

Medical and Behavioral Approaches to Engage People Who Inject Drugs Into Care for Hepatitis C Virus Infection

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Abstract

Direct-acting antivirals for hepatitis C virus infection may revolutionize treatment among persons with substance use disorders. Despite persons with substance use disorders having the highest hepatitis C virus prevalence and incidence, the vast majority have not engaged into care for the infection. Previously, interferon-based treatments, with substantial side effects and the propensity to exacerbate mental health conditions, were major disincentives to pursuit of care for the infection. Direct-acting antivirals with viral eradication rates of >90%, significantly improved side effect profiles, and shorter treatment duration are dramatic improvements over prior treatment regimens that should promote widespread hepatitis C virus care among persons with substance use disorders. The major unmet need is strategies to promote persons with substance use disorders engagement into care for hepatitis C virus. Although physical integration of treatment for substance use and co-occurring conditions has been widely advocated, it has been difficult to achieve. Telemedicine offers an opportunity for virtual integration of behavioral and medical treatments that could be supplemented by conventional interventions such as hepatitis C virus education, case management, and peer navigation. Furthermore, harm reduction and strategies to reduce viral transmission are important to cease reinfection among persons with substance use disorders. Widespread prescription of therapy for hepatitis C virus infection to substance users will be required to achieve the ultimate goal of global virus elimination. Combinations of medical and behavioral interventions should be used to promote persons with substance use disorders engagement into and adherence with direct-acting antiviral-based treatment approaches. Ultimately, either physical or virtual colocation of hepatitis C virus and substance use treatment has the potential to improve adherence and consequently treatment efficacy.

Key Words: HCV, persons with substance use disorders, HCV treatment

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BACKGROUND ON HEPATITIS C VIRUS INFECTION

Chronic infection with hepatitis C virus is a major cause of liver disease and is the most common chronic

blood-borne infection in the United States. Over 180 million people globally are affected by hepatitis C virus, representing a major global health problem.¹ The prevalence of the disease varies significantly depending upon geographic region and country, with the highest prevalence in Central and East Asia and in North Africa/Middle East. Epidemiological studies have reported that between 3 and 4 million people in the United States have chronic hepatitis C virus infection.^{1,2} However, an even larger number, possibly >5 million, may have chronic infection when accounting for high-risk populations including the homeless, incarcerated individuals, and people who inject drugs.³

A large percentage of hepatitis C virus-infected individuals in the United States remain undiagnosed and are at risk of progressive liver disease.⁴ Consequently, the health care burden related to hepatitis C virus is projected to continue to increase with associated increases in the prevalence of cirrhosis, liver failure, and hepatocellular carcinoma.^{5,6} Hepatitis C virus is currently the leading indication for liver transplantation in developed countries,^{7,8} and ~700,000 people globally die every year from hepatitis C virus-related liver diseases.⁹ As highly effective antiviral therapy for hepatitis C virus infection is now available, efforts to diagnose hepatitis C virus and to identify treatment-eligible candidates is an increasingly important priority, particularly among persons with substance use disorders.

As hepatitis C virus is a blood-borne pathogen, viral transmission as a consequence of illicit substance use is the most common acquisition risk

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factor in developed countries.^{7,10} Hepatitis C virus seroprevalence among persons who inject drugs is extremely high, reaching $\geq 60\%$ in most countries.¹¹ Likewise, the yearly incidence of hepatitis C virus in these individuals ranges from 5% to as high as 45%,¹² with a higher frequency among younger individuals and recent initiates to injection drug use.^{13,14} As a result, injection drug use accounts for 68% to 80% of all hepatitis C virus infections in the developed world.⁷ Therefore, targeting persons who inject drugs for hepatitis C virus prevention and treatment is critically important to its global elimination. Several groups have recently highlighted and continue to forcefully advocate for the importance of efforts to reduce the risk of hepatitis C virus transmission among persons who inject drugs.^{15,16}

NATURAL HISTORY OF HEPATITIS C VIRUS INFECTION

Acute hepatitis C virus infection is typically asymptomatic. Although spontaneous recovery occasionally occurs, the majority (up to 85%) progresses to chronic infection. Once chronic infection is established, progressive liver disease can result in cirrhosis in up to 30% of individuals within 20 years. Factors associated with rapid disease progression include chronic alcohol consumption, coexisting nonalcoholic fatty liver disease, and coinfection with hepatitis B or human immunodeficiency virus (HIV), which can result in intermittent elevation of alanine aminotransferase levels.^{17,18} Chronic hepatitis C virus infection has a major impact on survival, leading to an increase in both liver-related and non-liver-related mortality among those at any stage of hepatitis C virus-associated liver disease.¹⁹ Cirrhotic individuals are at increased risk of liver cancer and can progress relatively quickly from asymptomatic, clinically compensated disease to overt decompensation with portal hypertension characterized by the onset of ascites, hepatic encephalopathy, or variceal hemorrhage.²⁰ The development of liver cancer or clinical decompensation is associated with a

significant change in prognosis and an acute increase in mortality risk.

EVOLUTION OF HEPATITIS C VIRUS TREATMENT

Recent therapeutic advances have fundamentally changed the approach to treatment of hepatitis C virus. Unlike HIV infection, successful long-term clearance of hepatitis C virus after therapy is defined by achievement of a sustained virologic response, which is a durable endpoint and is equivalent to viral eradication. Viral eradication is associated with improved health-related quality of life, fibrosis regression, reduction in liver-related and all-cause mortality, and decreased risk of events related to cardiovascular disease, kidney disease, stroke, and malignancy.^{21–23} In the setting of advanced liver disease, successful treatment can significantly reduce the risk of clinical decompensation, liver cancer, need for liver transplantation, and mortality, independent of comorbidities or other risk factors.^{24,25}

Since shortly after the discovery of hepatitis C virus in 1989 and until very recently, interferon α was the cornerstone of treatment for chronic hepatitis C. Interferon-based regimens were associated with significant side effects and led to viral eradication in only $\sim 50\%$ of treated patients.^{26,27} In 2011, the first direct-acting antivirals, telaprevir, and boceprevir, received regulatory approval and were utilized in combination with interferon and ribavirin resulting in viral eradication in $\sim 70\%$ of treatment-naïve patients.^{28,29} In late 2014, the approval of interferon-free, all-oral treatment regimens was granted.^{30,31}

