



The Key to Hepatitis C Elimination: Eradication from Persons with Substance Use Disorders



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In this Issue...

In this issue, Dr. Andrew Talal from the University at Buffalo reviews recent articles that describe how the conventional approaches toward HCV management among potentially marginalized and disenfranchised populations, such as low-income individuals or persons with substance use disorders, have failed to adequately engage these population subgroups into HCV care. This gap in care calls for new approaches to both engage substance users into HCV management as well as to improve primary care knowledge about appropriate treatment.

Through expansion of screening, treatment, and educational programs targeted to populations with multiple risk factors for HCV, all clinicians can more effectively work toward eliminating this disease in the United States.

Volume 5 Issue 5

Program Information

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Length of Activity

- 1.0 hour Physicians
- 1.0 hour Nurses

Launch Date

July 13, 2017

Expiration Date

July 12, 2019

LEARNING OBJECTIVES

- Recognize that HCV screening and linkage to care programs should target venues (ie, health care settings, substance use treatment facilities, needle exchange programs) where large numbers of HCV seropositive individuals congregate.
- Explain why the clinical outcomes of HCV make it crucially important for providers and patients to adhere to HCV screening recommendations.
- Describe the factors associated with need for further HCV evaluation and retention in HCV management.

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GUEST AUTHOR OF THE MONTH

Commentary & Reviews

Guest Faculty Disclosure

Dr. Talal has disclosed that he has received research funding from Abbott Laboratories, AbbVie, Inc., Gilead Sciences, Inc., and Merck & Co., Inc., and he has served as a consultant for Abbott Laboratories and Merck & Co., Inc.



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Unlabeled/Unapproved uses

Dr. Talal has indicated that there will be no references to unlabeled or unapproved uses of drugs or products.

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KEY TAKEAWAYS

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The treatment cascade that has typically been recommended as a guide for hepatitis C virus (HCV) therapy fails at several points when applied to persons with substance use disorders (PWSUD),¹ who account for 68% to 80% of infections in developed countries.² Despite almost 20 years of recommendations that persons who inject drugs (PWID) should be screened for HCV, many remain unaware that they are infected. Indeed, approximately one half of those infected with HCV are unaware of their infection status.³ To facilitate HCV screening — and with the observation that 75% of the estimated 2.7 million HCV-infected individuals who are unaware of their infection status were born between 1945 and 1965⁴ — the Centers for Disease Control and Prevention (CDC) and the US Preventive Services Task Force (USPSTF) promoted the recommendation that all individuals in that birth cohort should have an HCV antibody test at least once.^{5,6}

Two of the papers (Turner et al, Sarkar et al) reviewed in this issue found that HCV detection rates can be much higher by targeting screening at venues where those with common HCV acquisition risk factors obtain health care — in these cases Safety Net and Veterans Administration hospitals, respectively. Besides both investigations identifying factors such as low income being significantly associated with HCV acquisition, 33% of patients in the Safety Net hospital had advanced fibrosis or cirrhosis. The rate was considerably lower in the VA system.

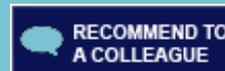
Continuing on the theme of screening for HCV to identify those who might inadvertently have advanced disease, the paper by Udompap and colleagues illustrates that cirrhosis is equally common in those who are aware and unaware of their infection status. Using National Health and Nutrition Examination Survey (NHANES) data, it also shows that while the prevalence of HCV has declined during the past 15 years, the prevalence of those with cirrhosis has been increasing during the same period. During the last time period (2007-2012) included in the report, an estimated 1.0% of the US population was HCV infected and 17% had cirrhosis. Early detection and diagnosis of HCV permits therapeutic interventions to potentially avoid development of cirrhosis and reduce the risk of hepatocellular carcinoma (HCC). This article suggests that many of those receiving a diagnosis of cirrhosis were not previously aware of an HCV diagnosis.

