133. doi: 10.1007/s10900-007-9083-3

Mistler, L. A., Brunette, M. F., Marsh, B. J., Vidaver, R. M., Luckoor, R., & Rosenberg, S. D. (2006). Hepatitis C treatment for people with severe mental illness. *Psychosomatics, 47*(2), 93-107. doi: 10.1176/appi.psy.47.2.93

Morgan, R. L., Baack, B., Smith, B. D., Yartel, A., Pitasi, M., & Falck-Ytter, Y. (2013). Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann Intern Med, 158*(5 Pt 1), 329-337. doi: 10.7326/0003-4819-158-5-201303050-00005

Myles, A., Mugford, G. J., Zhao, J., Krahn, M., & Wang, P. P. (2011). Physicians' attitudes and practice toward treating injection drug users with hepatitis C: results from a national specialist survey in Canada. *Can J Gastroenterol, 25*(3), 135-139.

National Institutes of Health, N. (2002). NIH Consensus Statement on Management of Hepatitis C: 2002. *NIH Consens State Sci Statements, 19*(3), 1-46.

Niederau, C., Huppe, D., Zehnter, E., Moller, B., Heyne, R., Christensen, S., . . . Mauss, S. (2012). Chronic hepatitis C: treat or wait? Medical decision making in clinical practice. *World J Gastroenterol, 18*(12), 1339-1347. doi: 10.3748/wjg.v18.i12.1339

Olson, M., & Jacobson, I. M. (2011). Role of the nurse practitioner in the management of patients with chronic hepatitis C. *J Am Acad Nurse Pract, 23*(8), 410-420. doi: 10.1111/j.1745-7599.2011.00603.x

Osburn, W. O., Fisher, B. E., Dowd, K. A., Urban, G., Liu, L., Ray, S. C., . . . Cox, A. L. (2010). Spontaneous control of primary hepatitis C virus infection and immunity against persistent reinfection. *Gastroenterology, 138*(1), 315-324. doi: 10.1053/j.gastro.2009.09.017

Page-Shafer, K., Hahn, J. A., & Lum, P. J. (2007). Preventing hepatitis C virus infection in injection drug users: risk reduction is not enough. *AIDS, 21*(14), 1967-1969. doi: 10.1097/QAD.0b013e3282ef7701

Page-Shafer, K., Pappalardo, B. L., Tobler, L. H., Phelps, B. H., Edlin, B. R., Moss, A. R., . . . Busch, M. P. (2008). Testing strategy to identify cases of acute hepatitis C virus (HCV) infection and to project HCV incidence rates. *J Clin Microbiol, 46*(2), 499-506. doi: 10.1128/jcm.01229-07

Page, K., Hahn, J. A., Evans, J., Shiboski, S., Lum, P., Delwart, E., . . . Busch, M. P. (2009). Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. *J Infect Dis, 200*(8), 1216-1226. doi: 10.1086/605947

Pockros, P. J., Jensen, D., Tsai, N., Taylor, R., Ramji, A., Cooper, C., . . . Thommes, J. (2013). JUMP-C: a randomized trial of mericitabine plus pegylated interferon alpha-2a/ribavirin for 24 weeks in

treatment-naive HCV genotype 1/4 patients. *Hepatology, 58*(2), 514-523. doi: 10.1002/hep.26275

Raison, C. L., Demetrashvili, M., Capuron, L., & Miller, A. H. (2005). Neuropsychiatric adverse effects of interferon-alpha: recognition and management. *CNS Drugs, 19*(2), 105-123.

Rein, D. B., Smith, B. D., Wittenborn, J. S., Lesesne, S. B., Wagner, L. D., Roblin, D. W., . . . Weinbaum, C. W. (2012). The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. *Ann Intern Med*(156), 263-270.

Rein, D. B., Wittenborn, J. S., Weinbaum, C. M., Sabin, M., Smith, B. D., & Lesesne, S. B. (2011). Forecasting the morbidity and mortality associated with prevalent cases of pre-cirrhotic chronic hepatitis C in the United States. *Dig Liver Dis, 43*(1), 66-72. doi: 10.1016/j.dld.2010.05.006

Rifai, M. A., Moles, J. K., & Short, D. D. (2006). Hepatitis C treatment eligibility and outcomes among patients with psychiatric illness. *Psychiatr Serv, 57*(4), 570-572. doi: 10.1176/appi.ps.57.4.570

Safren, S. A., O'Cleirigh, C. M., Bullis, J. R., Otto, M. W., Stein, M. D., & Pollack, M. H. (2012). Cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected injection drug users: a randomized controlled trial. *J Consult Clin Psychol, 80*(3), 404-415. doi: 10.1037/a0028208

Sander, P. M., Cole, S. R., Ostrow, D. G., Mehta, S. H., & Kirk, G. D. (2010). Determinants of alcohol consumption in HIV-uninfected injection drug users. *Drug Alcohol Depend, 111*(1-2), 173-176. doi: 10.1016/j.drugalcdep.2010.04.004

Schaefer, M., Hinzpeter, A., Mohmand, A., Janssen, G., Pich, M., Schwaiger, M., . . . Berg, T. (2007). Hepatitis C treatment in "difficult-to-treat" psychiatric patients with pegylated interferon-alpha and ribavirin: response and psychiatric side effects. *Hepatology, 46*(4), 991-998. doi: 10.1002/hep.21791

Schaefer, M., & Mauss, S. (2008). Hepatitis C treatment in patients with drug addiction: clinical management of interferon-alpha-associated psychiatric side effects. *Curr Drug Abuse Rev, 1*(2), 177-187.

Sherman, M., Shafran, S., Burak, K., Doucette, K., Wong, W., Girgrah, N., . . . Deschenes, M. (2007). Management of chronic hepatitis C: consensus guidelines. *Can J Gastroenterol, 21 Suppl C*, 25C-34C.

Stein, M. R., Soloway, I. J., Jefferson, K. S., Roose, R. J., Arnsten, J. H., & Litwin, A. H. (2012). Concurrent group treatment for hepatitis C: implementation and outcomes in a methadone maintenance treatment program. *J Subst Abuse Treat, 43*(4), 424-432. doi: 10.1016/j.jsat.2012.08.007

Strathdee, S. A., Latka, M., Campbell, J., O'Driscoll, P. T., Golub, E. T., Kapadia, F., . . . Hagan, H. (2005). Factors associated with interest in initiating treatment for hepatitis C Virus (HCV) infection among young HCV-infected injection drug users. *Clin Infect Dis, 40 Suppl 5*, S304-312. doi: 10.1086/427445

Sublette, V. A., Douglas, M. W., McCaffery, K., George, J., & Perry, K. N. (2013). Psychological, lifestyle and social predictors of hepatitis C treatment response: a systematic review. *Liver international : official journal of the International Association for the Study of the Liver*. doi: 10.1111/liv.12138

Sylvestre, D. L. (2005). Treating hepatitis C virus infection in active substance users. *Clin Infect Dis, 40 Suppl 5*, S321-324. doi: 10.1086/427447

Sylvestre, D. L., & Clements, B. J. (2007). Adherence to hepatitis C treatment in recovering heroin users maintained on methadone. *Eur J Gastroenterol Hepatol, 19*(9), 741-747. doi: 10.1097/MEG.0b013e3281bcb8d8

Thomas, D. L. (2013). Global control of hepatitis C: where challenge meets opportunity. *Nat Med, 19*(7), 850-858. doi: 10.1038/nm.3184

Thomas, D. L., Astemborski, J., Rai, R. M., Anania, F. A., Schaeffer, M., Galai, N., . . . Vlahov, D. (2000). The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA, 284*(4), 450-456.

Thomas, D. L., Thio, C. L., Martin, M. P., Qi, Y., Ge, D., O'Huigin, C., . . . Carrington, M. (2009). Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature, 461*(7265), 798-801. doi: 10.1038/nature08463

U.S. Food and Drug Administration. (2014a). Approval of Sovaldi (sofosvubir) tablets for the treatment of chronic hepatitis C Retrieved 5/19/14, 2014, from http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/ucm377920.htm

U.S. Food and Drug Administration. (2014b). Olysio (simeprevir) for the treatment of chronic hepatitis C in combination antiviral treatment Retrieved 5/19/14, 2014, from http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/ucm377234.htm

van der Meer, A. J., Veldt, B. J., Feld, J. J., Wedemeyer, H., Dufour, J. F., Lammert, F., . . . Janssen, H. L. (2012). Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA, 308*(24), 2584-2593. doi: 10.1001/jama.2012.144878

Vickerman, P., Grebely, J., Dore, G. J., Sacks-Davis, R., Page, K., Thomas, D. L., . . . Hellard, M. (2012). The more you look, the more you find: effects of hepatitis C virus testing interval on reinfection incidence and clearance and implications for future vaccine study design. *J Infect Dis, 205*(9), 1342-1350. doi: 10.1093/infdis/jis213

Vlahov, D., & Junge, B. (1998). The role of needle exchange programs in HIV prevention. *Public Health Rep, 113 Suppl 1*, 75-80.

Waizmann, M., & Ackermann, G. (2010). High rates of sustained virological response in hepatitis C virus-infected injection drug users receiving directly observed therapy with peginterferon alpha-2a (40KD) (PEGASYS) and once-daily ribavirin. *J Subst Abuse Treat, 38*(4), 338-345. doi: 10.1016/j.jsat.2010.02.002

Wedemeyer, H., Jensen, D., Herring, R., Jr., Ferenci, P., Ma, M. M., Zeuzem, S., . . . Thommes, J. (2013). PROPEL: a randomized trial of mericitabine plus peginterferon alpha-2a/ribavirin therapy in treatment-naive HCV genotype 1/4 patients. *Hepatology, 58*(2), 524-537. doi: 10.1002/hep.26274

Weiss, J. J. (2014). *Adherence in the age of HCV antiviral therapy*. Paper presented at the International Confernce on Viral Hepatitis, 2014, Fordham University, New York, New York. http://www.iapac.org/icvh/presentations/ICVH2014_Plenary9_Weiss.pdf

Wiley, T. E., McCarthy, M., Breidi, L., & Layden, T. J. (1998). Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology, 28*(3), 805-809. doi: 10.1002/hep.510280330

World Health Organization (2014). *Guidelines for the screening, care and treatment of persons living with hepatitis C infection.*

Hepatitis C treatment for people who inject drugs: Evaluation and management of substance use

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Summary of key points: Understanding a patient's relationship with drug use and their ability to adhere to hepatitis C treatment is more important than knowing that drug use occurs. Improvements are needed in the evaluation and management of drug use in hepatitis C treatment.

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Abstract: People who inject drugs (PWID) are at highest risk of HCV transmission. Treatment rates among PWID are extremely low, as they frequently lack medical care, and providers lack guidance and training. Although treatment guidelines do not exclude PWID from receiving HCV treatment, assumptions about the impact of drug use on adherence to HCV medications and reinfection likely reduce prescribing. However, evidence suggests that some concurrent drug use does not affect rates of sustained viral responses (SVR). Fully managing HCV treatment in this population is hampered by a limited guidance and training on how to evaluate or manage substance use. The purpose here is to review guidance on the evaluation and management of substance use from publicly available guidelines, and suggest recommendations on ways future guidelines can address substance use and guide providers to successful treatment outcomes among PWID.

People who inject drugs (PWID) are at high risk for HCV infection due to its efficient transmission via equipment used to inject drugs [56]. The NIH [36] and other updated practice guidelines [14, 37, 105, 106, 137, 138] recommend evaluation of PWID for HCV treatment, and research has demonstrated successful outcomes when treated [9]. In practice, however, PWID rarely receive treatment [4]. Barriers include provider bias, concerns about medication adherence and reinfection, and reluctance and lack of knowledge on the part of PWID and health care providers [4, 139, 140]. New medications recently approved for HCV treatment have significantly improved outcomes, shorter treatment duration, and fewer side effects [141]. This suggests the need to revisit the HCV treatment recommendations for PWID. This article reviews guidance on the evaluation and management of substance use from publicly available guidelines, reviews approaches used to manage substance use within the HCV treatment context, and suggests recommendations on ways future guidelines can address substance use and guide providers to successful treatment outcomes among PWID.

Background

Hepatitis C virus (HCV) is a source of increasing morbidity and mortality in the United States, affecting as many as 5.2 million Americans [34]. The public health impact of HCV can be greatly reduced with the recent introduction of highly effective antivirals [5]. All-oral medications can effectively cure HCV infection in the vast majority of patients [14], significantly reducing HCV-related morbidity [136]. These medications offer the possibility of HCV eradication [45, 142, 143]. However, low rates of HCV identification [144], co-morbidities [145, 146] and provider reluctance [7] all contribute to low rates of treatment, particularly among the group at highest risk of transmission, PWID.

Although guidelines issued by the American Association for the Study of Liver Disease (AASLD) and other authorities do not summarily exclude PWID from receiving HCV treatment [22, 84], they do not specify how to measure substance use or provide limits for what may be harmful and do not address management of use during treatment. Concerns about adherence, severe side effects related to interferon-based treatment, and reinfection impact provider's decisions about treating PWID [47, 48]. Sustained viral response (SVR) among PWID has been shown to near or equal that of non-drug using populations [9], but this is generally due to management of use before and during the treatment period. Some programs have explored the use of directly observed therapy (DOT) to improve HCV treatment outcomes for PWID. DOT protocols have been found effective, but not necessary [147]. Similar results have been found in RCTs in HIV patients on ART, suggesting DOT, which can be burdensome for providers and patients, is not necessary for adherence [148].

HCV treatment delivered concurrently with substance use treatment has been found to be effective [9]. Treatment programs particularly well-suited for PWID provide multiple services in a single location, including mental health support and primary care. Patients report satisfaction with co-location, and a high level of familiarity with and increased trust in the providers in these programs. Concurrent drug treatment, however, may provide other benefits. A retrospective observational study of twenty-one patients treated for HCV with interferon and ribavirin in a New York methadone clinic achieved SVR in 33% of patients [102]. Although 33% of patients reported substance use during treatment, only one patient had to stop HCV treatment when their substance use impacted their ability to adhere to the treatment. Most stopped due to complications from side effects. A cohort study initiated HCV treatment with interferon and ribavirin in 71 opiate users maintained on methadone for two months found 38% of patients

achieved SVR despite the short duration of drug use treatment prior to HCV treatment initiation and 60% reporting at least some illicit substance use during treatment [44]. Though evidence suggests that some concurrent drug use does not affect rates of SVR [44, 96],there is relatively little information about HCV treatment in substance users who are not undergoing some type of drug treatment program in conjunction with the HCV treatment.