The first, widely prescribed direct-acting antiviral combination approved was composed of the hepatitis C virus NS5A inhibitor, ledipasvir, and the NS5B polymerase inhibitor, sofosbuvir, coformulated in a fixed-dose, single tablet (Harvoni, Gilead Sciences). The combination is typically prescribed for either 8 or 12 weeks (depending upon hepatitis C virus RNA level) for genotype 1, it has superior efficacy with eradication rates of at least 90%, a high barrier to resistance, and minimal side effects.^{32,33} Other all oral

direct-acting antiviral regimens for treatment of hepatitis C virus genotype 1 include the combination of 3 agents, the NS5A inhibitor, ombitasvir, the NS5B polymerase inhibitor, dasabuvir, and the NS3/4A protease inhibitor, paritaprevir, together with the antiretroviral drug, ritonavir (Viekira Pak, AbbVie), which is included in the regimen for its ability to boost paritaprevir concentrations.³⁴ Another frequently prescribed direct-acting antiviral combination is the coformulation of the NS3/4A protease inhibitor, grazoprevir, with the NS5A inhibitor, elbasvir (Zepatier, Merck).³⁵ The combination of sofosbuvir and daclatasvir has been approved for treatment of hepatitis C virus genotypes

2 and 3.³⁶ Most recently, the pan-genotypic combination of sofosbuvir with the NS5A inhibitor, velpatasvir, has been approved (Epclusa, Gilead Sciences).³⁷ The availability of interferon-free, direct-acting antiviral regimens has led to significant improvements in treatment efficacy, in which viral eradication can be achieved in over 90% of patients regardless of hepatitis C virus genotype (Table 1).³⁸

Changes to the Therapeutic Regimen Enhance Uptake by Persons With Substance Use Disorders

Historically, hepatitis C virus-infected individuals who actively inject

TABLE 1. Summary of Direct-acting Antiviral Regimens

Generic Name	Brand Name	Manufacturer	HCV Genotype
Protease inhibitors (NS3/4A)			
Grazoprevir	Zepatier (in combination with Elbasvir)	Merck & Co.	1, 4
Paritaprevir	Viekira (in combination, see below)	AbbVie	1
Simeprevir	Olysio	Janssen	1
Nucleoside inhibitors (NS5B)			
Sofosbuvir	Sovaldi	Gilead Sciences	2, 3
Non-nucleoside inhibitors (NS5B)			
Dasabuvir	Viekira	AbbVie	1
NS5A inhibitors			
Daclatasvir	Daklinza	Bristol-Myers Squibb	3
Elbasvir (in combination with grazoprevir)	Zepatier	Merck & Co.	1, 4
Ledipasvir (in combination with sofosbuvir)	Harvoni	Gilead Sciences	1,4,5, 6
Ombitasvir	Viekira	AbbVie	1
Ribavirin	Rebetol	Merck & Co.	1,4
Combinations (NS5B and NS5A inhibitors)			
Sofosbuvir + Ledipasvir	Harvoni	Gilead Sciences	1,4,5, or 6
Sofosbuvir + Velpatasvir	Epclusa	Gilead Sciences	1,2,3,4,5,6
Elbasvir + Grazoprevir	Zepatier	Merck	1 or 4
Ombitasvir + Paritaprevir + Ritonavir	Technivie	AbbVie	4
Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir	Viekira	AbbVie	1

HCV indicates hepatitis C virus.

drugs as well as those who have transitioned to opioid replacement therapy were rarely treated, despite professional society guidelines and recommendations that advocated the opposite.^{39–41} Recent advances in hepatitis C virus therapeutics; however, have fundamentally changed the approach to treatment of persons with substance use disorders. Principal among these was elimination of interferon from the therapeutic regimen. Because of a similarity in symptomatology between the adverse effects of interferon and that of methadone withdrawal, many persons with substance use disorders reported that interferon was the major deterrent to pursuit of hepatitis C virus treatment. In addition, concerns regarding persons with substance use disorders likely adherence to the therapeutic regimen and the potential to develop resistant-associated variants to the first generation direct-acting antivirals, dampened provider's enthusiasm to treat hepatitis C virus among persons with substance use disorders.^{28,29,42}

Interferon elimination also removed its potential exacerbation of mental health conditions that are frequent co-occurrences among persons with substance use disorders, which could reduce treatment adherence and might be reasons for treatment failure.^{43,44} Shorter

treatment duration, 2 to 3 months as opposed to 6 or 11 months, is also a potential benefit of direct-acting antivirals that can increase treatment adherence among persons with substance use disorders. Although some drug-drug interactions exist, particularly with specific antiretroviral agents, concomitant use of direct-acting antiviral therapy with either methadone or buprenorphine is safe and effective. Although these interventions should increase direct-acting antiviral treatment among persons with substance use disorders, new restrictions on hepatitis C virus treatment provision particularly among persons with substance use disorders have arisen, such as restrictions established by third-party payers including the presence of active substance use and restricting treatment to those with late-stage liver disease, that is, advanced fibrosis and cirrhosis.^{45,46}

Several studies have now demonstrated high rates of viral eradication associated with direct-acting antiviral therapy in persons with substance use disorders, both in the setting of stable opioid replacement therapy and in those with recent hepatitis C virus exposure due to active drug use (Table 2). An open-label, prospective study of the 3 drug direct-acting antiviral combination regimen ombitasvir, dasabuvir, paritaprevir, and

TABLE 2. Studies Involving Direct-acting Antiviral Therapy for Genotype 1 Hepatitis C in People Who Inject Drugs^{47–51}

References	Regimen	Design	Population	SVR (%)
Lalezari et al ⁴⁷	Ombitasvir/dasabuvir/ paritaprevir/ ritonavir + ribavirin × 12 wk	Open-label, prospective	n = 38; stable opioid replacement therapy	97
Grebely et al ⁴⁸	Ledipasvir/ sofosbuvir ± ribavirin × 12 wk	Retrospective from phase 3 clinical trial	n = 70; stable opioid replacement therapy	94
Grebely et al ⁴⁹	Velpatasvir/ sofosbuvir × 12 wk	Retrospective from phase 3 clinical trial	n = 51; stable opioid replacement therapy	96
Dore et al ⁵⁰	Elbasvir/grazoprevir × 12 wk	Randomized, placebo- controlled, prospective	n = 301; opioid replacement therapy, 60% with active substance use	91
Basu et al ⁵¹	Ledipasvir/sofosbuvir × 4 wk vs. simeprevir/ sofosbuvir × 8 wk	Randomized, prospective	n = 29; acute HCV, drug rehab facilities	100 vs. 87

HCV indicates hepatitis C virus; rehab, rehabilitation; SVR, sustained virological response.

ritonavir plus ribavirin in patients with genotype 1 hepatitis C virus on a stable regimen of opioid replacement therapy reported no differences in antiviral efficacy and pharmacokinetics between those receiving methadone versus buprenorphine, with an overall sustained viral response of 97%.⁴⁷ In addition, retrospective data derived from large-scale phase 3 clinical trials of sofosbuvir-based therapy involving ledipasvir/sofosbuvir and velpatasvir/sofosbuvir revealed no differences in efficacy, adherence, or adverse events in those receiving opioid replacement therapy versus others, with viral eradication rates of 94% to 96%.^{48,49} A randomized, double-blind, placebo-controlled phase III study of 12 weeks of elbasvir/grazoprevir in persons with substance use disorders on opiate agonist therapy was notable for an overall viral eradication rate of 91% in genotypes 1, 4, and 6 despite active drug use in greater than one-half of patients.⁵⁰ An additional prospective study identified persons with substance use disorders presenting with recent hepatitis C virus exposure associated with active injection drug use, in which a shortened duration of direct-acting antiviral therapy of 4 weeks of ledipasvir/sofosbuvir or 8 weeks of simeprevir/sofosbuvir led to viral eradication in 93% by intention-to-treat and 100% by per-protocol analysis.⁵¹ The high efficacy associated with a short duration of direct-acting antiviral therapy in early hepatitis C virus infection suggests a cost benefit in identifying and treating recent hepatitis C virus exposures in persons with substance use disorders.