If HCV is not diagnosed and treated prior to development of cirrhosis, then HCC surveillance is important for early detection. Ultimately, both screening for HCV infection and HCC surveillance require that primary care physicians be knowledgeable about the disease, its manifestations, and methods of liver cancer surveillance. PCPs also have to be willing to put their knowledge into practice to effect change. Some of the barriers toward screening are included in the (reviewed) paper by Dalton-Fitzgerald and colleagues.

Equally important for primary care is the recognition of the populations that do *not* require screening. The paper by Bulteel et al discusses the factors associated with spontaneous resolution of HCV infection. These individuals can be identified by HCV seropositivity and HCV RNA negativity. Misunderstanding the parameters for identification of spontaneous resolvers is a frequent reason for referral to a hepatologist or infectious diseases physician. The recent implementation of reflex HCV RNA testing in HCV seropositivity by major commercial laboratories should increase the proper identification of these patients.

Finally, once we are able to successfully identify individuals with active HCV infection who are noncirrhotic and who do not have HCC, how can we efficiently link them to care? The conclusion of the reviewed paper by Norton and colleagues, and one that our own research team is actively pursuing, promotes HCV care integration into treatment for addiction. This work builds on our prior meta-analysis that showed that treatment of addiction leads to higher rates of HCV treatment completion.⁷ In this study by Norton, the authors found that retention in care for addiction with buprenorphine for at least six months led to increased HCV care rates among people with substance use disorders (PWSUD).

The laudable goal of global HCV elimination will not be possible without eliminating the virus from the population group with the highest prevalence and incidence of HCV infection: PWSUD. The traditional treatment cascade has failed to achieve high rates of viral elimination in this population. Clearly, new approaches are needed; integration of HCV care into addiction treatment has been recommended for several years but has been difficult to achieve. The development of novel telehealth approaches, together with the direct-acting



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antivirals for HCV, are definite facilitators of the process. Now is the time for practical studies to dictate the most effective paths forward to eliminating HCV in the PWSUD population.

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HCV Diagnosis Among High-risk Populations (1): Safety Net Hospitals

Turner BJ, Taylor BS, Hanson J, et al. High priority for hepatitis C screening in safety net hospitals: Results from a prospective cohort of 4582 hospitalized baby boomers. *Hepatology*. Nov 2015;62(5):1388-1395.



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In 2012 and 2013, the USPSTF and the CDC, respectively, recommended a one-time HCV antibody test as a screen among those born between 1945 and 1965.^{1,2} Consequently, birth cohort screening replaced risk-factor based screening since the latter was shown to be ineffective for two important reasons. First, many people are unaware of or unwilling to report HCV risk factors to their PCP. Second, even patients whose risk has been identified often remain unscreened.

Birth cohort screening was proposed as a method to identify a large percentage of those unaware of their HCV infection status. Specifically, those born between 1945 and 1965 were thought to account for 75% of the estimated 2.7 million HCV-infected individuals in the United States,³ of whom 50% are estimated to be unaware of the infection.⁴ Implementation of this recommendation, however, has been difficult to achieve for a variety of reasons, largely because of lack of uptake by primary care providers in the US. Since HCV prevalence has been shown to be nearly four times greater in persons with household incomes below the federal poverty level,⁵ prioritization for implementation of baby boomer screening recommendations should be given to health care settings that cater to largely minority populations. An estimated 800 safety net hospitals in the United States treat a disproportionately higher percentage of low-income individuals and Medicaid enrollees.⁶ These settings also frequently provide primary care services for low-income individuals who frequently have poor access to a PCP. This study evaluated HCV prevalence, screening, and linkage to care among a large safety net hospital serving South Texas.

All patients born between 1945 and 1965 who were admitted to University Hospital in Bexar County, Texas, between December 1, 2012 and August 30, 2014 were followed to assess subsequent evaluation of liver disease through June 1, 2015. Patients with unstable mental health conditions or poor prognoses (ie, metastatic cancer) were excluded. HCV screening



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was implemented as a result of an algorithm applied to the electronic medical record to assess screening within seven years prior to admission. HCV seropositive individuals had reflex HCV RNA testing, and HCV RNA-positive individuals had a follow-up plan developed with the assistance of a community health worker. The authors also assessed the presence of advanced fibrosis as determined using a combination of noninvasive tests (FIB[*fibrosis*]-4 and imaging).