It has been shown that people can benefit from antiviral treatment for HCV even if they use illicit drugs. Although this area of research has not been developed, ongoing substance use does not mitigate treatment for other chronic illnesses such as asthma or diabetes [132]. A 2010 study of 231 antiretroviral therapy (ART)-naïve HIV-positive PWID showed that use of methadone maintenance therapy is independently associated with more rapid uptake of ART and improved adherence [149]. HCV treatment non-response has been implicated in the development of cirrhosis [134], and research shows significantly better health outcomes for people who have been successfully treated than those who have not [136].

Despite research demonstrating successful treatment of PWID in many situations, and evidence that some concurrent drug use does not impact SVR [9, 150], it is important to acknowledge that substance use may complicate adherence and other factors that are necessary for SVR. While guidelines recommend treating PWID on a case-by-case basis, there is a lack of detail about what type and level of substance use may contraindicate antiviral treatment, and few precise recommendation on how to measure use [14, 22, 105, 106, 137, 138]. Treatment guidelines emphasize evaluation of substance use, but for the most part fail to specify how that evaluation should occur (Table 1) [14, 22, 105, 106, 137]. Research examining HCV treatment in PWID also frequently fails to describe how substance use is evaluated, compounding the difficulties determining when to treat [92, 102, 108, 151]. Widely available guidelines counsel

evaluating drug and alcohol use, but fail to provide guidance on how to perform such evaluations, and do not describe how to evaluate findings. There is no guidance on the implications of a positive toxicology test; screening for drug use may be misused in this context. Providers are left to subjectively interpret screening results and determine how they impact HCV treatment candidacy.

HCV Treatment

New agents to treat HCV infection are rapidly changing by eliminating the need for interferon and greatly improving the therapeutic response [83, 152]. Not only are these treatments highly efficacious, but treatment duration is shorter, and by eliminating interferon, adverse events are dramatically reduced. Recently approved medications have cut treatment time from 24-48 weeks with interferon-containing regimens to 8-24 weeks on all-oral medications [89]. Results from clinical trials are showing 95-100% SVR rates in people who are treatment naïve, null responders, previous partial responders, and even people with cirrhosis. However, these medications have a high price tag: costs for a 12-week course range from $83,320 (for AbbVie's paritaprevir, ritonavir, ombitasvir, plus dasabuvir) to $94,500 (Gilead's sofosbuvir plus ledipasvir) to $150,000 (Janssen's simeprevir plus Gilead's sofosbuvir) [86]. Those costs double for patients requiring a 24-week course. Some recent clinical trials for these new therapies have not summarily excluded PWID and other substance users [31-33], although others do [104]. Thus far there are no available data on the impact of substance use on these treatments.

Contraindications to all-oral regimens are not specific to drug users and are few, including administration to pregnant women and anyone with an allergy to an ingredient in the medications. However, PWID encounter substantial stigma in the healthcare setting. Concerns about ongoing substance use, adherence and reinfection impact providers' decision to treat or not.

The data on reinfection, though scant, suggest that the rate is low [150]. However, the high cost of these treatments may make providers and insurers reluctant to invest in a patient who they fear may become reinfected or fail to take the medications as prescribed.

Treatment eligibility

Leaving a decision to treat to the discretion of the provider may make a potentially life-saving treatment appear optional. It also may leave providers unsure of their ability to evaluate and manage substance use among other co-occurring disorders. As a consequence, they may decide to exclude all active PWID from treatment [13]. This may be in part due to a negative view of PWID in health care settings. There is a perception they cannot adhere to prescribed healthcare regimens [7]. This stigmatization impedes the provider-patient relationship and challenges communication around HCV and substance use [153, 154].

Assessing substance use

Providers may be reluctant to formally assess substance use, especially among those who may benefit most from such discussion [155]. They may not be well trained or experienced in asking sensitive questions about use and may have implicit biases [155]. Patients who are using may be hesitant to disclose behaviors or have impaired recall. Discussions may be difficult, time-limited and fraught with stigma and apprehension on the part of both patient and provider. Moreover, whether a patient uses drugs may not be as important as the frequency of their use and their ability to adhere to medication regimens and appointments. It may be that measuring other variables, such as adherence, would provide more valuable data in the evaluation process.

By talking with patients about their substance use providers can begin to understand the patient's relationship with their use and its impact on their life. However, verbally acknowledging use may not feel socially acceptable, so patients may not be truthful. The

accuracy of self-report depends on the rapport between the clinician and the patient, and the consequences, or perceived consequences, of disclosure. However, most research supports its use. Self-reported substance use is only somewhat less accurate than other methods such as urine testing [156].

There are a number of existing validated substance use screening tools, but many are too lengthy to use in the clinical setting [157]. The National Institute on Drug Abuse and the Substance Abuse and Mental Health Services Administration endorse several screening tests including the Drug Abuse Screening Test (DAST) and the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST). However, providers often do not utilize validated tools in the clinical setting [158]. When there is screening for substance use, the tendency is to rely on other measures to assess use, such as urine toxicology screening. These tests are used to detect metabolites indicative of recent use of alcohol, marijuana, methamphetamine, opiates, cocaine and benzodiazepines, among other drugs. They are easy to use, provide rapid results, and often have a higher sensitivity compared to other toxicology tests, such as serologic testing [159]. But although these screens can give information about recent use, they provide little comprehensive information about frequency, impact and duration of use, or, more importantly, on the patient's relationship with their drug use or the role it plays in their lives. Detection windows are generally limited to under seven days, and vary depending on a number of factors including drug class, use patterns, and physiologic factors [160]. Moreover, urine toxicology screening is intrusive and may feel demeaning, since it implies that patients' self-reports are not believed. Providers utilizing urine toxicology screens in the clinical setting may be more likely to withhold treatment for any evidence of drug use, regardless of the impact of the use.

Regardless of the method used to evaluate patients for substance use, the objectives must

be clear. While it is important for providers to have an understanding of what substances their patients are using, the extent of use, and patient's ongoing HCV risk, drug use should not negate HCV treatment. The NIH specifies that HCV therapy has been successful even when patients are not abstinent [22], but other guidelines promote abstinence while encouraging evaluation of active users [14, 106]. They fail to address the more nuanced reality: abstinence may be ideal, but not absolutely necessary.

Ethics of substance use screening in HCV treatment

There are many instances where substance use screening has been used not as a tool to improve patient care, but rather as a justification for withholding it. This has most notably been promulgated by insurance coverage policies, as demonstrated by Illinois Medicaid policy, and that of United Healthcare, which explicitly state that treatment be withheld for anyone with a recent history of substance use [161, 162]. The lack of explicit guidance from authoritative guidelines creates room for such discriminatory policies. The policies of screening for substance use as a criterion for withholding HCV treatment, however, violate basic ethical principles governing the practice of medicine. The US Department of Health and Human Services guidelines for the management of substance users living with HIV reminds providers of their 'duty to treat', especially the most marginalized patients, while balancing the principles of beneficence and nonmaleficence [133]. A positive substance use screening test should provide information to providers, and a point to begin a conversation with a patient, but should by no means rule out eligibility for antiviral treatment.

Managing substance use in HCV treatment

HCV treatment in drug treatment facilities

As noted, most research examining HCV treatment in PWID looks at the impact of locating HCV treatment within drug treatment institutions, but there are limitations; fewer than 11% of all drug users are in treatment [163] and most of these programs are targeted to opioid users. One advantage of providing HCV treatment in a methadone program may be that adherence is easily monitored. However, the data suggesting that DOT may be an unnecessary burden to both patients and providers [127, 164] points to a need to explore other interventions to promote adherence. Further, the placement of HCV treatment in substance use treatment programs may serve to propagate the notion that abstinence is necessary for HCV treatment.

Other substance use interventions

There appear to be no drug-drug interactions limiting the effectiveness of HCV treatment in an active drug user, or direct impact of substance use on HCV treatment outcomes. Rather, adherence, an important driver of SVR, is most impacted by substance use. Behavioral interventions can be effective in reducing drug use and increasing treatment adherence, at least for short periods [165, 166], but there is little research examining such interventions on HCV treatment outcomes [167]. Most guidelines recommend that any HCV treatment provided to someone with a history of substance use be done in coordination with addiction specialists [14, 22, 105, 138]. Though coordination may improve outcomes, it is not necessary for HCV treatment [44, 168]. Given the complexities of substance use, concurrent mental health issues and HCV treatment, coordinated care is beneficial.

Discussion

Despite injection drug use being the primary mode of transmission for HCV infection, methods for evaluating and managing substance use within the context of hepatitis C treatment are limited. Many guidelines endorse the treatment of 'active' users, but then limit treatment

candidacy to persons enrolled in drug treatment programs or those who have demonstrated abstinence for as long as six months [14, 105]. EASL guidelines acknowledge that recommendations are hampered by a lack of evidence, since the vast majority of HCV treatment research has explored treatment only in populations that have some period of abstinence. Future research should explore HCV treatment in substance using populations not abstinent or engaged in drug treatment. Further, as substance use in and of itself does not necessarily impede HCV treatment, it may be more appropriate to evaluate the impact of substance use, or the the ability to adhere to treatment regimens, better indicators of likelihood of achieving SVR [27, 43].

While not widely available in many parts of the US, syringe exchange programs (SEPs) have been largely underutilized as a setting for health interventions. PWID have been shown to access many resources at SEPs, including primary care when available [169]. SEPs can effectively reach people who use illicit drugs when they may otherwise not be engaged in programs. Future research directions should explore HCV treatment outcomes in substance users who are not abstinent or in a treatment program, but are otherwise engaged in programs such as SEPs. Tailoring the setting for HCV treatment to optimize uptake and outcomes might be necessary to improve population-level morbidity and mortality.

The lack of explicit language on how to evaluate and manage substance users potentially serves as an additional barrier to treatment for a population disproportionately affected by HCV. As morbidity in this population increases, providers are under increased public health pressure to respond, but may not have the necessary training and guidance to adequately do so. Left without clear direction of how to evaluate and manage substance use in HCV treatment, some providers will err on the side of caution and not provide treatment at all. Guidelines propagate this problem by emphasizing abstinence over adherence and largely failing to mention re-evaluation after

modification of behaviors. Newer guidelines should provide clear instructions on the evaluation and management of substance use, including parameters for use and measures for treatment adherence to support evaluations decisions. Guidelines should clarify that while abstinence is beneficial, it is not always necessary or attainable, and clearly state that the evidence shows that some drug use during treatment does not impact SVR. Without such clarity, providers are left to make subjective decisions not based in evidence. This has the potential to further marginalize PWID and increase the public health burden of HCV-related morbidity and mortality. Guidelines need to better impart evidence-based directives on HCV treatment for PWID. HCV eradication is not possible when guidelines fail to adequately address how to successfully treat the group at highest risk of transmission, PWID, and do not emphasize the risks of non-treatment.

Conclusion

A thorough assessment and evaluation of substance use can inform effective HCV treatment. Understanding the vulnerabilities of any patient is important, and assessing the impact substance use may have on treatment adherence is important. Current guidelines fail to adequately describe how to evaluate and manage substance use in HCV treatment, leaving providers to make conservative decisions out of concern for outcomes. Updated guidelines can mitigate this problem through a clear description of how to evaluate use, the role of adherence, and applying evidence-based research to support guidance. HCV-related morbidity and mortality among PWID can be reduced, but systematic change will require giving providers clear guidance on how to achieve this.

References

1. Hagan H, Pouget ER, Des Jarlais DC, Lelutiu-Weinberger C. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. Am J Epidemiol **2008** Nov 15;168(10):1099-109.
2. National Institute of Health (NIH). Management of Hepatitis C: 2002. National Institutes of Health Consensus Conference Statement. **2002**.
3. Ghany M, Strader D, Thomas D, Seeff L. Diagnosis, management, and treatment of hepatitis C: An update. Hepatology **2009**;49(4):39.
4. Robaeys G, Grebely J, Mauss S, et al. Recommendations for the management of hepatitis C virus infection among people who inject drugs. Clin Infect Dis **2013** Aug;57 Suppl 2:S129-37.
5. Yee HS, Chang MF, Pocha C, et al. Update on the management and treatment of hepatitis C virus infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. The American journal of gastroenterology **2012** May;107(5):669-89; quiz 90.
6. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of hepatitis C virus infection. J Hepatology **2011**;55:245-64.
7. Sherman M, Shafran S, Burak K, et al. Management of chronic hepatitis C: consensus guidelines. Can J Gastroenterol **2007** Jun;21 Suppl C:25C-34C.
8. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology **2009** Apr;49(4):1335-74.
9. Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clin Infect Dis **2009** Aug 15;49(4):561-73.

10. Mehta SH, Genberg BL, Astemborski J, et al. Limited uptake of hepatitis C treatment among injection drug users. J Community Health **2008** Jun;33(3):126-33.

11. Chen EY, North CS, Fatunde O, et al. Knowledge and attitudes about hepatitis C virus (HCV) infection and its treatment in HCV mono-infected and HCV/HIV co-infected adults. J Viral Hepat **2013** Oct;20(10):708-14.

12. Younossi ZM, Stepanova M, Afendy M, Lam BP, Mishra A. Knowledge about infection is the only predictor of treatment in patients with chronic hepatitis C. J Viral Hepat **2013** Aug;20(8):550-5.

13. Aghemo A, De Francesco R. New horizons in Hepatitis C antiviral therapy with direct-acting antivirals. Hepatology **2013** Mar 6.

14. Chak E, Talal AH, Sherman KE, Schiff ER, Saab S. Hepatitis C virus infection in USA: an estimate of true prevalence. Liver Int **2011** Sep;31(8):1090-101.

15. Chung RT, Baumert TF. Curing chronic hepatitis C--the arc of a medical triumph. N Engl J Med **2014** Apr 24;370(17):1576-8.

16. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA **2012** Dec 26;308(24):2584-93.

17. Burki T. Elimination on the agenda for hepatitis C. Lancet Infect Dis **2014** Jun;14(6):452-3.

18. Grebely J, Dore GJ. Can hepatitis C virus infection be eradicated in people who inject drugs? Antiviral Res **2014** Apr;104:62-72.

19. Edlin BR, Winkelstein ER. Can hepatitis C be eradicated in the United States? Antiviral Res **2014** Oct;110:79-93.

20. Smith BD, Morgan RL, Beckett GL, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. Morbidity and Mortality Weekly **2012**;61(RR04):1-18.

21. Batki SL, Canfield KM, Smyth E, Ploutz-Snyder R, Levine RA. Hepatitis C treatment eligibility and comorbid medical illness in methadone maintenance (MMT) and non-MMT patients: a case-control study. J Addict Dis **2010** Jul;29(3):359-69.

22. Bini EJ, Brau N, Currie S, et al. Prospective multicenter study of eligibility for antiviral therapy among 4,084 U.S. veterans with chronic hepatitis C virus infection. The American journal of gastroenterology **2005** Aug;100(8):1772-9.

23. Morrill JA, Shrestha M, Grant RW. Barriers to the treatment of hepatitis C. Patient, provider, and system factors. J Gen Intern Med **2005** Aug;20(8):754-8.

24. National Institutes of Health N. NIH Consensus Statement on Management of Hepatitis C: 2002. NIH Consens State Sci Statements **2002** Jun 10-12;19(3):1-46.

25. American Association for the Study of Liver Disease, Infectious Diseases Society of America. Recommendations for testing, managing and treating hepatitis C. Available at: http://www.hcvguidelines.org/full-report-view. Accessed 5/20/14.

26. Myles A, Mugford GJ, Zhao J, Krahn M, Wang PP. Physicians' attitudes and practice toward treating injection drug users with hepatitis C: results from a national specialist survey in Canada. Can J Gastroenterol **2011** Mar;25(3):135-9.

27. Shehab TM, Sonnad SS, Lok AS. Management of hepatitis C patients by primary care physicians in the USA: results of a national survey. Journal of viral hepatitis **2001** Sep;8(5):377-83.

28. Litwin AH, Soloway I, Gourevitch MN. Integrating services for injection drug users infected with hepatitis C virus with methadone maintenance treatment: challenges and opportunities. Clin Infect Dis **2005** Apr 15;40 Suppl 5:S339-45.

29. Lucas GM, Mullen BA, Galai N, et al. Directly Administered Antiretroviral Therapy for HIV-Infected Individuals in Opioid Treatment Programs: Results from a Randomized Clinical Trial. PloS one **2013**;8(7):e68286.

30. Harris KA, Jr., Arnsten JH, Litwin AH. Successful integration of hepatitis C evaluation and treatment services with methadone maintenance. J Addict Med **2010** Mar;4(1):20-6.

31. Sylvestre DL. Treating hepatitis C virus infection in active substance users. Clin Infect Dis **2005** Apr 15;40 Suppl 5:S321-4.

32. Stein MR, Soloway IJ, Jefferson KS, Roose RJ, Arnsten JH, Litwin AH. Concurrent group treatment for hepatitis C: implementation and outcomes in a methadone maintenance treatment program. J Subst Abuse Treat **2012** Dec;43(4):424-32.

33. Clark RE, Weir S, Ouellette RA, Zhang J, Baxter JD. Beyond health plans: behavioral health disorders and quality of diabetes and asthma care for Medicaid beneficiaries. Med Care **2009** May;47(5):545-52.

34. Uhlmann S, Milloy MJ, Kerr T, et al. Methadone maintenance therapy promotes initiation of antiretroviral therapy among injection drug users. Addiction **2010** May;105(5):907-13.

35. Cozen ML, Ryan JC, Shen H, et al. Nonresponse to interferon-alpha based treatment for chronic hepatitis C infection is associated with increased hazard of cirrhosis. PloS one **2013**;8(4):e61568.

36. Aspinall EJ, Corson S, Doyle JS, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2013** Aug;57 Suppl 2:S80-9.

37. Adeyemi OM, Jensen D, Attar B, et al. Hepatitis C treatment eligibility in an urban population with and without HIV coinfection. AIDS Patient Care STDS **2004** Apr;18(4):239-45.

38. Anand BS, Currie S, Dieperink E, et al. Alcohol use and treatment of hepatitis C virus: results of a national multicenter study. Gastroenterology **2006** May;130(6):1607-16.

39. Grebely J, Petoumenos K, Matthews GV, et al. Factors associated with uptake of treatment for recent hepatitis C virus infection in a predominantly injecting drug user cohort: The ATAHC Study. Drug Alcohol Depend **2010** Mar 1;107(2-3):244-9.

40. Zeng QL, Zhang JY, Zhang Z, Wang LF, Wang FS. Sofosbuvir and ABT-450: terminator of hepatitis C virus? World J Gastroenterol **2013** Jun 7;19(21):3199-206.

41. Asselah T, Marcellin P. Interferon free therapy with direct acting antivirals for HCV. Liver Int **2013** Feb;33 Suppl 1:93-104.

42. Gilead. Gilead announced U.S. FDA priority review for designation for ledipasvir/sofosbuvir fixed-dose combination tablet for chronic hepatitis C genotype 1 infection. Available at: http://www.gilead.com/news/press-releases/2014/4/gilead-announces-us-fda-priority-review-designation-for-ledipasvirsofosbuvir-fixeddose-combination-tablet-for-chronic-hepatitis-c-genotype-1-infection. Accessed 5/19/14.

43. Thomas DL. Global control of hepatitis C: where challenge meets opportunity. Nat Med **2013** Jul;19(7):850-8.

44. Pockros PJ, Jensen D, Tsai N, et al. JUMP-C: a randomized trial of mericitabine plus pegylated interferon alpha-2a/ribavirin for 24 weeks in treatment-naive HCV genotype 1/4 patients. Hepatology **2013** Aug;58(2):514-23.

45. Wedemeyer H, Jensen D, Herring R, Jr., et al. PROPEL: a randomized trial of mericitabine plus peginterferon alpha-2a/ribavirin therapy in treatment-naive HCV genotype 1/4 patients. Hepatology **2013** Aug;58(2):524-37.

46. Kowdley KV, Lawitz E, Crespo I, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. Lancet **2013** Jun 15;381(9883):2100-7.

47. Lawitz EJ, Rodriguez-Torres M, Denning J, et al. All-oral therapy with nucleotide inhibitors sofosbuvir and GS-0938 for 14 days in treatment-naive genotype 1 hepatitis C (NUCLEAR). J Viral Hepat **2013** Oct;20(10):699-707.

48. McGowan CE, Monis A, Bacon BR, et al. A global view of hepatitis C: Physician knowledge, opinions, and perceived barriers to care. Hepatology **2013** Jan 12.

49. Brener L, Horwitz R, von Hippel C, Bryant J, Treloar C. Discrimination by health care workers versus discrimination by others: Countervailing forces on HCV treatment intentions. Psychol Health Med **2015** Mar;20(2):148-53.

50. Treloar C, Newland J, Rance J, Hopwood M. Uptake and delivery of hepatitis C treatment in opiate substitution treatment: perceptions of clients and health professionals. J Viral Hepat **2010** Dec;17(12):839-44.

51. Ray MK, Beach MC, Nicolaidis C, Choi D, Saha S, Korthuis PT. Patient and provider comfort discussing substance use. Fam Med **2013** Feb;45(2):109-17.

52. Wilcox CE, Bogenschutz MP, Nakazawa M, Woody G. Concordance between self-report and urine drug screen data in adolescent opioid dependent clinical trial participants. Addict Behav **2013** Oct;38(10):2568-74.

53. McPherson TL, Hersch RK. Brief substance use screening instruments for primary care settings: a review. J Subst Abuse Treat **2000** Mar;18(2):193-202.

54. Pilowsky DJ, Wu LT. Screening for alcohol and drug use disorders among adults in primary care: a review. Subst Abuse Rehabil **2012** Apr;3(1):25-34.

55. Ellison ST, Brewer WE, Morgan SL. Comprehensive analysis of drugs of abuse in urine using disposable pipette extraction. J Anal Toxicol **2009** Sep;33(7):356-65.

56. LabCorp Inc. Drugs of Abuse Reference Guide. **2007**.

57. Silverman E. How Illinois allocates $84,000 drug for hepatitis C. Wall Street Journal. **2014** August 3, 2014.

58. United Healthcare. United Healthcare pharmacy Sovaldi prior authorization form. **2014**.

59. Bakti SL, Selwyn PA. Substance abuse treatment for persons with HIV/AIDS. In: Health and Human Services, ed. Rockville, **2000**.

60. Substance Abuse and Mental Health Services Administration; (SAMHSA). Results from the 2011 National Survey on Drug Use and Health: Summary of national findings, NSDUH Series H-44. In: Administration SAaMHS, ed. Rockville: HHS, **2012**.

61. Cioe PA, Stein MD, Promrat K, Friedmann PD. A Comparison of Modified Directly Observed Therapy to Standard Care for Chronic Hepatitis C. J Community Health **2013** Mar 8.

62. Grebely J, Raffa JD, Meagher C, et al. Directly observed therapy for the treatment of hepatitis C virus infection in current and former injection drug users. J Gastroenterol Hepatol **2007** Sep;22(9):1519-25.

63. Tucker T, Fry CL, Lintzeris N, et al. Randomized controlled trial of a brief behavioural intervention for reducing hepatitis C virus risk practices among injecting drug users. Addiction **2004** Sep;99(9):1157-66.

64. Garfein RS, Golub ET, Greenberg AE, et al. A peer-education intervention to reduce injection risk behaviors for HIV and hepatitis C virus infection in young injection drug users. AIDS **2007** Sep 12;21(14):1923-32.

65. Sun X, Patnode CD, Williams C, Senger CA, Kapka TJ, Whitlock EP. Interventions to Improve Patient Adherence to Hepatitis C Treatment: Comparative Effectiveness. Rockville MD, **2012**.

66. Sylvestre DL. Approaching treatment for hepatitis C virus infection in substance users. Clin Infect Dis **2005** Jul 1;41 Suppl 1:S79-82.

67. Mulhall BP, Younossi Z. Impact of adherence on the outcome of antiviral therapy for chronic hepatitis C. J Clin Gastroenterol **2005** Jan;39(1 Suppl):S23-7.

68. Gish RG, Afdhal NH, Dieterich DT, Reddy KR. Management of hepatitis C virus in special populations: patient and treatment considerations. Clin Gastroenterol Hepatol **2005** Apr;3(4):311-8.

69. Islam MM. Needle Syringe Program-Based Primary HealthCare Centers: Advantages and Disadvantages. J Prim Care Community Health **2010** Jul 1;1(2):100-3.

Clinician's view of hepatitis C virus treatment candidacy with direct-acting antiviral regimens for people who inject drugs

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Abstract

Background: Since the introduction of direct-acting antivirals, treatment for the hepatitis C virus (HCV) is curative in the vast majority of cases. However, high cost and concerns about adherence and reinfection may present continued barriers to treatment, particularly for people who inject drugs (PWID).

Methods: Clinicians attending the Liver Meeting® in 2014 who reported prescribing HCV treatment in the past three years were invited to complete a survey. Participants assessed their likelihood to provide HCV treatment given time since last injection drug use. Clinicians also assessed the importance of factors such as adherence, drug use and cost on their decision to provide treatment using interferon and all-oral medications.

Results: 108 clinicians completed the survey; 10% were willing to treat an active PWID (last injection within last 30 days) using interferon-containing regimens, and 15% with all-oral regimens. For each category of time since last injection (> 12 months, 6-12 months, 1-6 months and last 30 days), the odds of a clinician providing treatment increased with longer duration of abstinence (2.22 odds ratio for interferon-based treatments and 2.57 for all oral treatment). Providers were significantly more likely to treat persons with any length of abstinence over current users. There was no difference in willingness to treat patients with 6-12 months abstinence compared to those with more than 12 months abstinent. Concerns about reinfection and medication cost were cited as most important when determining treatment candidacy.

Conclusion: As HCV treatment evolves, there is an increasing need to address barriers to this curative treatment for PWID. Understanding changes in treatment candidacy assessments is essential to addressing HCV-related morbidity and mortality among PWID. This study provides insight into how clinicians view treatment candidacy in this era of direct-acting antivirals. The information can help clinicians provide supportive treatment environments and concurrent programs.

Key words: hepatitis C treatment, injection drug use, direct-acting antiviral hepatitis treatment candidacy, providers, hepatitis C cure

Introduction

Since the introduction of highly active direct-acting antiviral, all-oral medications, treatment for the hepatitis C virus (HCV) is curative in the vast majority of cases [61, 141]. Despite these medications, the high cost of HCV-related morbidity and mortality [33, 48, 170] and the public health burden of HCV infection [2, 23, 171], the decision to treat is often left to the discretion of individual health care clinicians, as well as by managed care groups and insurers [21, 84, 85, 105]. While the traditional standard of care for HCV treatment, combination therapy with interferon and ribavirin, has many contraindications, severe side effects and relatively low efficiency, new, all-oral medications have few contraindications, cure HCV infections over 90% of the time with a shorter treatment course and few side effects [104, 172, 173], suggesting the possibility of eradication of HCV infection through treatment [45, 86, 143]. However, high cost [174], and concerns about adherence [100] and reinfection [13, 95] may present continued barriers to treatment, particularly for the population with the highest prevalence, people who inject drugs (PWID). Until HCV treatment is accessible to PWID, eradication cannot be possible. This study sought to understand how the availability of all-oral HCV treatment medications impacts health care providers' decisions to treat PWID, and to identify barriers to treatment in this population.