New Barriers to Hepatitis C Virus Treatment Uptake by Persons With Substance Use Disorders

The high costs of new hepatitis C virus treatments have resulted in the implementation of onerous requirements to obtain approval for direct-acting antivirals in the United States. In some cases, 6 months of documented abstinence from illicit substance use or excessive alcohol intake, in addition to enrollment in a formal substance use treatment program, may be mandated. Additional requirements may include written informed consent stipulating that patients will be adherent to the

therapeutic regimen. The importance of maximizing adherence and the risk of reinfection continue to be concerns for medical providers who are largely unfamiliar with the issues of treatment of persons with substance use disorders. In actuality, though, high adherence and low rates of reinfection have been observed among persons with substance use disorders irrespective of injection drug use before or during treatment with interferon-based regimens.^{52,53} More recent data involving direct-acting antiviral regimens have also noted high adherence rates, with no difference in efficacy, adherence, and adverse events in patients receiving opioid replacement therapy versus others.⁴⁷⁻⁵⁰ Similarly, as described below, reinfection after successful viral eradication remains exceedingly low.^{50,54,55} As many persons with substance use disorders are uninsured, underfunded, and without social support, the onerous cost of hepatitis C virus treatment and payers' requirements for direct-acting antiviral approval can become major obstacles to their treatment.

STATUS OF US FEDERAL GOVERNMENT STRATEGIES TO END THE HEPATITIS C VIRUS EPIDEMIC

Surveillance programs have identified significant health disparities attributed to viral hepatitis, in which more than one-half of individuals with chronic hepatitis C virus have incomes lower than twice the poverty level and less than a high school education. Racial disparities also exist, in which American Indians and Alaska Natives have the highest rate of new hepatitis C virus infections, whereas African Americans account for 25% of people with chronic hepatitis C virus but comprise only 11% of the US population.⁵⁶ In addition to persons with substance use disorders, other vulnerable populations with a high prevalence of hepatitis C virus infection include individuals with HIV infection (~20%), HIV-infected drug users (60% to 90%), incarcerated individuals (33%), and the homeless (up to 70%).^{3,57} After declining (2000 to 2005) or remaining stable (2006 to 2010), the

number of cases of acute hepatitis C virus doubled between 2011 and 2014.⁵⁸ In the period between 2010 and 2013, the greatest increase occurred among those aged 20 to 29 years mostly among young, nonminority, persons who inject drugs and many of whom also use oral prescription opioid drugs.^{58,59} The largest increases in acute hepatitis C virus occurred among the states in central Appalachia (Kentucky, Tennessee, Virginia, and West Virginia) among individuals aged 18 to 29 years old, predominantly white, equally female and male, and who resided in nonurban or suburban areas.⁶⁰ Some areas within the United States seem to be particularly vulnerable to outbreaks of HIV and hepatitis C virus among persons with substance use disorders. As reported by the Centers for Disease Control, at least 220 counties are at risk for hepatitis C virus, with associated increases in unemployment rates, prescription opioid sales, and overdose deaths being factors responsible for the increase.⁶¹

To address emerging data indicating a significant increase in hepatitis C virus exposure risk among persons with substance use disorders and the large proportion of new hepatitis C virus infections occurring in this population, new guidance on the use of syringe services programs has been developed. In 2015, the US Congress passed legislation to allow federal funds to be used to support some components of syringe services program. On the basis of this change, funds from several federal agencies can be used after “determination of need” is established. Key initiatives associated with this change in policy are integration of HIV and hepatitis C virus testing into syringe services programs, promoting linkage to care, and facilitating referrals to substance abuse treatment.⁶² Additional educational programs have been implemented with a focus on hepatitis C virus awareness and screening. Hopefully, these funds will result in several improvements related to hepatitis C virus since in 2013, less than one-quarter of all reporting substance use treatment facilities offered hepatitis C virus screening, representing missed opportunities for screening and linkage

to care, and highlighting major gaps in health care provider education.⁶³

In response to the rising incidence of acute hepatitis C virus in the United States and in recognition of the long-term impact of viral hepatitis on the overall health care burden in the United States, a national Viral Hepatitis Action Plan has been established with the intent of providing a pathway to achieve viral hepatitis elimination in this country.⁶⁴ Specific goals outlined in the Viral Hepatitis Action Plan include the prevention of new hepatitis B and hepatitis C infections, reductions in mortality and improvements in the health of individuals living with viral hepatitis, reductions in viral hepatitis health disparities, and to coordinate, monitor, and report on the implementation of viral hepatitis actions. Although the Viral Hepatitis Action Plan provides a framework for setting goals, priorities, and measurable targets, it is recognized that these goals cannot be achieved through federal action alone and that active involvement and innovation from a broad mix of nonfederal stakeholders from various sectors, both public and private, is essential.

GOALS OF INTERVENTIONS TO END THE HEPATITIS C VIRUS EPIDEMIC

Screening

Hepatitis C virus is primarily transmitted through parenteral exposure, and injection drug use is currently the principal risk factor for transmission of hepatitis C virus infection.¹⁰ Other risk factors include transmission via blood transfusion, noninjection drug use, and unprofessional tattoos.⁶⁵ Consequently, hepatitis C virus screening recommendations have been designed to identify populations with the greatest risk of viral acquisition. In 1998, the Centers for Disease Control and Prevention recommended that all persons who inject drugs be screened for hepatitis C virus.⁶⁶ In 2012, the hepatitis C virus screening recommendations were revised to shift focus from risk factor based to age-based screening based upon the observation that up to 40% of hepatitis C virus-infected individuals were not aware

of their diagnosis.⁶⁷ Consequently, hepatitis C virus screening recommendations were refocused to emphasize screening among individuals born between 1945 and 1965, a population with extremely high rates of undiagnosed hepatitis C virus infection.⁶⁸ Although the birth cohort comprises up to 75% of prevalent hepatitis C virus infections in the United States, injection drug use accounts for the vast majority of incident hepatitis C virus infections.^{10,69} The prevalence of chronic hepatitis C virus within cohorts of persons who use injection drugs can reach as high as 30% within the first year and increases to >50% within 5 years of habitual injection drug use, with further increases in prevalence resulting from continued substance use.⁷⁰

Despite these recommendations, hepatitis C virus screening rates and linkage to care remain low in the United States, especially among persons with substance use disorders. Overall, only 1 in 3 patients with chronic hepatitis C virus are referred to care and as few as 1 in 10 patients have undergone antiviral therapy with interferon-based regimens.⁷¹ Adherence to hepatitis C virus evaluation and treatment recommendations among persons with substance use disorders is even lower. To ultimately reduce the transmission of hepatitis C virus, efforts to screen persons who inject drugs will be critical in identifying infected individuals and to implementation of educational programs, to initiate transition to opioid replacement therapy, and to identify potential candidates for antiviral therapy.