During the 21-month study period, 9037 patients who were members of the birth cohort were admitted. Mean age was 56.6 years, 44.7% were women, 59.1% were of Hispanic ethnicity, and 7.8% were African-American. Of those, 43.6% were either HCV seropositive (10.9%) or had been tested previously (32.7%). Of the remaining patients, 4582 (90%) received anti-HCV testing; the majority of those not tested were excluded from the study because of unstable mental health or comorbid conditions with a poor prognosis. HCV RNA testing was performed on 91% of HCV seropositive individuals.

Of screened patients, 316 (6.9%) were HCV seropositive, and the odds of HCV seropositivity were 25% higher among uninsured compared with insured individuals. Of seropositive individuals with HCV RNA testing, 175 (61%) were viremic (comprising 3.8% overall in the cohort); 148 (84.6%) received follow-up care with noninvasive staging. Of those, 50 (33%) patients had advanced fibrosis or cirrhosis. Hispanic ancestry was associated with an odds ratio of 3.2 of advanced fibrosis/cirrhosis vs non-Hispanic whites/Asians. Other factors significantly associated with advanced fibrosis/cirrhosis included obesity, alcohol abuse/dependence, and lack of insurance.

In conclusion, this low-income, largely minority population had HCV seroprevalence twice that obtained in a representative sample of the US population. Very high seropositivity rates have also been reported by other investigators.^{7,8} One third of those with noninvasive testing available had advanced fibrosis/cirrhosis. These data provide convincing evidence that screening should target low-income populations who likely have a high prevalence of advanced fibrosis/cirrhosis.

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HCV Diagnosis Among High-Risk Populations (2): VA Hospitals

Sarkar S, Esserman DA, Skanderson M, Levin FL, Justice AC, Lim JK. Disparities in hepatitis C testing in U.S. veterans born 1945-1965. *J Hepatol.* Aug 2016;65(2):259-265.

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The United States Veterans Administration (VA) is the largest integrated health care network in the country. Based on cross-sectional data, the HCV prevalence at VA facilities is threefold that encountered in the general population.^{1,2} The goal of this investigation was to identify predictors of HCV testing, identify targets of intervention, and refine the testing strategy. The study was conducted using data from the VA Cooperative Data Warehouse, a repository of over eight million records (compiled since October 1, 1999) of data from veterans with at least one outpatient visit. Veterans seeking care between January 1, 2000 and December 31, 2013 were the target population for the present study. To be included in the study, veterans had to have had two visits to a VA facility and had to have been born in the 1945-1965 interval. The FIB-4 and aspartate aminotransferase to platelet ratio index (APRI) were used as surrogates for fibrosis assessment.^{3,4}

A total of 6,669,388 veterans born between 1945 and 1965 presented at the VA between 2000 and 2013. Among them, 4,221,135 veterans had two or more visits — these defined the study population. Of those individuals, 2,139,935 (51%) were tested for HCV as of December 31, 2013. As expected, the cohort was predominantly male (84.7%), white (54.7%), HIV (99.4%) and hepatitis B virus (HBV) (90.9%) seronegative. Overall, 8.1% were HCV antibody positive and 5.4% were HCV RNA positive. At least 2.4% to 4.4% of veterans had advanced fibrosis/cirrhosis.

Individuals born between 1950 and 1959 had the highest seropositivity and RNA positivity rates. Black patients had higher sero- and RNA-positivity rates than either Caucasian or Asian patients. Younger patients (born 1960 to 1965), as well as all female patients, had lower odds of being tested for HCV and of being HCV RNA positive. Veterans with alanine aminotransferase (ALT) > 40, FIB-4 (based on age, ALT and AST level, and platelet count) > 3.25, APRI (AST-platelet ratio index) > 1.5, or who were HIV or HBV positive, were at higher odds of being tested and found to be HCV RNA positive.