Background

HCV infection is a major health concern affecting millions of Americans at a high public health cost. HCV-related mortality outpaces that of HIV [175], and PWID have the highest prevalence of HCV in the United States [54]. Notwithstanding, PWID have had limited HCV treatment access in the past [4]. Traditional interferon-based treatment for HCV was suboptimal

due to low efficacy and severe side effects, forcing clinicians and patients to carefully weigh the risks and benefits of treatment [4, 7, 125]. The many complications and absolute contraindications related to interferon-based HCV treatment limited the proportion of patients considered eligible, and even when eligible, many patients opted not to pursue treatment due to concerns about side effects and poor outcomes. Although all-oral medications have far fewer clinical contraindications, it is not clear that clinicians have adapted their eligibility criteria at the same rate as medications are evolving [18]. Further, these new treatments are costly - a single pill may cost as much as $1000, and total treatment costs can exceed $100,000, also impacting access [17, 20].

Despite some of the issues impacting HCV treatment, the high burden of the disease suggests that one way to successfully achieve reductions in HCV incidence and decrease the sequelae of long-term HCV infection is through increased HCV treatment coverage [35]. 'Cure as prevention' is theoretically plausible in HCV, where treatment is of finite duration and leads to a true cure [35, 63]. Many of the criteria that traditionally have excluded PWID from receiving HCV treatment may not apply to all-oral medication regimens, and in many cases, the barriers have not been shown to be justified in existing literature [9, 101, 176-178].

Given the many recent improvements in HCV treatment, it is necessary to improve our understanding of what influences a provider's determination of treatment eligibility. Understanding who may receive treatment and under what conditions can inform clinicians about changing eligibility criteria, and provide information about which ancillary support programs are needed to improve treatment uptake for those who need it most, and plan for the future burden of HCV-related morbidity and mortality for those who do not receive treatment. The purpose of this study was (1) to identify changes in the proportion of PWID considered eligible to receive HCV

treatment given the availability of new medication regimens; and (2) to identify barriers to treatment provision in this population.

Research Methods

This cross-sectional study enrolled clinicians attending the American Association for the Study of Liver Disease (AASLD) Conference (the Liver Meeting®) in 2014 who reported prescribing a HCV treatment medication in the past three years. The investigator and research assistants staffed a booth in the exhibition hall at the conference and invited conference attendees to participate in a 15 minute survey on an iPad at the booth, or by scanning a QR code, and responding on a mobile phone. The survey was developed in two focus groups held in the fall of 2014 with experienced HCV treatment clinicians who provided feedback and input on question validity and overall survey content. In focus groups, provider's main concerns about treating PWID were identified, revealing concerns such as adherence, drug use, housing status and clinical capacity on their decision to provide treatment using either interferon or all-oral medications. A five-point Likert scale (1=not important, 5=very important) was developed to assess the importance of these factors in the decision to treat with a given medication regimen, allowing an assessment of barriers to treatment, and changes in what is considered important given advances in HCV treatment. In addition to the focus groups, other feedback on the survey was solicited from non-clinician HCV experts.

Participants were asked to assess their likelihood to provide HCV treatment with interferon-based and all-oral medications given time since last injection drug use. Clinicians were also asked to assess the importance of patient and provider-related factors using the developed five-point scale. Data were captured using an electronic platform on tablets or via a

website and included four domains of knowledge and attitudes impacting HCV treatment candidacy: (1) Clinician demographics (specialty, training, sex, etc); (2) clinician perceptions (of patient's drug use, of patient's ability to be adherent etc); (3) clinical settings (public vs. private vs. government, multidisciplinary vs primary care), and; (4) clinician experience (with HCV treatment, with drug users, etc). The study protocol and procedures were reviewed and approved by the University of California San Francisco Institutional Review Board.

Data Analysis

Data was coded and imported into Stata/SE Version 13 [179] for analysis. Descriptive statistics were generated, including frequencies for categorical variables and medians, means and standard deviations for continuous variables. Differences between provider assessments for willingness to treat with interferon-containing regimens compared to all-oral regimens depending on time since last injection were calculated using piecewise ordinal logistic regression. Differences between clinicians' willingness to treat given interferon-based or all-oral treatments were tested with a Wald chi-square statistic for the two slopes for time since last injection. Willingness to provide treatment using either medication type predicted from recency of injection drug use was calculated using piecewise ordinal logistic regression. The Bonferroni procedure was used to compare differences between the time points. Bootstrapped t-tests with 1,000 repetitions examined the differences in the mean Likert scale rating between barriers to treatment given each the medication regimen [180-182]. The bootstrap was used to provide bias-corrected nonparametric confidence intervals for drawing statistical conclusions given the non-normal distributions.

Results

Of 108 participants, 64% were male, 46% practiced in North America, Europe or Australia, with the remainder who practiced in North Africa, South America or the Middle East; 70% reported working in a research hospital or veteran's administration hospital (Table 1). By specialty, 48% were in hepatology, 24% were in gasterenterology; 19% were in infectious diseases. All respondents reported prescribing HCV treatment medications beyond the traditional interferon combination regimen, with half (48-51%) reporting experience using boceprivir or telaprivir triple therapy, respectively; 33% had prescribed sofosbuvir or simeprivir. The median for the percent of total patient load in a panel who were HCV-infected patients was 30% interquartile range [IQR]: 11, 60.

Among their HCV infected patients, the percent of patients clinicians would describe as a PWID varied, with 80% reporting that fewer than 10% of their patient panel could be described as a current PWID, and the others reporting 10-50% were current PWIDs. No clinician described more than 50% of their HCV-infected patients as a current PWID. The vast majority of participants (94%) reported assessing substance use in their patients. A variety of methods were used: 68% reported directly asking their patients about their substance use, 32% reported assessing use based on the patient's behavior, and 41% reported utilizing toxicology screens in their practice.

When asked to consider treatment candidacy using an interferon-based regimen, half (55%) of participants reported being willing to treat a patient with a history of injecting drugs when last injection was more than twelve months ago, as long as the patient was completely abstinent. One quarter were willing to treat a patients whose last injection was more than twelve months ago, but still engaged in non-injection drug use, and 20% indicated that they would not

treat a patient with any history of injection drug use in the last six to twelve months. One-third reported willingness to treat HCV infection if the patient's last injection was within the past six months, and 10% reported willingness to treat a patient who was currently injecting (within the last 30 days). Compared to current (last 30 day) use, for each unit of time increase in the duration of abstinence since last injection drug use, the odds of a clinician reporting willingness to treat increased (3.92 OR [CI 1.99, 1.74] for 1-6 months vs. <30 days, 13.98 OR [CI 6.86. 28.48] for 6-12 months vs. <30 days, and 24.28 OR [CI 11.45, 51.49] for <12 months vs. <30 days). Post-hoc analyses showed significant differences between last use 6-12 months ago compared to 1-6 months ago, and when last use was more than twelve months ago compared to when last use was 1-6 months ago. There was no significant difference between clinician's willingness to treat if last use was 6-12 months ago or more than 12 months ago (Table 2).

When asked the same questions given all-oral regimens, half of respondents reported willingness to treat a patient whose last injection drug use was six or more months ago, and one-third reported willingness to treat a patient who had used one to six months ago. Fifteen percent of responders were willing to treat an active PWID with all-oral regimens. For each category of time since last injection (more than 12 months, six- to twelve months, one to six months and last 30 days), the odds of a provider providing treatment increased with longer duration of abstinence (2.2 higher odds for interferon-based treatments and 2.57 higher odds for all oral treatment). Compared to current use, for each unit of time increase in the duration of abstinence since last injection drug use, the odds of a clinician reporting willingness to treat increased (4.80 OR [CI 2.49, 9.26] for 1-6 months vs. <30 days, 17.10 OR [CI 8.31. 35.21] for 6-12 months vs. <30 days, and 17.46 OR [CI 8.44, 36.10] for <12 months vs <30 days). Post-hoc analyses showed significant differences between most of the time points, but showed no significant difference

between clinician's willingness to treat if last use was 6-12 months ago or more than 12 months ago.

Injection drug use and non-injection drug use were 'important or very important' considerations in determining treatment candidacy, regardless of treatment type (Table 3). For interferon-containing regimens, clinicians considered adherence, injection drug use and pre-existing mental illness as the most important when evaluating candidacy. For all-oral regimens, adherence, reinfection and medication cost were the most important considerations, with reinfection and cost seen as significantly more important when considering all-oral medications compared to interferon-containing medications. All oral regimens caused less concerns about side effects and contraindications when prescribing for PWID compared to interferon-containing regimens. Although considered very important, there were no differences between provider's assessment of the importance of injection drug use and non-injection drug use given either interferon-containing regimens and all-oral medications (Injection drug use mean 4.10 for interferon-based treatment and 3.91 for all-oral treatment (95% bias-corrected confidence interval (CI) -0.38, 0.6); non-injection drug use mean 3.73 vs 3.60 (95% bias-corrected CI -0.39, 0.74).

Discussion

The major finding of this study is the small increase in the overall proportion of clinicians who would prescribe an all oral HCV treatment regimen (15%) versus an interferon based regimen (10%). Despite the advantages of the newer treatment regimens (oral, fewer contraindications and toxicities, higher cure rates, shorter treatment duration), clinicians continue to have reservations about prescribing these newer regimens to PWID. Although current PWID

remain unlikely to receive treatment, abstinence for as little as six months was associated with a significant increase in willingness to treat using either medication, suggesting that engagement in substance use treatment may be an important facilitator to increased HCV treatment. It is notable there was no significant difference in willingness to treat when last injection drug use was 6-12 months or more than twelve months. Patients may feel more motivation to engage in substance use treatment if HCV treatment were available after a relatively short time of abstinence.

In this cross-sectional study, clinicians had fewer concerns about co-morbidities such as pre-existing mental illness when considering HCV treatment with all-oral regimens compared to interferon-based regimens, but were significantly more concerned with issues such as adherence, reinfection, and cost. While concerns about injection drug use and non-injection drug use were no different given medication regimen, interferon-based vs. all-oral, both were considered very important, suggesting they present ongoing barriers to HCV treatment provision. Concerns about reinfection given all-oral medications were significantly higher than when considering interferon regimens. This suggests that although there is a lower threshold for treatment with all-oral regimens in terms of clinical parameters, housing status and side effects, the barriers presented by ongoing injection drug use may in fact be higher than ever.

Clinicians were least likely to treat someone who has injected drugs in the past 30 days, and most likely to treat when a patient had not used any drugs in at least six months. Clinicians cited recency of injection drug use as an important barrier to treatment provision. However, evidence in studies using interferon-based treatment demonstrate that some concurrent drug use does not impact SVR (though daily use has been shown to decrease SVR) [9]. There is no published research on outcomes for PWID using all-oral medications. More research is needed to understand this, and to examine the impact of withholding treatment for this population.

Interventions involving a closer look at the impact of relatively short periods of engagement in substance use on HCV treatment uptake and outcome are also needed.

It has been suggested that all-oral treatment regimens be withheld from PWID due to the high cost of treatment and concerns about reinfection [183]. In this study, clinicians had increasing concerns about HCV reinfection after treatment when using an all-oral regimen compared to an interferon-based regimen. However, the evidence suggests that reinfection after treatment with interferon-containing regimens is rare, varying from 0.8 to 4.7 per 100 person-years [94, 95, 184]. While there is no evidence that reinfection would increase with new treatments, the highly selective nature of how patients with drug use history are chosen for research participation may have resulted in lower risk patients being treated [185]. Results from this study also suggest that physicians are more likely to treat lower risk patients, which would likely result in low reinfection rates. There is some evidence that receiving HCV treatment or being considered for treatment helps decrease injection drug use [24], lowering HCV risk. Further, although HCV related costs increase with disease progression, pointing to a prioritization of patients with advanced liver disease, benefits of HCV treatment include improved quality of life and lower all-cause mortality [23, 30, 136]. Treatment may also decrease transmission events [61, 186, 187]. Given the high cost of HCV and that injection drug use accounts for approximately 60% of all HCV transmissions in the United States [54], it is important to lower HCV prevalence in the population most at risk and reduce the overall disease burden among PWID.

Side effects, pre-existing mental illness and clinic capacity were significantly less important considerations for treatment with all-oral medications compared to interferon-containing regimens. All-oral regimens are associated with few side effects, and the significant

neuropsychiatric effects related to interferon have not been reported in all-oral medications. The decreased concern about these effects may be why clinic capacity is also less of a concern to clinicians. Patients undergoing HCV therapy using all-oral medications require less monitoring than do patients on interferon-containing regimens, freeing clinic staff and potentially limiting patient appointments. The decreased concern about clinic capacity may also allow more patients to receive treatment for their HCV infection.

Although we asked whether clinicians assessed their patients for substance use, we did not ask specifically about interventions or referrals to decrease use. Given the desire providers demonstrated to provide treatment to patient abstinent or engaged in a substance use program, more work needs to be done to engage high risk patients in substance use programs. Overall only a small percentage of substance users are engaged in drug treatment at any given time. Increased access to substance use treatment programs may support increased access to HCV treatment for PWID and allay provider concerns about the risk of reinfection.

This study has several limitations. This was a cross-sectional survey conducted at a large conference targeted at clinicians working in liver disease. It is unclear if non-specialists, such as primary care clinicians would make the same treatment decisions as these specialists. However, HCV treatment is most often provided by specialists, so it may be that this sample is representative of HCV treatment clinicians. The diversity of respondents may have had an effect on responses. It is possible that some countries may have specific policies about treatment for PWID, impacting how providers answered the questions. However, questions were designed to examine provider's attitudes towards treating PWID, not policies impacting their choices about who to treat.

The results show a significant disparity between what is known about outcomes when PWID are treated for their HCV infection and provider's willingness to provide treatment. Although reinfection is possible and costs of treatment are high, research demonstrates a low incidence of reinfection, and the social and financial burden of HCV-related morbidity should be weighed against treatment cost in this context. Despite the barriers to treatment current PWID continue to face, recent users may be able to access treatment. More work is needed to explore facilitators to treatment in this group. Although new treatments for HCV infection are promising, the population in highest need continues to face significant barriers and stigma preventing access to treatment.

Conclusion

Healthcare costs related to HCV infection are high, and the population most impacted by the disease, PWID, do not currently have substantial access to treatment. However, as HCV treatment becomes easier to provide and tolerate, it may be possible that PWID will have increased opportunities to receive curative treatment, ultimately lowering transmission events. Understanding how treatment candidacy may be evolving as HCV treatment evolves is essential to decreasing HCV-related morbidity and mortality among PWID. This study will provide important insight into how clinicians view treatment candidacy in an era of highly effective, all-oral antiviral treatment. The information gained from this study can help public health officials understand how to provide supportive treatment environments and concurrent programs. As HCV treatment improves, policies should address barriers to HCV treatment for PWID, including increased access to substance use programs, to improved HCV screening and the right to a curative treatment, paving the way for eradication of HCV.