Prevention of Transmission and Reinfection

As no hepatitis C virus vaccine currently exists, the only truly effective means of hepatitis C virus prevention is limiting the potential for viral exposure. In addition to needle sharing, other transmission risks exist in persons who inject drugs, including contact with hepatitis C virus-contaminated blood through preparation equipment, highlighting the need for education on safe injection practices and other transmission routes. Drug administration via mucosal routes, such as intranasal

cocaine use, is also considered a risk factor for viral acquisition, although significantly less efficient than via blood contamination.⁷² Hepatitis C virus RNA levels are typically at least 10-fold higher than HIV RNA, leading to increased virulence and increased opportunities for viral acquisition per exposure.⁷³ Interventions to control HIV and consequent reductions in HIV transmission have not translated into equivalent reductions in hepatitis C virus transmission.⁷⁴ Thus, hepatitis C virus prevalence is higher than HIV prevalence and chronic hepatitis C virus is more virulent than HIV. Mortality due to hepatitis C virus, particularly among those aged 55 to 64 years, has been increasing, surpassing that due to HIV and all 60 other reportable infectious diseases combined.⁷⁵

Needle exchange programs have led to a decrease in the use of contaminated needles; however, access to these programs varies widely. Ultimately, a combined reduction in the number of contacts and a reduction in the probability of transmission per contact through safe injection practices and equipment, regular testing within networks of persons who inject drugs, and successful viral eradication through antiviral therapy could have major impacts on decreasing the overall hepatitis C virus prevalence and the risk of exposure within this population.

One of the major reasons for low hepatitis C virus treatment uptake among active substance users is providers' misconceptions about poor treatment adherence as well as the false impression that there is a high rate of reinfection in this patient population. Published data, however, counter each of these assertions. A recent meta-analysis and systemic review that evaluated studies of active injectors treated with pegylated-interferon and ribavirin reported a rigorous adherence to therapy in 82% of patients and pooled rates of reinfection were 2.1% and 2.4% per year.^{21,55} In addition, as mentioned above, high adherence and low reinfection rates have been identified in studies of direct-acting antiviral therapy among persons with substance use disorders.

Hepatitis C Virus Transmission Among Men Who Have Sex With Men

Among certain populations of persons with substance use disorders, namely men who have sex with men, rates of hepatitis C virus infection have reached epidemic proportions in North America,^{76–79} Europe,^{80–84} Australia,⁸⁵ and Asia.^{86,87} This new epidemic of hepatitis C virus among HIV-infected men who have sex with men has been due to sexual transmission, with only rare injection drug use, although non-injection drug use, especially with methamphetamine, seems to have fueled the epidemic in many urban centers.^{88,89} In the decade as the first recognition of this epidemic, hepatitis C virus incidence increased among HIV-infected men who have sex with men globally, with incidence of primary hepatitis C virus as high as 4%,⁹⁰ and annual reinfection rates as high as 15%,^{91,92} in some cohorts. We therefore need a better understanding of routes and mechanisms of transmission among these men to develop prevention strategies to decrease the infection rate.

Seven case-controlled studies have been performed to identify risk factors for hepatitis C virus acquisition among HIV-infected men who have sex with men in the United States and Europe.^{90,93–98} Overall, the most frequently identified risk factors for hepatitis C virus acquisition were unprotected anal intercourse (5 of 7 studies), fisting (4 of 5 studies), group sex (3 of 5 studies), and drug use (3 of 5 studies). One of the early studies, in New York City found that sex while high on methamphetamine was associated with an adjusted odds ratio of 29. Although an early study from London did not find hepatitis C virus acquisition associated with drug use, subsequent studies from England evaluating drug use among men who have sex with men have shown a high proportion of men who have sex with men using drugs to have sex, which they have called “chemsex,” as well as an association with hepatitis C virus infection.⁹⁹ The actual source of hepatitis C virus that is transmitted has been controversial as the hepatitis C virus field has been focused on blood as the infecting agent through

injection drug use and investigators seem loath to accept the likelihood that other infection sources could be responsible for virus transmission during sex, where neither fists nor penises bleed during insertion into the rectum. Hepatitis C virus has long been known to present in semen, and has again recently been shown to be present in one-third to one-half of HIV-infected men who have sex with men, further evidence that the hepatitis C virus-containing fluid that infects anal receptive partners is most plausibly semen.^{100,101} Hepatitis C virus in semen could be absorbed through the rectal mucosa that was mildly abraded by the action of the inserted penis in the absence of more serious rectal trauma, possibly enhanced by changes induced by rectal douching, and possibly further enhanced by the mucosa compromised by the CD4⁺ T-cell depletion caused by primary HIV infection. The epidemiological findings of fisting and group sex as risk factors further suggest fomite/fomite-like transmission through, or direct infection of unprotected penises or fists. Rectal shedding of hepatitis C virus has just recently been demonstrated at sufficient concentration to explain transmissions in these settings without positing visible rectal bleeding, which rarely occurs in any case.¹⁰² With this emerging understanding of sex among HIV-infected men who have sex with men being fueled by mostly noninjection drug use with hepatitis C virus being transmitted by semen and rectal fluid, we can now begin a campaign of education about these elements to the men at risk, as well as the physicians who care for them, as most are currently unaware of these mechanisms of hepatitis C virus transmission among this new risk group.