The study also provides important information on the determinants of screening at individual centers. For example, urban (53%) centers conducted more screening than rural (47%) centers. Complexity of the care provided at centers also played a role in screening activities. The centers in the lowest quartile of HCV testing (less than 43% HCV testing rate) were more likely to be rural, of lower complexity, and have a lower volume of patients.

This study is important because it documents a higher rate of HCV infection in the VA system compared to its occurrence in the general US population. It also documents the extent of advanced liver disease and cirrhosis in this population. An important limitation is that 60% of veterans are not enrolled in the VA network, and therefore these results may not be generalizable to the overall US veteran population. Based on the differences in HCV screening rates between different VA centers, regional or center-specific educational interventions may be required.

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Unawareness of HCV Infection and Cirrhosis

Udompap P, Mannalithara A, Heo NY, Kim D, Kim WR. Increasing prevalence of cirrhosis among U.S. adults aware or unaware of their chronic hepatitis C virus infection. *J Hepatol*. May 2016;64(5):1027-1032.



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The major point of this work is that cirrhosis secondary to HCV infection is the major etiology leading to end-stage liver disease, HCC, and death. HCV-related deaths have surpassed those from HIV,¹ and mortality due to HCV is expected to triple by 2020 (compared to 2010 rates).² The asymptomatic nature of HCV-related cirrhosis is a major difficulty in making the diagnosis. This article addresses the prevalence of cirrhosis in the US, specifically its prevalence in individuals with undiagnosed HCV.

For this study, the authors evaluated data collected as part of NHANES and divided the data into three eras: Era 1 (1988-1994), Era 2 (1999-2006), and Era 3 (2007-2012). NHANES participants with detectable serum levels of HCV RNA, platelets, alanine aminotransferase, and aspartate aminotransferase were included in the study. Those without available laboratory values were excluded. To assess those who had cirrhosis, the authors used the APRI and FIB-4 scores. Cirrhosis was defined by APRI > 2.0 and advanced fibrosis/cirrhosis by a FIB-4 score > 3.25.

A total of 52,644 NHANES participants at least 20 years of age underwent laboratory testing. Of those, 49,429 (93.9%) had available HCV serologic results; 1047 (2.1%) were HCV seropositive, 736 (70.3%) were HCV RNA positive, and 725 (98.5%) had complete laboratory values that permitted calculation of APRI and FIB-4 scores. Several informative observations can be derived from this dataset:

- A trend toward decreasing HCV infection prevalence was observed with extrapolation by era to the adult US population: Era 1 — 1.5% (2.7 million individuals); Era 2 — 1.2% (2.5 million individuals); Era 3 — 1.0% (2.2 million individuals).
- The proportion of individuals with a high probability for cirrhosis (assessed using the AST-platelet ratio index, APRI) increased: Era 1 — 6.6% (170,000 individuals); Era 2 — 7.6% (189,000 individuals); Era 3 — 17.0% (370,000 individuals).
- Similar results were obtained when advanced fibrosis was assessed using the FIB-4 score.
- Age, diabetes, and obesity were significant predictors of cirrhosis in a multivariate logistic regression model.
- Prevalence of cirrhosis did not differ significantly among those aware or unaware of their HCV diagnoses (11.2% vs 10.8%, respectively).

In conclusion, the authors found that the overall HCV prevalence decreased over time, while the prevalence of cirrhosis more than doubled, reaching 17% (or 26% including the upper limit of the confidence interval) during the last time period. Cirrhosis prevalence was equivalent among those who were aware or unaware of their HCV diagnosis. These findings indicate the need for targeted interventions to identify those with HCV infection, since at least 200,000 cirrhotic Americans have not been screened for HCV. The number is likely higher, since NHANES excluded individuals with high HCV prevalence, such as those who are homeless or incarcerated. An HCV diagnosis could also provide an opportunity for appropriate individual counseling of factors associated with fibrosis progression, including alcohol consumption and diabetes and obesity management.

Data from other population-based longitudinal reports (ie, Veterans Administration) also illustrated an increase in HCV-related cirrhosis prevalence, from 9% in 1996 to 18.5% in 2006.³ Limitations of the study were lack of treatment information and reliance on noninvasive measures of hepatic fibrosis that may not entirely reflect histologic changes.