References

1. Aghemo A, De Francesco R. New horizons in Hepatitis C antiviral therapy with direct-acting antivirals. Hepatology. 2013 Mar 6.

2. Hagan LM, Wolpe PR, Schinazi RF. Treatment as prevention and cure towards global eradication of hepatitis C virus. Trends Microbiol. 2013 Dec;21(12):625-33.

3. Kowdley KV, Lawitz E, Crespo I, Hassanein T, Davis MN, DeMicco M, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. Lancet. 2013 Jun 15;381(9883):2100-7.

4. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013 May 16;368(20):1878-87.

5. Myles A, Mugford GJ, Zhao J, Krahn M, Wang PP. Physicians' attitudes and practice toward treating injection drug users with hepatitis C: results from a national specialist survey in Canada. Can J Gastroenterol. 2011 Mar;25(3):135-9.

6. El Khoury AC, Klimack WK, Wallace C, Razavi H. Economic burden of hepatitis C-associated diseases in the United States. J Viral Hepat. 2012 Mar;19(3):153-60.

7. Menzin J, White-LA, Nichols C, Deniz B. The economic-burden of advanced liver disease among patients with Hepatitis C Virus: a large state Medicaid perspective. BMC Health Serv Res. 2012;12:459.

8. Razavi H, El Khoury A, Elbasha E, Estes C, Pasini K, Poynard T, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. Hepatology. 2012 Dec 22.

9. American Association for the Study of Liver Disease, Infectious Diseases Society of America. Recommendations for testing, managing and treating hepatitis C. 2014 [cited 2014 5/20/14]; Available from: http://www.hcvguidelines.org/full-report-view.

10. Department of Veterans Affairs. Hepatitis C: Guidelines and best practices. Washington DC2013.

11. World Health Organization Guidelines for the screening, care and treatment of persons living with hepatitis C infection. 2014.

12. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of hepatitis C virus infection. J Hepatology. 2011;55:245-64.

13. Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet. 2014 Jul 26.

14. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014 Jan 16;370(3):211-21.

15. Lawitz EJ, Rodriguez-Torres M, Denning J, Mathias A, Mo H, Gao B, et al. All-oral therapy with nucleotide inhibitors sofosbuvir and GS-0938 for 14 days in treatment-naive genotype 1 hepatitis C (NUCLEAR). J Viral Hepat. 2013 Oct;20(10):699-707.

16. Burki T. Elimination on the agenda for hepatitis C. Lancet Infect Dis. 2014 Jun;14(6):452-3.

17. Edlin BR, Winkelstein ER. Can hepatitis C be eradicated in the United States? Antiviral Res. 2014 Oct;110:79-93.

18. Thomas DL. Global control of hepatitis C: where challenge meets opportunity. Nat Med. 2013 Jul;19(7):850-8.

19. Hoofnagle JH, Sherker AH. Therapy for hepatitis C--the costs of success. N Engl J Med. 2014 Apr 17;370(16):1552-3.

20. Weiss JJ. Adherence in the age of HCV antiviral therapy. International Confernce on Viral Hepatitis, 2014; Fordham University, New York, New York2014.

21. Grebely J, Knight E, Ngai T, Genoway KA, Raffa JD, Storms M, et al. Reinfection with hepatitis C virus following sustained virological response in injection drug users. J Gastroenterol Hepatol. 2010 Jul;25(7):1281-4.

22. McGowan CE, Monis A, Bacon BR, Mallolas J, Goncales FL, Goulis I, et al. A global view of hepatitis C: Physician knowledge, opinions, and perceived barriers to care. Hepatology. 2013 Jan 12.

23. Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med. 2012;156(4):271-8.

24. Holmberg SD, Spradling PR, Moorman AC. Hepatitis C in the United States. N Engl J Med. 2013 May 16;368(20):1857-9.

25. Mehta SH, Genberg BL, Astemborski J, Kavasery R, Kirk GD, Vlahov D, et al. Limited uptake of hepatitis C treatment among injection drug users. J Community Health. 2008 Jun;33(3):126-33.

26. Morrill JA, Shrestha M, Grant RW. Barriers to the treatment of hepatitis C. Patient, provider, and system factors. J Gen Intern Med. 2005 Aug;20(8):754-8.

27. Strathdee SA, Latka M, Campbell J, O'Driscoll PT, Golub ET, Kapadia F, et al. Factors associated with interest in initiating treatment for hepatitis C Virus (HCV) infection among young HCV-infected injection drug users. Clin Infect Dis. 2005 Apr 15;40 Suppl 5:S304-12.

28. Maasoumy B, Port K, Markova AA, Serrano BC, Rogalska-Taranta M, Sollik L, et al. Eligibility and safety of triple therapy for hepatitis C: lessons learned from the first experience in a real world setting. PloS one. 2013;8(2):e55285.

29. Cohen J. Pharmaceuticals. Advocates protest the cost of a hepatitis C cure. Science. 2013 Dec 13;342(6164):1302-3.

30. Lange CM, Zeuzem S. Perspectives and challenges of interferon-free therapy for chronic hepatitis C. J Hepatol. [Review]. 2013 Mar;58(3):583-92.

31. Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. J Hepatol. [Research Support, Non-U.S. Gov't]. 2011 Jun;54(6):1137-44.

32. Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, et al. HCV treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. Hepatology. 2013 Mar 28.

33. Belfiori B, Chiodera A, Ciliegi P, Tosti A, Baldelli F, Stagni G, et al. Treatment for hepatitis C virus in injection drug users on opioid replacement therapy: a prospective multicentre study. Eur J Gastroenterol Hepatol. 2007 Aug;19(8):731-2.

34. Dalgard O. Follow-up studies of treatment for hepatitis C virus infection among injection drug users. Clin Infect Dis. 2005 Apr 15;40 Suppl 5:S336-8.

35. Grebely J, Genoway K, Khara M, Duncan F, Viljoen M, Elliott D, et al. Treatment uptake and outcomes among current and former injection drug users receiving directly observed therapy within a multidisciplinary group model for the treatment of hepatitis C virus infection. Int J Drug Policy. 2007 Oct;18(5):437-43.

36. Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clin Infect Dis. 2009 Aug 15;49(4):561-73.

37. Jafferbhoy H, Miller MH, Dunbar JK, Tait J, McLeod S, Dillon JF. Intravenous drug use: not a barrier to achieving a sustained virological response in HCV infection. J Viral Hepat. 2012 Feb;19(2):112-9.

38. StataCorp. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP; 2013.

39. Efron B. The bootstrap and modern statistics. Journal of the American Statistical Association. 2000;95(452):1293-6.

40. Erceg-Hurn DM, Mirosevich VM. Modern robust statistical methods: An easy way to maximize the accuracy and power of your research. American Psychologist. 2008;63(7):591-601.

41. Wehrens R, Putter H, Buydens LMC. The bootstrap: a tutorial. Chemometrics and Intelligent Laboratory Systems. 2000;54(1):35-52.

42. Ghany MG. The ongoing debate of who to treat for chronic hepatitis c virus. JAMA Internal Medicine. 2015;175(2):169-70.

43. Backmund M, Meyer K, Edlin BR. Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users. Clin Infect Dis. 2004 Nov 15;39(10):1540-3.

44. Grady BP, Vanhommerig JW, Schinkel J, Weegink CJ, Bruisten SM, Lindenburg CE, et al. Low incidence of reinfection with the hepatitis C virus following treatment in active drug users in Amsterdam. Eur J Gastroenterol Hepatol. 2012 Nov;24(11):1302-7.

45. Lazarus JV, Sperle I, Maticic M, Wiessing L. A systematic review of Hepatitis C virus treatment uptake among people who inject drugs in the European Region. BMC Infect Dis. 2014;14 Suppl 6:S16.

46. Asher A, Lum PJ, Page K. Assessing candidacy for acute hepatitis C treatment among active young injection drug users: a case-series report. J Assoc Nurses AIDS Care. 2012 Jan-Feb;23(1):16-29.

47. El-Kamary SS, Jhaveri R, Shardell MD. All-cause, liver-related, and non-liver-related mortality among HCV-infected individuals in the general US population. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2011 Jul 15;53(2):150-7.

48. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012 Dec 26;308(24):2584-93.

49. Hagan LM, Schinazi RF. Best strategies for global HCV eradication. Liver Int. 2013 Feb;33 Suppl 1:68-79.

50. Hellard M, Doyle JS, Sacks-Davis R, Thompson AJ, McBryde E. Eradication of hepatitis C infection: the importance of targeting people who inject drugs. Hepatology. 2014 Feb;59(2):366-9.

Table 1. Participant Demographics

Table 1. Participant demographics	N = 108 %
Region of Practice	
North America	30
Europe	15
Asia	9
Africa	18
Middle East	14
Australia	1
South America	13
Clinical Licensure	
Medical Doctor	76
Physician's Assistant	6
Nurse Practitioner	11
Doctor of Osteopathy	1
Other	6
Practice Environment	
Research Institution	44
Private hospital/HMO	8
Veteran's Administration	25
Private clinic	13
Community/Public Health Clinic	10
Specialty	
Hepatology	48
Gasteroenterology	24
Internal Medicine	4
Family/community	1
Infectious Disease	19
HIV	3
Other	1
Years in Practice	
0-5	42
6-10	16
11-15	17
16-20	25
Proportion of patients with HCV infection	
0-25%	57
26-50%	19
51-75%	8
76-100%	16
Gender	
Male	64

Female	36

Table 2. Pairwise Comparisons of Willingness to Treat Between Timepoints

Interferon-based regimen		
Last injection drug use	Contrast	95% confidence interval*
6-12 months vs. 1-6 months	1.27	0.42, 2.12**
>12 months vs 1-6 months	1.83	0.94, 2.71**
>12 months vs 6-12 months	0.55	-0.26, 1.36
All-oral regimen		
Last injection drug use	Contrast	95% confidence interval*
6-12 months vs. 1-6 months	1.27	0.46, 2.08**
>12 months vs 1-6 months	1.29	0.47, 2.11**
>12 months vs 6-12 months	0.21	-0.77, 0.81

*Bonferroni-corrected

**Significant difference between time points

Table 3. Importance of consideration for HCV treatment

	Interferon Mean[+]	All oral Mean[+]	Difference	95% confidence interval*
Adherence	4.53	4.64	0.11	-0.83, 0.32
Reinfection	3.74	4.03	0.29	0.46, 0.55**
Cost	3.69	4.44	0.75	0.47, 1.01**
Housing	3.84	3.81	-0.03	-0.25, 0.19
Neuropsychiatric effects	4.08	3.17	-0.92	-1.18, -0.64**
Other side effects	3.96	3.21	-0.75	-1.02, -0.52**
Pre-existing mental illness	4.19	3.11	-1.07	-1.38, -0.81**
Clinic capacity	3.51	3.24	-0.31	-0.05, -0.09**
Alcohol use	4.00	3.84	-0.16	-0.37, 0.41
Injection drug use	4.10	3.91	-0.17	-0.38, 0.6
Non-injection drug use	3.73	3.60	-0.13	-0.39, 0.74

[+] Mean of Likert scale rating (1=not important, 5=very important)

*Bias-corrected and accelerated bootstrapped confidence interval due to highly skewed non-normal distributions

**significant difference between treatment types

Conclusion

PWID are at highest risk of HCV transmission, yet are among the least likely to receive treatment. Since the introduction of highly active direct-acting antiviral medications, treatment for the HCV is curative in most cases [61, 141]. Despite their availability, and the high cost of HCV-related morbidity and mortality [33, 48, 170], and the public health burden of HCV infection [2, 23, 171], the decision to treat is often left to the discretion of individual health care clinicians, as well as by managed care groups and insurers [21, 84, 85, 105], and PWID are all too frequently omitted from considerations. Direct-acting antivirals offer the possibility of HCV eradication, but this cannot happen without a significant increase in the number of PWID who receive treatment. The shared purpose of the three papers that constitute this dissertation is to understand the barriers to HCV treatment for PWID, including provider knowledge, patient-related factors and stigma of PWID. Although the three papers vary in terms of methodology, they bring together the various factors influencing access to this curative treatment, identifying points of intervention in the continuum of HCV care and facilitators of treatment success for PWID.

Summary of the Research

The overarching purpose of the research in this dissertation was to examine factors affecting HCV treatment in people who inject drugs. Each paper represents a different area impacting treatment access and treatment success. Paper one, 'HCV Treatment in PWID: An update for nurses' describes HCV treatment, focusing on advances since the approval of direct-acting antiviral, and the evidence around patient related barriers impacting treatment access. As HCV therapies improve, treatment will increasingly be provided in the community setting, and nurses will increasingly become an essential part of HCV treatment and care. Evidence suggests

that nurses in HCV care improve outcomes, particularly for PWID. All nurses should be well-poised to provide this care. This paper reviews the evidence that PWID can be successfully treated, and discusses the positive impact nurses can have on HCV treatment outcomes.

This paper identified specific interventions that can improve treatment uptake for PWID. Interventions proven to be successful include increased comprehensive screening to increase HCV identification and improved education around treatment, including addressing misconceptions about treatment, and the impact of medication advances. Other interventions to improve treatment outcomes for PWID include concurrent treatment for substance use and mental health comorbidities, and community-based treatment. The evidence that PWID can be successfully treated for HCV infection was proven in the era of interferon-based treatment. The significant improvement in treatments provided by direct-acting antivirals, coupled with increasing HCV-related health expenditures, point to a need to improve the care provided to PWID, and raises questions about the ethics of current practices limiting or denying a curative treatment to a population most impacted by a disease.