Treatment of Addiction

Of the estimated 23.5 million Americans who are currently addicted to alcohol and/or other drugs, only 11% receives treatment for addiction.¹⁰³ Addressing the underlying addictive disorder and implementing a treatment plan are critical to reducing exposure risk and to obtaining further decreases in transmission of hepatitis C virus in persons with substance use disorders. Changes in the epidemiology of injection

drug use can influence patterns of acute hepatitis C virus infection. Over the last decade, the numbers of prescription opioid sales, opioid-related deaths, and opioid treatment admissions have all increased significantly, although data from 2010 to 2013 suggest that the trend has waned.¹⁰⁴ Simultaneously, however, heroin use has increased sharply, including not only a rise in the number of heroin users but also in the number of deaths attributed to heroin overdose.¹⁰⁵ Consequently, the demographics of hepatitis C virus has changed as a result of changes in the characteristics of people using heroin, which has increased in whites, women, and those living in suburban or rural areas.^{60,106}

Effect of Substance Use Treatment on Pursuit of Hepatitis C Virus Treatment

Engagement in treatment of addiction and integration with primary medical care has been shown to be cost-effective, to improve medical outcomes, and to result in decreased numbers of hospitalizations.^{107,108} Treatment of addiction may have other health benefits from a psychosocial perspective. Indeed, the combination of opioid replacement therapy and needle exchange has been shown to decrease hepatitis C virus transmission compared with a single intervention.¹⁰⁹ Specifically with regard to hepatitis C virus, engagement of active persons with substance use disorders into hepatitis C virus care could serve as a gateway into the health care system. Among patients on opioid replacement therapy, those who self-report hepatitis C virus seropositivity and those with higher levels of knowledge about the virus and its management have demonstrated increased willingness to undergo hepatitis C virus treatment.¹¹⁰ In addition, hepatitis C virus education of persons with substance use disorders results in increases in hepatitis C virus-related knowledge.¹¹¹ Lack of information about hepatitis C virus has been associated with unwillingness to pursue treatment.¹¹² Thus, hepatitis C virus-related education and ultimately, therapy, could further result in engagement in substance use therapy and the assessment of

other comorbidities. Informing persons who inject drugs about hepatitis C virus seropositivity, providing education regarding risk factors for viral transmission, and establishing a linkage to hepatitis C virus care can lead to reductions in both drug use behavior and injection frequency.^{112–114} Therefore, a diagnosis of hepatitis C virus may offer an opportunity for a “teachable moment,” the concept of utilizing health events to motivate individuals to spontaneously adopt risk-reduction health behaviors.¹¹⁵

Active drug use in the months preceding the initiation of antiviral therapy is not associated with a decline in efficacy^{116–118}; however, the amount or frequency of drug use may influence the degree of adherence to antiviral therapy and therefore efficacy.^{118–120} In active drug users, interferon-based hepatitis C virus treatment has been shown to result in slightly lower rates of viral eradication.⁵⁵ In these individuals, treatment of addiction during receipt of interferon-based therapies for hepatitis C virus has been shown to result in higher treatment completion and viral eradication rates, similar to those obtained in registration trials and in the general population.^{121,122} The extent to which ongoing drug use affects treatment efficacy in patients treated with direct-acting antivirals remains to be determined, although in studies performed to date, no effect has been observed. In HIV infection, however, a meta-analysis has shown that better treatment outcomes are obtained among former drug users, those on opioid substitution therapy and/or psychosocial support.¹²³ In addition, active drug users demonstrated significantly worse medication adherence than did nonusers (79% vs. 63%).¹²⁴ To eliminate hepatitis C virus, we will need to treat populations such as active injectors. Although the optimal treatment strategy remains to be determined in persons with substance use disorders, interventions will be needed to support them during hepatitis C virus therapy to optimize treatment efficacy. An additional consideration might be the use of directly observed therapy or modified directly observed therapy, an effective strategy demonstrated in

interferon-based regimens,^{119,125} which may also be applied to direct-acting antiviral therapy. In light of challenges associated with treatment of active drug users, systematic approaches will be required to include education, treatment of addiction, transition to opioid replacement therapy if possible, and considerations of directly observed therapy to optimize adherence and treatment efficacy.

Treatment as Prevention

The advances in the effectiveness of hepatitis C virus treatment suggest the possibility of global viral eradication. To achieve this goal, however, treatment must be extended to marginalized and disenfranchised populations, such as persons with substance use disorders. As a consequence of the highest hepatitis C virus incidence and prevalence, persons with substance use disorders, especially those who engage in unsafe injection practices, continue to serve as reservoirs for hepatitis C virus transmission.

Recently, the concept of the use of antiviral therapy as a method to prevent hepatitis C virus transmission among persons who inject drugs has been promoted.^{126–128} Even a small increase in the number of treated persons who inject drugs can result in substantial reductions in hepatitis C virus transmission. It has been estimated that a 12-week interferon-free, oral direct-acting antiviral regimen could reduce hepatitis C virus prevalence by 26% to 75% within 15 years depending upon the number of persons who inject drugs treated annually.¹²⁹ The same principle of treatment as prevention in the epidemic among HIV-infected men who have sex with men has been considered in similar mathematical modeling in England, suggesting this would be an important intervention.¹³⁰ On its face, treatment as prevention as the sole intervention to eliminate hepatitis C virus would be unprecedented in the history of infectious diseases, where prevention (in the form of vaccine) has been the only method of eradication to date. In line with this historical observation, a different model of the epidemic in Switzerland showed that significant behavioral

changes must be effected before even a decrease in incidence, let alone prevalence, can be accomplished.¹³¹ These same factors are likely to be important in considering hepatitis C virus prevention or even elimination among persons who inject drugs. The observation that hepatitis C virus phylogeny is associated with injection networks and that injecting networks substantially impact transmission suggest that targeting treatment to the heaviest injectors and their immediate contacts may be the most cost-effective strategy to reduce viral transmission.^{132–134} However, challenges remain in the provision of hepatitis C virus treatment to persons who inject drugs (as below) and in minimizing the potential for reinfection among those who continue to inject.¹²⁹

MODELS OF HEPATITIS C VIRUS TREATMENT DELIVERY TO MARGINALIZED AND DISENFRANCHISED PERSONS WITH SUBSTANCE USE DISORDERS

Substance users are a heterogeneous population with different patterns of drug use, frequency, and engagement in the health care system. These variables are important determinants of this population's engagement in hepatitis C virus management. The substance use paradigm includes users who continue to actively inject, those in early recovery, and those who have a remote history of substance use and who may or may not currently receive treatment for addiction. The frequency of drug use is another consideration, and it can range from active daily use to periods of abstinence with persistent risk of relapse. For substance users in recovery, the type and level of support services provided among substance use treatment programs is another important determinant of engagement in hepatitis C virus management. Multidisciplinary programs offering primary care, behavioral medicine, and social services are more likely to be equipped for hepatitis C virus

screening and management.¹³⁵ Therefore, obstacles to engagement into hepatitis C virus care and treatment as well as approaches to overcome these obstacles will vary for different subpopulations of persons with substance use disorders.

Opportunities to interact with different populations of persons with substance use disorders may vary based on local programs and resources, which may include opioid replacement therapy clinics, needle exchange programs, safe injection facilities, detoxification centers, correctional facilities, or federally qualified health centers (Fig. 1). Efforts to provide outreach to and to deliver integrated care focusing on hepatitis C virus prevention, screening, and treatment directly within these locations may be

critical in establishing access to larger numbers of persons with substance use disorders and to achieve a greater impact in reducing the prevalence of hepatitis C virus infection. Medical and behavioral approaches to engage persons with substance use disorders into hepatitis C virus care are summarized below (Table 3).