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If HCC Develops, How Is It Detected?

Dalton-Fitzgerald E, Tiro J, Kandunoori P, Halm EA, Yopp A, Singal AG. Practice patterns and attitudes of primary care providers and barriers to surveillance of hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol*. Apr 2015;13(4):791-798.



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HCC is the fastest-growing cause of cancer-related deaths in the United States,¹ with a dismal five-year survival rate of 12%.² The only population subgroup in whom HCC is potentially curable are those in whom it is detected early, who have a chance to receive potentially curative therapy including liver transplantation, surgical resection, or local ablation therapy. In patients with early HCC, five-year survival rates are near 70%. Even in cirrhotic individuals who eradicate HCV, HCC continues to develop at a rate of 1% per year.³ While modest evidence obtained from randomized controlled trials has shown the benefit of HCC surveillance, the strongest evidence has come from observational studies that show a survival advantage for screening.⁴ Unfortunately, however, less than 20% of cirrhotic patients in the United States undergo HCC surveillance,⁵ despite professional society guidelines from the American Association for the Study of Liver Disease (AASLD) and the National Comprehensive Cancer Network that recommend surveillance using ultrasound, with or without alpha -fetoprotein levels (AFP), at six-month intervals in cirrhotic individuals.⁶ Rates of compliance with guideline recommendations for screening every six months are less than 5%.⁵ This study focused on the role of providers in the recommendation to undergo HCC surveillance, which is one of the strongest predictors for its fulfillment.⁷

Screening for HCC is extremely important because of the increase in prevalence as a result of aging of the birth cohort. As indicated in the paper by Udompap et al (reviewed elsewhere in this issue) many cirrhotic individuals are unaware that they are infected with HCV. While early HCV diagnosis and linkage to care are the primary strategies to prevent HCC development, it is important that PCPs implement HCC surveillance for their cirrhotic patients. The need for HCC surveillance does not appear to diminish once HCV is eradicated; posteradication HCC surveillance should also be pursued among cirrhotic individuals.

This study focused on PCP knowledge about and adherence to HCC screening recommendations. Poor provider knowledge or negative attitudes about surveillance may affect PCP recommendations. In this study of 131 PCPs (general practice, family practice, and general internal medicine) from a safety net health care system, physicians who indicated treatment of at least one cirrhotic patient per week were asked to complete a survey assessing their knowledge of HCC screening practices. Providers were asked to report HCC surveillance from their own practices and also to judge surveillance strategies based on clinical vignettes.

A total of 77 of 131 (59%) responded to the survey, with 90% reporting that HCC surveillance should be the responsibility of both PCP and gastroenterologists. Self-reported annual ultrasound surveillance rates were 65% among cirrhotic individuals, although

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median biannual rates were only 15%. Several misconceptions regarding HCC surveillance exist among this cohort of PCP, including that only one-half (52%) believed that HCC surveillance reduces all-cause mortality. Significant knowledge gaps also exist in the screening modality: 45% believed that clinical examination, 59% that liver enzyme testing, and 89% that AFP levels were effective HCC surveillance tests. Identified barriers to effective screening included 68% who reported not being up to date with current guidelines, 56% who reported difficulty with effective patient communication about screening, and 52% who reported having more important issues to manage in the clinic.

The clinical vignettes provided insight into the PCP view of the correct surveillance techniques in particular situations. Based on cases presented, the only significant predictor of surveillance underuse was the belief that ultrasound and AFP were ineffective at reducing HCC-related mortality. In contrast, 77% indicated that surveillance should be performed in noncirrhotic individuals.

This study has important implications for HCC surveillance since 60% to 80% of cirrhotic individuals in the United States are followed by PCPs.⁸ A particularly important factor in screening is provider recommendation. This study indicates that targeted education to primary care on HCC, especially in the area of new therapeutic modalities, is needed. Decision support tools integrated into the electronic health record are an additional strategy that can be employed to increase HCC surveillance rates.