As substance use is a major risk factor for HCV infection, and many people living with HCV have substance use disorders, the second paper that composes this dissertation examines how substance use is addressed in publically available guidelines on HCV treatment. Substance use is complicated, and many providers are uncomfortable addressing substance use in practice [155]. Despite the successful outcomes when PWID are treated for HCV infection, and the low rates of reinfection following treatment, many providers assume that active substance use necessarily negates HCV treatment [19, 48]. Existing guidelines state that providers should determine treatment candidacy for active substance users on a case-by-case basis, but fail to provide further guidance on how providers might determine candidacy. Guidelines emphasize

abstinence, further clouding the issue, and fail to address how to manage substance use during treatment. The lack of clarity around substance use in HCV treatment can lead providers to assume that abstinence is a necessity for treatment, though this is not supported by the evidence.

Substance use is often viewed as a surrogate marker for factors that do impact HCV treatment outcomes such as adherence to appointments or medications. Guidelines, however, fail to address these key issues in HCV treatment, though the evidence suggests that these are most important in achieving SVR. They rarely provide tools to measure these key criteria, and do not provide parameters for what level of use might be acceptable. Further, as addiction is marked by relapse, there is a failure to address how to manage use throughout treatment. This may leave providers feeling as if they are unable to handle PWID in HCV treatment, an elect to deny treatment altogether.

There are, however, interventions that can improve provider's abilities to determine who is a good HCV treatment candidate, and to support provider's confidence in treating PWID. Education is key to this, as provider's report little training in this complex issue [155, 188]. Guidelines can improve their discussion of the role of substance use, and emphasize the importance of adherence over use. Providers should be counseled that substance use is less of an issues than how substance use impacts an individual. While concurrent substance use treatment is beneficial to HCV treatment outcomes and the individual in question, it is not necessary for successful treatment. Other interventions such as nurse-led treatment, patient navigation and incentivization have all been shown to be successful in improving patient adherence to appointments and medications, and even to cut down on drug use. While it is important to address substance use in HCV treatment, giving providers a better understanding of why this

issue is important and how to navigate these issues with their patient can do much to improve treatment uptake for PWID.

The first two papers address some of the issues impacting HCV treatment access for PWID in terms of helping providers understand that treatment in this population has proven success, and how they can best manage treatment for PWID. Less is known about the impact of provider bias of PWID on access to treatment for PWID. The third paper in this dissertation describes a cross-sectional study of HCV treatment providers and asks if they are more likely to provide HCV treatment to PWID now that medications are safer and more efficacious than ever before. The survey also collected information to better understand what are barriers to treatment in this age of direct-acting antivirals. This information is essential to best facilitate improved treatment uptake.

The study found that providers are more willing to treat an active PWID (last injection within last 30 days) using direct-acting medications than interferon-containing regimen, and the odds of a provider providing treatment increased with longer duration of abstinence. Overall, providers were only about five percent more likely to treat an active PWID using all-oral medications than they were with an interferon-based regimen. However, providers were as likely to be willing to provide treatment to someone who had been abstinent for six to twelve months as they were to someone who had been abstinence for more than one year. Concerns about adherence, injection drug use and cost of medications were cited as the most important considerations when determining treatment candidacy and continue to be significant barriers. Despite the availability of safe and highly effective medications, providers are likely to continue to withhold treatment to PWID.

Understanding how treatment candidacy may be evolving as HCV treatment evolves is essential to decreasing HCV-related morbidity and mortality among PWID. Until HCV treatment is accessible to PWID, eradication cannot be possible. This study provides important insight into how clinicians view treatment candidacy in an era of direct-acting, all-oral antiviral treatment. The information gained can help public health officials understand how to provide supportive treatment environments and concurrent programs.

Implications

The three papers focus on the evidence that PWID have been and can be successfully treated for their HCV infection, but significant barriers continue to exist to treatment access for this population at many levels. Research has focused on PWID engaged in drug treatment programs, and providers are given few tools to work with people who are not already engaged in these types of services. Treatment guidelines emphasize abstinence for more than twelve months, though there is no evidence to support this, and providers appear willing to treat patients earlier than this. However, HCV treatment guidelines and engagement in substance use treatment programs are not the only existing barrier to HCV treatment today. The high cost of direct-acting antivirals further impedes their use in this population. The fear of reinfection, though in fact unfounded, can be prohibitive to treatment access, and there may be a lack of understanding about how frequently this actually occurs.

All-oral regimens offer the possibility of HCV eradication, but more needs to be done if the population most at risk for transmission can receive treatment. A 'cure as prevention' approach necessitates a significant shift in provider's perceptions about the ability of PWID to complete what has become a relatively simple medication regimen. Access to substance treatment programs needs to be improved, and more work needs to be done to ensure that

providers understand the role that HCV treatment can have on the overall improvement in PWID's lives, including possibly decreasing drug use [24], and improving the overall morbidity of the individual [30]. Currently, there is no published research specifically looking at outcomes of HCV treatment using all-oral regimens in PWID. Research has not examined a dose-based relationship between substance use and treatment outcomes, nor has there been enough research on effective adherence interventions for PWID undergoing treatment. This information will help identify areas that need to be addressed in order to improve treatment uptake in PWID. Given the many recent improvements in HCV treatment, it is necessary to improve understanding of treatment eligibility in this new paradigm. Understanding who may receive treatment and under what conditions can inform providers about changing eligibility criteria, help public health officials provide ancillary support programs to improve treatment uptake for those who need it most, and plan for the future burden of HCV-related morbidity and mortality for those who do not receive treatment.

Although huge advances have been made in HCV treatment medications, little has changed in regards to treatment access for PWID. Barriers such as ongoing injection drug use, and other substance use continue to impact provider's decision to treat PWID as they did when only interferon-containing regimens were available, and new barriers such as cost and increasing concerns about medication adherence have also emerged with the availability of direct-acting antivirals. Providers need to understand the positive impact HCV treatment has on many outcomes for PWID including improved all-cause mortality and an increased engagement in substance use programs. Future research should examine outcomes when PWID are treated with direct-acting antivirals, reinfection rates, and other outcomes such as all-cause mortality and substance use. Future research should also examine effective interventions to improve adherence

and decrease the risk of reinfection. While it is evident that PWID would benefit substantially from HCV treatment, more needs to be done to demonstrate that the public health cost of treatment is far outweighed by these benefits.

Implications for nursing

The evidence demonstrates that nurses play an important role when HCV treatment is provided. Nurses have been shown to facilitate communication around treatment [51, 189], and improve adherence and SVR [128-130]. An increase in HCV treatment first requires improved HCV screening. Nurses are among the first contact patients may have with a health care setting, and are in an ideal position to identify who should be screened for HCV infection, completeness of screening, and provide associated counseling. Nurses can help educate patient about the availability of curative treatment, dispel myths and misconceptions about treatment, and identify treatment candidates. Once treatment is initiated, nurses can facilitate adherence to appointments and medications, educate patients on the risks of reinfection, and provide referrals for treatment of comorbidities, including ongoing substance use. As treatment regimens improve, treatment can increasingly move from specialty care into the primary care sector. Nurses are in an ideal position to facilitate this transition, and to facilitate an improvement in treatment provision for PWID.

Conclusion

Injection drug use is a primary mode of HCV transmission, and PWID are disproportionately impacted by the virus. Direct-acting antivirals make HCV eradication plausible, but significant barriers must be addressed before this can be a reality. More research needs to be done to better understand treatment outcomes for PWID using direct-acting antivirals, and research into improved adherence and reinfection prevention interventions are

necessary. The significant HCV-related morbidity and mortality in the United States and the growing rates of HCV transmission among PWID suggests that increased treatment rates may be the solution to curbing the negative sequelea related to HCV infection. PWID should have increased access to this curative treatment, however, much needs to be done to address existing barriers if HCV eradication is to move from plausible to possible.

References

1. Razavi, H., et al., *Chronic hepatitis C virus (HCV) disease burden and cost in the United States.* Hepatology, 2013. **57**(6): p. 2164-70.
2. El Khoury, A.C., et al., *Economic burden of hepatitis C-associated diseases in the United States.* J Viral Hepat, 2012. **19**(3): p. 153-60.
3. Centers for Disease Control and Prevention, C., ;, *Viral hepatitis surveillance, United States 2011;*, V.H. Division of Viral Hepatitis; National Center for HIV/AIDS, STD, & TB Prevention,;, Editor 2011.
4. Mehta, S.H., et al., *Limited uptake of hepatitis C treatment among injection drug users.* J Community Health, 2008. **33**(3): p. 126-33.
5. Chung, R.T. and T.F. Baumert, *Curing chronic hepatitis C--the arc of a medical triumph.* The New England journal of medicine, 2014. **370**(17): p. 1576-8.
6. Harris, M. and T. Rhodes, *Hepatitis C treatment access and uptake for people who inject drugs: a review mapping the role of social factors.* Harm Reduct J, 2013. **10**: p. 7.
7. Morrill, J.A., M. Shrestha, and R.W. Grant, *Barriers to the treatment of hepatitis C. Patient, provider, and system factors.* J Gen Intern Med, 2005. **20**(8): p. 754-8.
8. Westergaard, R.P., et al., *Provider and clinic-level correlates of deferring antiretroviral therapy for people who inject drugs: a survey of North American HIV providers.* J Int AIDS Soc, 2012. **15**(1): p. 10.
9. Hellard, M., R. Sacks-Davis, and J. Gold, *Hepatitis C treatment for injection drug users: a review of the available evidence.* Clin Infect Dis, 2009. **49**(4): p. 561-73.
10. Ng, V. and S. Saab, *Effects of a sustained virologic response on outcomes of patients with chronic hepatitis C.* Clin Gastroenterol Hepatol, 2011. **9**(11): p. 923-30.
11. Arora, S., et al., *Expanding Access to HCV Treatment - Extension for Community Healthcare Outcomes (ECHO) Project: Disruptive Innovation in Specialty Care.* Hepatology, 2010. **52**(3): p. 1124-33.
12. McGinn, T.G., et al., *Treating chronic hepatitis C in the primary care setting.* Semin Liver Dis, 2005. **25**(1): p. 65-71.
13. McGowan, C.E., et al., *A global view of hepatitis C: Physician knowledge, opinions, and perceived barriers to care.* Hepatology, 2013.
14. Ghany, M.G., et al., *Diagnosis, management, and treatment of hepatitis C: an update.* Hepatology, 2009. **49**(4): p. 1335-74.
15. Dabbouseh, N.M. and D.M. Jensen, *Future therapies for chronic hepatitis C.* Nat Rev Gastroenterol Hepatol, 2013.
16. Doyle, J.S., et al., *Current and emerging antiviral treatments for hepatitis C infection.* British journal of clinical pharmacology, 2012.
17. Lange, C.M. and S. Zeuzem, *Perspectives and challenges of interferon-free therapy for chronic hepatitis C.* Journal of hepatology, 2013. **58**(3): p. 583-92.
18. Maasoumy, B., et al., *Eligibility and safety of triple therapy for hepatitis C: lessons learned from the first experience in a real world setting.* PloS one, 2013. **8**(2): p. e55285.
19. Thompson, V.V., et al., *Provider assessment of eligibility for hepatitis C treatment in HIV-infected homeless and marginally housed persons.* AIDS, 2005. **19 Suppl 3**: p. S208-14.

20. Cohen, J., *Pharmaceuticals. Advocates protest the cost of a hepatitis C cure.* Science, 2013. **342**(6164): p. 1302-3.
21. Department of Veterans Affairs, *Hepatitis C: Guidelines and best practices*, 2013: Washington DC.
22. National Institutes of Health, N., *NIH Consensus Statement on Management of Hepatitis C: 2002.* NIH Consens State Sci Statements, 2002. **19**(3): p. 1-46.
23. Menzin, J., et al., *The economic burden of advanced liver disease among patients with Hepatitis C Virus: a large state Medicaid perspective.* BMC Health Serv Res, 2012. **12**: p. 459.
24. Asher, A., P.J. Lum, and K. Page, *Assessing candidacy for acute hepatitis C treatment among active young injection drug users: a case-series report.* J Assoc Nurses AIDS Care, 2012. **23**(1): p. 16-29.
25. Charlebois, A., et al., *Factors associated with HCV antiviral treatment uptake among participants of a community-based HCV programme for marginalized patients.* J Viral Hepat, 2012. **19**(12): p. 836-42.
26. Edlin, B.R., *Prevention and treatment of hepatitis C in injection drug users.* Hepatology, 2002. **36**(5 Suppl 1): p. S210-9.
27. Gish, R.G., et al., *Management of hepatitis C virus in special populations: patient and treatment considerations.* Clin Gastroenterol Hepatol, 2005. **3**(4): p. 311-8.
28. Hagan, H., et al., *Eligibility for treatment of hepatitis C virus infection among young injection drug users in 3 US cities.* Clin Infect Dis, 2006. **42**(5): p. 669-72.
29. Mehta, S.H., et al., *A framework for understanding factors that affect access and utilization of treatment for hepatitis C virus infection among HCV-mono-infected and HIV/HCV-co-infected injection drug users.* AIDS, 2005. **19 Suppl 3**: p. S179-89.
30. El-Kamary, S.S., R. Jhaveri, and M.D. Shardell, *All-cause, liver-related, and non-liver-related mortality among HCV-infected individuals in the general US population.* Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 2011. **53**(2): p. 150-7.
31. Pockros, P.J., et al., *JUMP-C: a randomized trial of mericitabine plus pegylated interferon alpha-2a/ribavirin for 24 weeks in treatment-naive HCV genotype 1/4 patients.* Hepatology, 2013. **58**(2): p. 514-23.
32. Wedemeyer, H., et al., *PROPEL: a randomized trial of mericitabine plus peginterferon alpha-2a/ribavirin therapy in treatment-naive HCV genotype 1/4 patients.* Hepatology, 2013. **58**(2): p. 524-37.
33. Kowdley, K.V., et al., *Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial.* Lancet, 2013. **381**(9883): p. 2100-7.
34. Chak, E., et al., *Hepatitis C virus infection in USA: an estimate of true prevalence.* Liver international : official journal of the International Association for the Study of the Liver, 2011. **31**(8): p. 1090-101.
35. Martin, N.K., et al., *Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility.* Journal of hepatology, 2011. **54**(6): p. 1137-44.
36. National Institute of Health (NIH) *Management of Hepatitis C: 2002. National Institutes of Health Consensus Conference Statement*. 2002.