Referral to Specialty Care

Although numerous interventions have been used to engage substance users into treatment, most of them fall into 2 distinct categories: referral to a liver or infectious diseases specialist or integration of hepatitis C virus care with substance use treatment. Referral, the most frequently used strategy for hepatitis C virus treatment of persons with substance use disorders, is inefficient

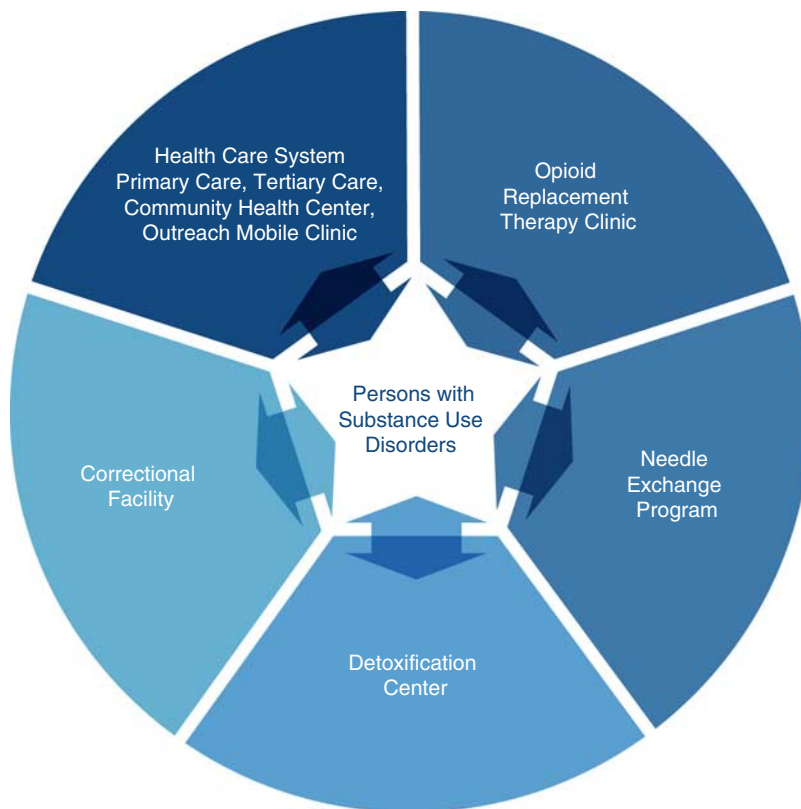


FIGURE 1. Venues providing access to different populations of persons with substance use disorders. Efforts to provide care to populations of persons with substance use disorders may frequently require expansion beyond the conventional health care setting. The ability to access persons with substance use disorders directly at venues where they habitually congregate or receive treatment could be a means to overcome the stigmatization associated with hepatitis C virus infection and the reluctance to seek care within a conventional health care setting. These alternative sites vary greatly in terms of accessibility and degree of health care services administered and in many cases may require outreach or integration of the hepatitis C virus provider into the particular setting.

TABLE 3. Medical and Behavioral Models of Care

	Intervention Description	Barriers	Relevance to DAA
Medical			
Specialty care	PWSUD referral to health care provider	PWSUD reluctance to obtain care in conventional health care venue	Third-party payers frequently restrict DAA prescription to liver specialists. Specialists may not be comfortable treating PWSUD
Integrated care	Provider establishes care to PWSUD onsite	Resources to establish clinic or practice in offsite location	Limited number of specialists may be willing to practice in substance use treatment facilities
Virtual integration	Telemedicine	Infrastructure, resources, perception of lower quality of care	Facilitated by point-of-care diagnostics and easy administration of all-oral DAA regimens
Behavioral			
Education	HCV-related education provided to patients	Requires educational materials and resources for onsite teaching	Potential to clarify misconceptions regarding HCV therapy; emphasize elimination of interferon
Case management	Assessment, planning, facilitation, care coordination, and advocacy to obtain services for patients	Availability and support from case workers, social workers, and ancillary staff	Potential to facilitate linkage to care and procurement of DAA-based therapy
Patient and peer navigation	Guidance provided to patient by designated patient volunteers or health care personnel	Requires advocacy and recruitment of volunteers	Potential to facilitate linkage to care and in dispelling HCV therapy misconceptions

DAA indicates direct-acting antiviral; HCV, hepatitis C virus; PWSUD, persons with substance use disorders.

and somewhat ineffective due to a variety of reasons including persons with substance use disorders mistrust of the health care system and stigmatization encountered in conventional health care settings. As a result, less than one third of persons with substance use disorders referred to specialty clinics appear for appointments, and <20% of those evaluated for treatment eligibility actually initiates antiviral therapy.^{112,136–138}

Integrated Care

When treatment for substance use disorders and hepatitis C virus care are colocalized, studies have shown that persons with substance use disorders are more likely to pursue an hepatitis C virus evaluation.^{139–142} To foster adaptation of colocalized care, a variety of integrated

medical care models have been developed.¹⁴³ An integrated, multidisciplinary care model, which typically emanates from substance use treatment facilities, has been shown to be extremely effective.¹⁴⁴ Similar models have also been developed in prison-based settings, community health centers, and general medical practices. These models utilize members from a variety of health care specialties who are able to address the diverse medical issues affecting persons with substance use disorders. In addition, the majority of opioid replacement therapy programs have psychosocial support with counselors, psychologists, psychiatrists, patient navigators, and peer support programs that may enhance medication adherence, thereby increasing the likelihood of achieving viral eradication. Furthermore, the daily

administration of methadone offers an opportunity for modified directly observed hepatitis C virus therapy, which has been shown to be effective in improving therapeutic outcomes.¹⁴⁵ Other colocalized care models include an internist-addiction medicine specialist from an opioid replacement therapy program embedded in the viral hepatitis clinic or hepatitis C virus treatment initiation by an addiction medicine specialist onsite in the opioid replacement therapy program.^{146,147}