37. Ghany, M., et al., *Diagnosis, management, and treatment of hepatitis C: An update.* Hepatology, 2009. **49**(4): p. 39.
38. Wilkins, T., et al., *Hepatitis C: Diagnosis and treatment.* Am Fam Physician, 2010. **81**(11): p. 2.
39. Chuang, W.L. and M.L. Yu, *Host factors determining the efficacy of hepatitis C treatment.* J Gastroenterol, 2013. **48**(1): p. 22-30.
40. Lin, C.Y., et al., *Patients younger than forty years old with hepatitis C virus genotype-1 chronic infection had treatment responses similar to genotype-2 infection and not related to interleukin-28B polymorphism.* Ann Hepatol, 2013. **12**(1): p. 62-9.
41. Toyoda, H., et al., *Baseline factors and early viral response (week 4) to antiviral therapy with peginterferon and ribavirin for predicting sustained virologic response in patients infected with hepatitis C virus genotype 1: a multicenter study.* J Med Virol, 2013. **85**(1): p. 65-70.
42. Kelly, E.M. and C.L. Cooper, *Hepatitis C antiviral treatment outcomes are comparable between clinical trial participants and recipients of standard-of-care therapy: an analysis of trial effect.* Eur J Gastroenterol Hepatol, 2013.
43. Mulhall, B.P. and Z. Younossi, *Impact of adherence on the outcome of antiviral therapy for chronic hepatitis C.* J Clin Gastroenterol, 2005. **39**(1 Suppl): p. S23-7.
44. Sylvestre, D.L., *Treating hepatitis C virus infection in active substance users.* Clin Infect Dis, 2005. **40 Suppl 5**: p. S321-4.
45. Burki, T., *Elimination on the agenda for hepatitis C.* Lancet Infect Dis, 2014. **14**(6): p. 452-3.
46. World Health Organization, *A Guide to Developing Knowledge, Attitude and Practice Surveys*, n.d.: Geneva, Switzerland.
47. Shehab, T.M., S.S. Sonnad, and A.S. Lok, *Management of hepatitis C patients by primary care physicians in the USA: results of a national survey.* Journal of viral hepatitis, 2001. **8**(5): p. 377-83.
48. Myles, A., et al., *Physicians' attitudes and practice toward treating injection drug users with hepatitis C: results from a national specialist survey in Canada.* Can J Gastroenterol, 2011. **25**(3): p. 135-9.
49. Blansfield, H.N., *Addictophobia.* Conn Med, 1991. **55**(6): p. 361.
50. Hamilton, H.E., et al., *How physicians describe outcomes to HCV therapy: prevalence and meaning of "cure" during provider-patient in-office discussions of HCV.* J Clin Gastroenterol, 2008. **42**(4): p. 419-24.
51. Hamilton, H.E., et al., *Provider-patient in-office discussions of response to hepatitis C antiviral therapy and impact on patient comprehension.* Clin Gastroenterol Hepatol, 2006. **4**(4): p. 507-13.
52. Wong, J.B., et al., *Estimating future hepatitis C morbidity, mortality, and costs in the United States.* American journal of public health, 2000. **90**(10): p. 1562-9.
53. Martin, N.K., et al., *Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations.* Hepatology, 2012. **55**(1): p. 49-57.
54. Holmberg, S.D., P.R. Spradling, and A.C. Moorman, *Hepatitis C in the United States.* The New England journal of medicine, 2013. **368**(20): p. 1857-9.
55. Gidding, H.F., et al., *Predictors of deferral of treatment for hepatitis C infection in Australian clinics.* Med J Aust, 2011. **194**(8): p. 398-402.

56. Hagan, H., et al., *Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place.* Am J Epidemiol, 2008. **168**(10): p. 1099-109.
57. Centers for Disease Control and Prevention, C., *Viral hepatitis and injection drug users*, 2002.
58. Vlahov, D. and B. Junge, *The role of needle exchange programs in HIV prevention.* Public Health Rep, 1998. **113 Suppl 1**: p. 75-80.
59. Page-Shafer, K., J.A. Hahn, and P.J. Lum, *Preventing hepatitis C virus infection in injection drug users: risk reduction is not enough.* AIDS, 2007. **21**(14): p. 1967-9.
60. Doerrbecker, J., et al., *Inactivation and survival of hepatitis C virus on inanimate surfaces.* J Infect Dis, 2011. **204**(12): p. 1830-8.
61. Hagan, L.M., P.R. Wolpe, and R.F. Schinazi, *Treatment as prevention and cure towards global eradication of hepatitis C virus.* Trends Microbiol, 2013. **21**(12): p. 625-33.
62. Halliday, J., P. Klenerman, and E. Barnes, *Vaccination for hepatitis C virus: closing in on an evasive target.* Expert Rev Vaccines, 2011. **10**(5): p. 659-72.
63. Martin, N.K., et al., *HCV treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals.* Hepatology, 2013.
64. Carney, K., et al., *Association of tattooing and hepatitis C virus infection: a multicenter case-control study.* Hepatology, 2013. **57**(6): p. 2117-23.
65. Rein, D.B., et al., *The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings.* Ann Intern Med, 2012(156): p. 263-270.
66. Vickerman, P., et al., *The more you look, the more you find: effects of hepatitis C virus testing interval on reinfection incidence and clearance and implications for future vaccine study design.* J Infect Dis, 2012. **205**(9): p. 1342-50.
67. Thomas, D.L., et al., *The natural history of hepatitis C virus infection: host, viral, and environmental factors.* JAMA, 2000. **284**(4): p. 450-6.
68. Page, K., et al., *Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection.* J Infect Dis, 2009. **200**(8): p. 1216-26.
69. Thomas, D.L., et al., *Genetic variation in IL28B and spontaneous clearance of hepatitis C virus.* Nature, 2009. **461**(7265): p. 798-801.
70. Kim, A.Y., et al., *Spontaneous control of HCV is associated with expression of HLA-B 57 and preservation of targeted epitopes.* Gastroenterology, 2011. **140**(2): p. 686-696 e1.
71. Lauer, G.M., *Immune responses to hepatitis C virus (HCV) infection and the prospects for an effective HCV vaccine or immunotherapies.* J Infect Dis, 2013. **207 Suppl 1**: p. S7-S12.
72. Lauer, G.M., et al., *High resolution analysis of cellular immune responses in resolved and persistent hepatitis C virus infection.* Gastroenterology, 2004. **127**(3): p. 924-36.
73. Grebely, J., et al., *Hepatitis C virus reinfection in injection drug users.* Hepatology, 2006. **44**(5): p. 1139-45.
74. Osburn, W.O., et al., *Spontaneous control of primary hepatitis C virus infection and immunity against persistent reinfection.* Gastroenterology, 2010. **138**(1): p. 315-24.
75. Mehta, S.H., et al., *Protection against persistence of hepatitis C.* Lancet, 2002. **359**(9316): p. 1478-83.

76. Makuria, A.T., et al., *The clinical relevance of persistent recombinant immunoblot assay-indeterminate reactions: insights into the natural history of hepatitis C virus infection and implications for donor counseling.* Transfusion, 2012. **52**(9): p. 1940-8.
77. Cribier, B., et al., *High hepatitis C viraemia and impaired antibody response in patients coinfected with HIV.* AIDS, 1995. **9**(10): p. 1131-6.
78. Page-Shafer, K., et al., *Testing strategy to identify cases of acute hepatitis C virus (HCV) infection and to project HCV incidence rates.* J Clin Microbiol, 2008. **46**(2): p. 499-506.
79. Gara, N. and M.G. Ghany, *What the Infectious Disease Physician Needs to Know About Peginterferon and Ribavirin.* Clin Infect Dis, 2013.
80. Fellay, J., et al., *ITPA gene variants protect against anaemia in patients treated for chronic hepatitis C.* Nature, 2010. **464**(7287): p. 405-8.
81. U.S. Food and Drug Administration. *Olysio (simeprevir) for the treatment of chronic hepatitis C in combination antiviral treatment*. 2014 [cited 2014 5/19/14]; Available from: http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/ucm377234.htm.
82. U.S. Food and Drug Administration. *Approval of Sovaldi (sofosvubir) tablets for the treatment of chronic hepatitis C*. 2014 [cited 2014 5/19/14]; Available from: http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/ucm377920.htm.
83. Asselah, T. and P. Marcellin, *Interferon free therapy with direct acting antivirals for HCV.* Liver international : official journal of the International Association for the Study of the Liver, 2013. **33 Suppl 1**: p. 93-104.
84. American Association for the Study of Liver Disease and Infectious Diseases Society of America. *Recommendations for testing, managing and treating hepatitis C*. 2014 [cited 2014 5/20/14]; Available from: http://www.hcvguidelines.org/full-report-view.
85. World Health Organization *Guidelines for the screening, care and treatment of persons living with hepatitis C infection*, 2014.
86. Thomas, D.L., *Global control of hepatitis C: where challenge meets opportunity.* Nat Med, 2013. **19**(7): p. 850-8.
87. Abbievie. *Abbievie submits new drug application to U.S. FDA for its investigational, all-oral, interferfon-free therapy for the treatment of hepaititis C*. 2014 [cited 2014 5/19/14]; Available from: http://abbvie.mediaroom.com/2014-04-22-AbbVie-Submits-New-Drug-Application-to-U-S-FDA-for-its-Investigational-All-Oral-Interferon-Free-Therapy-for-the-Treatment-of-Hepatitis-C.
88. Bryistol-Myers Squibb. *Bristol-Myers Squibb submits NDAs for Daclatasvir and Asunaprevir to US FDA for the treatment of hepatitis C*. 2014 [cited 2014 5/19/14]; Available from: http://news.bms.com/press-release/bristol-myers-squibb-submits-ndas-daclatasvir-and-asunaprevir-us-fda-treatment-hepatit.
89. Gilead. *Gilead announced U.S. FDA priority review for designation for ledipasvir/sofosbuvir fixed-dose combination tablet for chronic hepatitis C genotype 1 infection*. 2014 [cited 2014 5/19/14]; Available from: http://www.gilead.com/news/press-releases/2014/4/gilead-announces-us-fda-priority-review-designation-for-ledipasvirsofosbuvir-fixeddose-combination-tablet-for-chronic-hepatitis-c-genotype-1-infection.
90. Edlin, B.R., et al., *Overcoming barriers to prevention, care, and treatment of hepatitis C in illicit drug users.* Clin Infect Dis, 2005. **40 Suppl 5**: p. S276-85.

91. Lawitz, E.J., *Diagnosis and management of telaprevir-associated rash.* Gastroenterol Hepatol (N Y), 2011. **7**(7): p. 469-71.
92. Grebely, J., et al., *Factors associated with uptake of treatment for recent hepatitis C virus infection in a predominantly injecting drug user cohort: The ATAHC Study.* Drug Alcohol Depend, 2010. **107**(2-3): p. 244-9.
93. Department of Veterans Affairs, *Managing side effects of hepatitis C treatment*, 2007, VA Hepatitis C Resource Center.
94. Grady, B.P., et al., *Low incidence of reinfection with the hepatitis C virus following treatment in active drug users in Amsterdam.* Eur J Gastroenterol Hepatol, 2012. **24**(11): p. 1302-7.
95. Grebely, J., et al., *Reinfection with hepatitis C virus following sustained virological response in injection drug users.* J Gastroenterol Hepatol, 2010. **25**(7): p. 1281-4.
96. Stein, M.R., et al., *Concurrent group treatment for hepatitis C: implementation and outcomes in a methadone maintenance treatment program.* J Subst Abuse Treat, 2012. **43**(4): p. 424-32.
97. Waizmann, M. and G. Ackermann, *High rates of sustained virological response in hepatitis C virus-infected injection drug users receiving directly observed therapy with peginterferon alpha-2a (40KD) (PEGASYS) and once-daily ribavirin.* J Subst Abuse Treat, 2010. **38**(4): p. 338-45.
98. Sylvestre, D.L. and B.J. Clements, *Adherence to hepatitis C treatment in recovering heroin users maintained on methadone.* Eur J Gastroenterol Hepatol, 2007. **19**(9): p. 741-7.
99. McHutchison, J.G., et al., *Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C.* Gastroenterology, 2002. **123**(4): p. 1061-9.
100. Weiss, J.J., *Adherence in the age of HCV antiviral therapy*, in *International Confernce on Viral Hepatitis, 2014*2014: Fordham University, New York, New York.
101. Belfiori, B., et al., *Treatment for hepatitis C virus in injection drug users on opioid replacement therapy: a prospective multicentre study.* Eur J Gastroenterol Hepatol, 2007. **19**(8): p. 731-2.
102. Harris, K.A., Jr., J.H. Arnsten, and A.H. Litwin, *Successful integration of hepatitis C evaluation and treatment services with methadone maintenance.* J Addict Med, 2010. **4**(1): p. 20-6.
103. Litwin, A.H., et al., *Successful treatment of chronic hepatitis C with pegylated interferon in combination with ribavirin in a methadone maintenance treatment program.* J Subst Abuse Treat, 2009. **37**(1): p. 32-40.
104. Lawitz, E.J., et al., *All-oral therapy with nucleotide inhibitors sofosbuvir and GS-0938 for 14 days in treatment-naive genotype 1 hepatitis C (NUCLEAR).* J Viral Hepat, 2013. **20**(10): p. 699-707.
105. European Association for the Study of the Liver, *EASL clinical practice guidelines: Management of hepatitis C virus infection.* J Hepatology, 2011. **55**: p. 245-264.
106. Sherman, M., et al., *Management of chronic hepatitis C: consensus guidelines.* Can J Gastroenterol, 2007. **21 Suppl C**: p. 25C-34C.