The development of direct-acting antiviral-based therapy and the provision of noninvasive alternatives to liver biopsy have suggested that treatment might be delivered onsite in the opioid replacement therapy program. In the United States, current requirements for obtaining third-party payer approval for direct-acting antivirals require quantitative hepatitis C virus RNA, hepatitis C virus genotype, and an assessment of hepatic fibrosis. Although the liver biopsy has been considered the gold standard for the assessment of hepatic fibrosis and steatosis, several noninvasive indices have been developed over the past decade. Fibrosure (Laboratory Corporation of America) is one of the most widely utilized indices, especially in the clinical care of patients. Fibrosure is performed on peripheral blood, can be drawn at the point-of-care, and can be used as a replacement for the biopsy. Another noninvasive liver fibrosis technique is vibration-controlled transient elastography, a modified ultrasound-based technique that assesses liver stiffness. Vibration-controlled transient elastography can reliably identify cirrhosis with an area under the receiver operator characteristic curve of 90 or higher, and it provides an estimate of liver stiffness ranging from 1.5 to 75 kPa. Results <5 kPa are considered normal and values >12.7 kPa indicate cirrhosis.¹⁴⁸ Vibration-controlled transient elastography has also recently been proposed as an alternative methodology to assess hepatic steatosis,¹⁴⁹ especially after the development of the controlled attenuation parameter technology.^{150,151} A recent meta-analysis of 11 studies comprising 13 cohorts reported that controlled attenuation parameter has reasonable sensitivity and specificity for

the detection of steatosis grades 1 to 3.¹⁵² A portable vibration-controlled transient elastography machine has recently been approved in the United States that could easily permit onsite assessment of hepatic fibrosis within the opioid replacement therapy program. Thus, liver biopsy is no longer required; liver histology assessments using either blood or vibration-controlled transient elastography can both be performed at the point-of-care.

Virtual Integration

Although colocalized care models have been shown to be effective, few opioid replacement therapy or other types of substance use treatment facilities have the capability to offer hepatitis C virus management onsite.^{153,154} A survey of 269 US substance use treatment facilities found that only ~50% had hepatitis C virus-related medical history and physical examination services, whereas only 30% offered hepatitis C virus treatment.¹⁵⁵ Similar results have been obtained in a nationwide survey of programs offering hepatitis C virus screening.⁶³ A telehealth approach may be an alternative modality to deliver hepatitis C virus treatment services to opioid replacement therapy programs.¹⁵⁶

Telehealth and Telemedicine

Telehealth and telemedicine are a growing field of patient care that involves the use of telecommunication devices to treat patients across space and/or time (Fig. 2A). Telehealth is a more general term than telemedicine, which is specifically defined as synchronous interaction between a patient and physician via a telecommunications device across distance. In contrast, telehealth is a more broadly defined general concept and includes other forms of telecommunication device enabled, patient-physician interactions such as store and forward systems (ie, transmission of videos and digital images such as x-rays and photos through a secure electronic communications environment), remote patient monitoring (ie, personal health and medical data collection from an individual in one location and transferred to a provider in a

different location), and mobile health (ie, certain smartphone apps, Fitbit, etc.).¹⁵⁷

Telemedicine seems to be a promising alternative for health care delivery that is positioned to grow considerably in the next decade.¹⁵⁸ Potential benefits from increased use of telemedicine can result from cost savings, increased patient satisfaction, and increased access to care for difficult-to-engage patient populations. In addition, increased ease of and expanded access for providers who care for these populations is an additional benefit that can accrue. Primary patient populations that could benefit from telemedicine are those who are medically disenfranchised, that is, those who reside in medically isolated locales, rural communities, and those whose treatment and care regimens adapt well to the telemedicine model such as treatment and management of long-term, chronic conditions in which specialty knowledge can be helpful, such as chronic hepatitis C virus.

We propose that persons with substance use disorders and persons who inject drugs with chronic hepatitis C virus infection might also benefit from telemedicine-based treatment of the infection. Colocating hepatitis C virus telemedicine-based treatment in opioid replacement therapy programs has been shown in a pilot study to result in high levels of patient satisfaction and adherence to hepatitis C virus treatment.^{159,160} In contrast, potential limitations of the telemedicine-based treatment model are infrastructural limitations in the opioid replacement therapy program and lack of broadband connectivity. However, as the technology improves and broadband coverage increases, such as through innovative programs calling for entire New York State coverage by broadband by 2018,¹⁶¹ telemedicine coverage will likely become a more established means of health care delivery.

Additional largely regulatory concerns are: (1) differences in third-party reimbursement for telemedicine services depending upon geography and payer, (2) variations in state-mandated medical license requirements and potential additional certifications required for out-of-state physicians consulting on

patients across state boundaries, and (3) concerns about the quality and security of the telemedicine-based care.¹⁶²

SUPPORT SERVICES TO PROMOTE PERSONS WITH SUBSTANCE USE DISORDERS ENGAGEMENT INTO CARE FOR HEPATITIS C VIRUS INFECTION

As persons with substance use disorders frequently lack knowledge about hepatitis C virus and have coexisting psychosocial and economic difficulties, educational programs and medical interventions with behavioral components may be required to address issues specific to persons with substance use disorders engagement into hepatitis C virus care. Behavioral interventions, such as educational programs, case management, and peer and patient navigators and could also motivate hepatitis C virus screening, enrollment, and retention in hepatitis C virus care among substance users (Fig. 2B).

Educational Interventions

The inclusion of support systems for hepatitis C virus treatment is critical to optimizing efforts to achieve greater awareness, education, and active participation by persons with substance use disorders. Hepatitis C virus-related education has been shown to promote patient engagement into hepatitis C virus care through increased screening, vaccination, and treatment adherence.¹⁶³ Regular educational interactions delivered by physicians, physician-extenders, counselors, or other health care personnel during hepatitis C virus treatment have played an important role in maximizing treatment adherence. Topics that might be important for persons with substance use disorders are the importance of hepatitis C virus screening, the significance of hepatitis C virus RNA positivity, the long-term complications of chronic infection, and the availability of curative treatment regimens. Educational programs might also specifically target active injectors, promote harm reduction, and facilitate persons with substance use disorders entry into multidisciplinary programs for treatment of both substance use and hepatitis C virus.

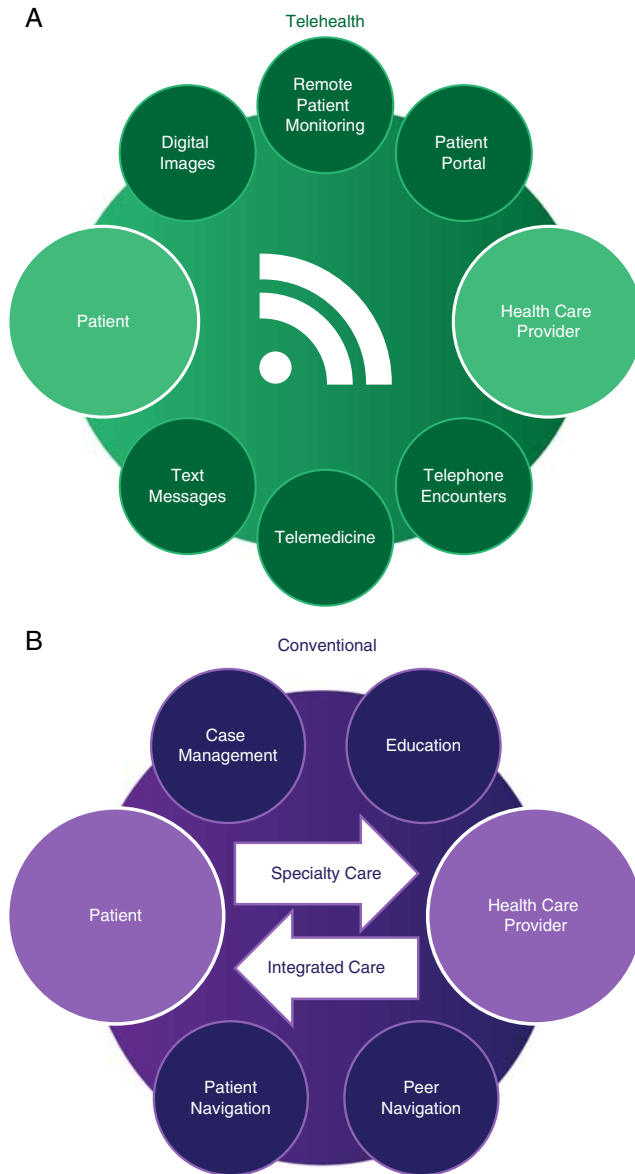


FIGURE 2. Models of care in telehealth (A) and conventional settings (B). A, In a telehealth model, the patient and the health care provider are each geographically separated and connected using technology, such as through the use of text messages, telephones, or telemedicine (ie, 2-way videoconferencing between a patient and a physician each located remotely). Technology can also be used to transmit data from a physician to a patient, vice versa, or between physicians. For example, a patient portal enables patients to view their test results, remote patient monitoring permits results (ie, glucose or blood oxygenation) to be transmitted from a patient to a physician, and digital images can be transmitted for remote review by a radiologist. B, In conventional health care settings, persons with substance use disorders are typically referred to a health care provider to obtain treatment for hepatitis C virus infection. Alternatively, a health care provider could engage directly with persons with substance use disorders through an integrated care model in which hepatitis C virus care is delivered directly in the venue that offers treatment for substance use. Case management, patient education, peer navigation, and patient navigation are important interventions that can support persons with substance use disorders access to care and adherence.

Case Management

Case management involves a collaborative process of assessment, planning, facilitation, care coordination, and advocacy in an effort to obtain services to meet an individual's health needs. As substance users may face limited economic and social support, case management may play a central role in the coordination of care within a complex health care system and could facilitate hepatitis C virus screening as well as linkage to care for substance users. Case management could also be instrumental in the acquisition of hepatitis C virus medications for substance users through providing assistance with obtaining health insurance and enrollment in medication reimbursement programs. Once antiviral therapy is initiated, case managers can also provide guidance with maintaining adherence to the treatment regimen and consistent follow-up with provider appointments.

The impact of care coordination can be substantial in establishing linkage to care and optimizing the potential for delivery of care for hepatitis C virus infection care to persons with substance use disorders. A prospective randomized-controlled trial of patients attending opioid replacement therapy clinics found that individuals randomized to an intervention arm in which they received onsite screening, education, counseling, and case management had a significantly greater likelihood of follow-up for an evaluation for hepatitis C virus infection, which occurred in 65% in contrast with only 37% of controls.¹⁶⁴ Efforts to target populations at risk within community health centers and needle exchange programs involving onsite rapid hepatitis C virus screening tests with immediate blood draws for hepatitis C virus RNA and linkage to care with patient navigators, have reported follow-up for an evaluation and care in the majority of hepatitis C virus-positive individuals screened.¹⁶⁵

Patient and Peer Navigation

Patient navigation promotes initiation, linkage, and retention in medical care through the guidance and support of health care personnel. Peer navigation involves patients, many of whom

may have been treated for hepatitis C virus infection, providing guidance regarding hepatitis C virus management to their peers. Both patient and peer navigation aim to facilitate patient access to and transition into the health care system so that they receive standard of care treatment in a timely and efficient manner.¹⁶⁶ Navigators are similar to case managers, except that the navigator's responsibilities are more narrowly defined as a result of focusing exclusively on health care processes.¹⁶⁷

The benefits of navigation include improvements in access to care, increased adherence to care programs, increased independence, reduced social isolation, improved quality of care, and increased patient satisfaction.^{168,169} In addition, navigation can lead to a reduction in overall health care costs and fewer hospitalizations. As navigators are frequently laypeople rather than licensed medical professionals, the cost is usually modest in comparison with other interventions.¹⁷⁰ Health navigation is most effective when targeted to patient groups, such as substance users, who are not highly engaged in medical care due to perceived or actual barriers.^{167,170,171}

CONCLUSIONS

Recent advances in hepatitis C virus therapy have revolutionized treatment approaches to marginalized and disenfranchised populations such as persons with substance use disorders. Many previously existent barriers to engagement into hepatitis C virus care among this population were attributed to interferon; interferon elimination from the therapeutic regimen has been enthusiastically celebrated among this population. Simultaneously, however, new obstacles to widespread provision of direct-acting antivirals have emerged, principally related to the cost of medications.

To achieve the goal of universal elimination of hepatitis C virus infection or, at a minimum, its elimination from developed countries, new initiatives are required to engage substance users into therapy for hepatitis C virus infection. The combination of medical interventions,

such as colocalized treatment for hepatitis C virus and substance use, with behavioral interventions, such as case management, peer navigation, and education, will likely have the greatest effect at engaging the largest number of persons with substance use disorders into therapy for hepatitis C virus infection. To halt virus transmission, harm reduction techniques, such as needle exchange programs, and opioid replacement therapy, must also be included. Expansion of treatment availability to venues involved in provision of medical care to persons with substance use disorders, such as substances use treatment facilities, correctional facilities, and psychiatric institutions, could substantially increase the number of treated individuals. Broad collaboration between specialists of diverse fields is required to increase persons with substance use disorders access to health care and to develop novel care models to increase direct-acting antiviral-based treatment uptake and adherence. By utilizing multicomponent interventions, substance users can likely be successfully and fully engaged into care for hepatitis C virus infection.

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CME ACTIVITY

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<http://www.chronicliverdisease.org/TripleE>

Target Audience

This educational program is targeted at physicians and other healthcare providers who specialize in the management of patients with addictive disorders.

Learning Objectives

Upon completion of this activity, the participants should be better able to:

- Review the importance of Hepatitis C screening, diagnosis, and linkage to care
- Describe new developments in HCV that have eliminated many of the previous barriers to pursuit of HCV therapy in individuals with substance use disorders
- Develop strategies for the engagement of patients with substance use disorders into HCV care.

Accreditation Statement

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the joint providership of the Annenberg Center for Health Sciences at Eisenhower and the Chronic Liver Disease Foundation (CLDF). The Annenberg Center for Health Sciences at Eisenhower is accredited by the ACCME to provide continuing medical education for physicians.

The Annenberg Center for Health Sciences at Eisenhower designates this activity for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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