107. Rein, D.B., et al., *Forecasting the morbidity and mortality associated with prevalent cases of pre-cirrhotic chronic hepatitis C in the United States.* Dig Liver Dis, 2011. **43**(1): p. 66-72.
108. Anand, B.S., et al., *Alcohol use and treatment of hepatitis C virus: results of a national multicenter study.* Gastroenterology, 2006. **130**(6): p. 1607-16.
109. Arasteh, K., D.C.D. Jarlais, and T.E. Perlis, *Alcohol and HIV Sexual Risk Behaviors among Injection Drug Users.* Drug Alcohol Depend, 2008. **95**(1-2): p. 54-61.
110. Le Marchand, C., et al., *Hazardous alcohol consumption among young adult IDU and its association with high risk behaviors*.* Drug Alcohol Depend, 2013. **127**(0): p. 143-9.
111. Sander, P.M., et al., *Determinants of alcohol consumption in HIV-uninfected injection drug users.* Drug Alcohol Depend, 2010. **111**(1-2): p. 173-6.
112. Wiley, T.E., et al., *Impact of alcohol on the histological and clinical progression of hepatitis C infection.* Hepatology, 1998. **28**(3): p. 805-9.
113. Sublette, V.A., et al., *Psychological, lifestyle and social predictors of hepatitis C treatment response: a systematic review.* Liver international : official journal of the International Association for the Study of the Liver, 2013.
114. Costentin, C.E., et al., *Management of Hepatitis C Virus Infection in Heavy Drinkers.* Alcohol Alcohol, 2013.
115. Gilead, *Sovaldi prescribing information*, in *Package insert*2013.
116. Janssen and Medivir AB, *Olysio full prescribing information*, 2013.
117. American Psychiatric Association, *Diagnostic and statistical manual of mental disorders (4th ed., text rev.)*, 2000.
118. Schaefer, M. and S. Mauss, *Hepatitis C treatment in patients with drug addiction: clinical management of interferon-alpha-associated psychiatric side effects.* Curr Drug Abuse Rev, 2008. **1**(2): p. 177-87.
119. Raison, C.L., et al., *Neuropsychiatric adverse effects of interferon-alpha: recognition and management.* CNS Drugs, 2005. **19**(2): p. 105-23.
120. Mistler, L.A., et al., *Hepatitis C treatment for people with severe mental illness.* Psychosomatics, 2006. **47**(2): p. 93-107.
121. Schaefer, M., et al., *Hepatitis C treatment in "difficult-to-treat" psychiatric patients with pegylated interferon-alpha and ribavirin: response and psychiatric side effects.* Hepatology, 2007. **46**(4): p. 991-8.
122. Rifai, M.A., J.K. Moles, and D.D. Short, *Hepatitis C treatment eligibility and outcomes among patients with psychiatric illness.* Psychiatr Serv, 2006. **57**(4): p. 570-2.
123. Daughters, S.B., et al., *ACT HEALTHY: A Combined Cognitive-Behavioral Depression and Medication Adherence Treatment for HIV-Infected Substance Users.* Cogn Behav Pract, 2010. **17**(3): p. 309-321.
124. Safren, S.A., et al., *Cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected injection drug users: a randomized controlled trial.* J Consult Clin Psychol, 2012. **80**(3): p. 404-15.
125. Strathdee, S.A., et al., *Factors associated with interest in initiating treatment for hepatitis C Virus (HCV) infection among young HCV-infected injection drug users.* Clin Infect Dis, 2005. **40 Suppl 5**: p. S304-12.
126. Niederau, C., et al., *Chronic hepatitis C: treat or wait? Medical decision making in clinical practice.* World J Gastroenterol, 2012. **18**(12): p. 1339-47.

127. Cioe, P.A., et al., *A Comparison of Modified Directly Observed Therapy to Standard Care for Chronic Hepatitis C.* J Community Health, 2013.
128. Lloyd, A.R., et al., *Safety and Effectiveness of a Nurse-Led Outreach Program for Assessment and Treatment of Chronic Hepatitis C in the Custodial Setting.* Clin Infect Dis, 2013.
129. Larrey, D., et al., *Education by a nurse increases response of patients with chronic hepatitis C to therapy with peginterferon-alpha2a and ribavirin.* Clin Gastroenterol Hepatol, 2011. **9**(9): p. 781-5.
130. Olson, M. and I.M. Jacobson, *Role of the nurse practitioner in the management of patients with chronic hepatitis C.* J Am Acad Nurse Pract, 2011. **23**(8): p. 410-20.
131. Arora, S., et al., *Outcomes of Hepatitis C Treatment by Primary Care Providers.* The New England journal of medicine, 2011. **364**(23).
132. Clark, R.E., et al., *Beyond health plans: behavioral health disorders and quality of diabetes and asthma care for Medicaid beneficiaries.* Med Care, 2009. **47**(5): p. 545-52.
133. Bakti, S.L. and P.A. Selwyn, *Substance abuse treatment for persons with HIV/AIDS*, Health and Human Services, Editor 2000: Rockville.
134. Cozen, M.L., et al., *Nonresponse to interferon-alpha based treatment for chronic hepatitis C infection is associated with increased hazard of cirrhosis.* PloS one, 2013. **8**(4): p. e61568.
135. Morgan, R.L., et al., *Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies.* Ann Intern Med, 2013. **158**(5 Pt 1): p. 329-37.
136. van der Meer, A.J., et al., *Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis.* JAMA, 2012. **308**(24): p. 2584-93.
137. Robaeys, G., et al., *Recommendations for the management of hepatitis C virus infection among people who inject drugs.* Clin Infect Dis, 2013. **57 Suppl 2**: p. S129-37.
138. Yee, H.S., et al., *Update on the management and treatment of hepatitis C virus infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office.* The American journal of gastroenterology, 2012. **107**(5): p. 669-89; quiz 690.
139. Chen, E.Y., et al., *Knowledge and attitudes about hepatitis C virus (HCV) infection and its treatment in HCV mono-infected and HCV/HIV co-infected adults.* J Viral Hepat, 2013. **20**(10): p. 708-14.
140. Younossi, Z.M., et al., *Knowledge about infection is the only predictor of treatment in patients with chronic hepatitis C.* J Viral Hepat, 2013. **20**(8): p. 550-5.
141. Aghemo, A. and R. De Francesco, *New horizons in Hepatitis C antiviral therapy with direct-acting antivirals.* Hepatology, 2013.
142. Grebely, J. and G.J. Dore, *Can hepatitis C virus infection be eradicated in people who inject drugs?* Antiviral Res, 2014. **104**: p. 62-72.
143. Edlin, B.R. and E.R. Winkelstein, *Can hepatitis C be eradicated in the United States?* Antiviral Res, 2014. **110**: p. 79-93.
144. Smith, B.D., et al., *Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965.* Morbidity and Mortality Weekly, 2012. **61**(RR04): p. 1-18.

145. Batki, S.L., et al., *Hepatitis C treatment eligibility and comorbid medical illness in methadone maintenance (MMT) and non-MMT patients: a case-control study.* J Addict Dis, 2010. **29**(3): p. 359-69.
146. Bini, E.J., et al., *Prospective multicenter study of eligibility for antiviral therapy among 4,084 U.S. veterans with chronic hepatitis C virus infection.* The American journal of gastroenterology, 2005. **100**(8): p. 1772-9.
147. Litwin, A.H., I. Soloway, and M.N. Gourevitch, *Integrating services for injection drug users infected with hepatitis C virus with methadone maintenance treatment: challenges and opportunities.* Clin Infect Dis, 2005. **40 Suppl 5**: p. S339-45.
148. Lucas, G.M., et al., *Directly Administered Antiretroviral Therapy for HIV-Infected Individuals in Opioid Treatment Programs: Results from a Randomized Clinical Trial.* PloS one, 2013. **8**(7): p. e68286.
149. Uhlmann, S., et al., *Methadone maintenance therapy promotes initiation of antiretroviral therapy among injection drug users.* Addiction, 2010. **105**(5): p. 907-13.
150. Aspinall, E.J., et al., *Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis.* Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 2013. **57 Suppl 2**: p. S80-9.
151. Adeyemi, O.M., et al., *Hepatitis C treatment eligibility in an urban population with and without HIV coinfection.* AIDS Patient Care STDS, 2004. **18**(4): p. 239-45.
152. Zeng, Q.L., et al., *Sofosbuvir and ABT-450: terminator of hepatitis C virus?* World J Gastroenterol, 2013. **19**(21): p. 3199-206.
153. Brener, L., et al., *Discrimination by health care workers versus discrimination by others: Countervailing forces on HCV treatment intentions.* Psychol Health Med, 2015. **20**(2): p. 148-53.
154. Treloar, C., et al., *Uptake and delivery of hepatitis C treatment in opiate substitution treatment: perceptions of clients and health professionals.* J Viral Hepat, 2010. **17**(12): p. 839-44.
155. Ray, M.K., et al., *Patient and provider comfort discussing substance use.* Fam Med, 2013. **45**(2): p. 109-17.
156. Wilcox, C.E., et al., *Concordance between self-report and urine drug screen data in adolescent opioid dependent clinical trial participants.* Addict Behav, 2013. **38**(10): p. 2568-74.
157. McPherson, T.L. and R.K. Hersch, *Brief substance use screening instruments for primary care settings: a review.* J Subst Abuse Treat, 2000. **18**(2): p. 193-202.
158. Pilowsky, D.J. and L.T. Wu, *Screening for alcohol and drug use disorders among adults in primary care: a review.* Subst Abuse Rehabil, 2012. **3**(1): p. 25-34.
159. Ellison, S.T., W.E. Brewer, and S.L. Morgan, *Comprehensive analysis of drugs of abuse in urine using disposable pipette extraction.* J Anal Toxicol, 2009. **33**(7): p. 356-65.
160. LabCorp Inc, *Drugs of Abuse Reference Guide*, 2007.
161. Silverman, E., *How Illinois allocates $84,000 drug for hepatitis C*, in *Wall Street Journal*2014.
162. United Healthcare, *United Healthcare pharmacy Sovaldi prior authorization form*, 2014.

163. Substance Abuse and Mental Health Services Administration; (SAMHSA), *Results from the 2011 National Survey on Drug Use and Health: Summary of national findings, NSDUH Series H-44*, S.A.a.M.H.S. Administration, Editor 2012, HHS: Rockville.
164. Grebely, J., et al., *Directly observed therapy for the treatment of hepatitis C virus infection in current and former injection drug users.* J Gastroenterol Hepatol, 2007. **22**(9): p. 1519-25.
165. Tucker, T., et al., *Randomized controlled trial of a brief behavioural intervention for reducing hepatitis C virus risk practices among injecting drug users.* Addiction, 2004. **99**(9): p. 1157-66.
166. Garfein, R.S., et al., *A peer-education intervention to reduce injection risk behaviors for HIV and hepatitis C virus infection in young injection drug users.* AIDS, 2007. **21**(14): p. 1923-32.
167. Sun, X., et al., *Interventions to Improve Patient Adherence to Hepatitis C Treatment: Comparative Effectiveness*2012, Rockville MD.
168. Sylvestre, D.L., *Approaching treatment for hepatitis C virus infection in substance users.* Clin Infect Dis, 2005. **41 Suppl 1**: p. S79-82.
169. Islam, M.M., *Needle Syringe Program-Based Primary HealthCare Centers: Advantages and Disadvantages.* J Prim Care Community Health, 2010. **1**(2): p. 100-3.
170. Lawitz, E., et al., *Sofosbuvir for previously untreated chronic hepatitis C infection.* The New England journal of medicine, 2013. **368**(20): p. 1878-87.
171. Razavi, H., et al., *Chronic hepatitis C virus (HCV) disease burden and cost in the United States.* Hepatology, 2012.
172. Lawitz, E., et al., *Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study.* Lancet, 2014.
173. Sulkowski, M.S., et al., *Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection.* The New England journal of medicine, 2014. **370**(3): p. 211-21.
174. Hoofnagle, J.H. and A.H. Sherker, *Therapy for hepatitis C--the costs of success.* The New England journal of medicine, 2014. **370**(16): p. 1552-3.
175. Ly, K.N., et al., *The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007.* Ann Intern Med, 2012. **156**(4): p. 271-278.
176. Dalgard, O., *Follow-up studies of treatment for hepatitis C virus infection among injection drug users.* Clin Infect Dis, 2005. **40 Suppl 5**: p. S336-8.
177. Grebely, J., et al., *Treatment uptake and outcomes among current and former injection drug users receiving directly observed therapy within a multidisciplinary group model for the treatment of hepatitis C virus infection.* Int J Drug Policy, 2007. **18**(5): p. 437-43.
178. Jafferbhoy, H., et al., *Intravenous drug use: not a barrier to achieving a sustained virological response in HCV infection.* J Viral Hepat, 2012. **19**(2): p. 112-9.
179. StataCorp, *Stata Statistical Software: Release 13.*, 2013, StataCorp LP: College Station, TX.
180. Efron, B., *The bootstrap and modern statistics.* Journal of the American Statistical Association, 2000. **95**(452): p. 1293-1296.
181. Erceg-Hurn, D.M. and V.M. Mirosevich, *Modern robust statistical methods: An easy way to maximize the accuracy and power of your research.* American Psychologist, 2008. **63**(7): p. 591-601.

182. Wehrens, R., H. Putter, and L.M.C. Buydens, *The bootstrap: a tutorial.* Chemometrics and Intelligent Laboratory Systems, 2000. **54**(1): p. 35-52.
183. Ghany, M.G., *The ongoing debate of who to treat for chronic hepatitis c virus.* JAMA Internal Medicine, 2015. **175**(2): p. 169-170.
184. Backmund, M., K. Meyer, and B.R. Edlin, *Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users.* Clin Infect Dis, 2004. **39**(10): p. 1540-3.
185. Lazarus, J.V., et al., *A systematic review of Hepatitis C virus treatment uptake among people who inject drugs in the European Region.* BMC Infect Dis, 2014. **14 Suppl 6**: p. S16.
186. Hagan, L.M. and R.F. Schinazi, *Best strategies for global HCV eradication.* Liver international : official journal of the International Association for the Study of the Liver, 2013. **33 Suppl 1**: p. 68-79.
187. Hellard, M., et al., *Eradication of hepatitis C infection: the importance of targeting people who inject drugs.* Hepatology, 2014. **59**(2): p. 366-9.
188. Rocca, L.G., et al., *Management of patients with hepatitis C in a community population: diagnosis, discussions, and decisions to treat.* Ann Fam Med, 2004. **2**(2): p. 116-24.
189. Hamilton, H.E., et al., *Physicians, nonphysician healthcare providers, and patients communicating in hepatitis C: an in-office sociolinguistic study.* Gastroenterol Nurs, 2006. **29**(5): p. 364-70.

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