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Factors Predicting Spontaneous Clearance in Chronic HCV Infection

Bulteel N, Partha Sarathy P, Forrest E, et al. Factors associated with spontaneous clearance of chronic hepatitis C virus infection. *J Hepatol*. Aug 2016;65(2):266-272.



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HCV exposure can result in antibody production, which serves as a marker of prior infection. However, unlike in other viral infections, when exposed to HCV during the **acute** phase of the infection, up to 25% of individuals spontaneously clear the virus. These individuals will not have detectable HCV RNA circulating in the blood, indicating that they do not have active infection. Factors that have been associated with HCV clearance during the acute phase of the infection include gender, immune response, IL28B polymorphisms, HCV genotype, and quasispecies diversity.¹

HCV RNA that remains detectable six months after exposure is defined as chronic HCV infection.² Although it can occur, spontaneous HCV resolution during the **chronic** phase of the infection is quite rare, and our knowledge of factors associated with its resolution is quite limited. The goal of this study was to evaluate factors associated with viral clearance during the chronic phase of the infection, defined as a minimum of six months postviral exposure.

The authors report a low rate of spontaneous viral clearance during the chronic phase, with an incidence rate of 0.19 to 0.36 per 100 person years follow-up. The factors significantly associated with viral clearance were female gender, a lower median HCV RNA value, and hepatitis B surface antigen positivity. Of note, injection drug use was negatively associated with HCV clearance. The authors indicated that PWID are at risk of superinfection with distinct HCV strains that may negatively impact the likelihood of spontaneous clearance.^{3,4}

The issue of reinfection of PWID following either spontaneous or treatment-induced resolution is another consideration when addressing the issue of HCV infection in substance users. Recent work from two studies that evaluated the reinfection rates reported 2.1% and 2.4% per year, respectively.^{5,6}

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Substance Use Treatment and Improved HCV Outcomes

Norton BL, Beitin A, Glenn M, DeLuca J, Litwin AH, Cunningham CO. Retention in buprenorphine treatment is associated with improved HCV care outcomes. *J Subst Abuse Treat.* Apr 2017;75:38-42.

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The HCV treatment cascade has failed to engage persons with substance use disorders (PWSUD) into HCV care, resulting in effectiveness reduction of 75%.¹ This study, conducted in the interferon era, illustrated that retention in buprenorphine treatment was significantly associated with referral, evaluation, and treatment initiation for HCV.

Medication-assisted therapy, consisting of methadone and buprenorphine, has been known for the past 50 and 20 years, respectively, to be effective treatment modalities for heroin addiction. Although methadone has been used most commonly, buprenorphine has been gaining in popularity. Buprenorphine has an advantage that it can be prescribed in an office-based setting. As a result of the opioid epidemic, considerable efforts have been expended to increase buprenorphine prescription.

In this study, the authors evaluated the HCV care cascade among patients treated with buprenorphine. Out of a total of 390 patients who attended a buprenorphine clinic between January 2009 and January 2014, 123 were confirmed to be HCV RNA-positive. Of these, 52% were referred for an HCV evaluation, 33% were evaluated, 17% were offered HCV treatment, 8% initiated HCV treatment. Seven patients obtained a sustained virological response. Retention in the buprenorphine clinic for at least six months was significantly associated with referral for HCV evaluation, successfully undergoing an HCV evaluation, and an offer to initiate antiviral treatment.

This study underscores the importance of integrating treatment for opioid use disorders with treatment for HCV infection. Although the study was conducted before the availability of DAA therapy, recent results have demonstrated that only 39% of PWSUD enrolled in a NYC linkage to care program in 2014 were ever referred to care, and many fewer actually started HCV treatment.²

The authors of the manuscript strongly argue for integrated care; that is, simultaneous delivery of HCV and addiction treatment. Integrated care takes advantage of medical settings that patients are already accessing, are culturally appropriate, and can facilitate involvement of the multidisciplinary team.³ In our own research, we have shown that virtual integration of HCV and substance use care is highly efficacious and is actually preferred to off-site referral⁴. This is a research question that we are actively investigating through a recent award from the Patient-Centered Outcomes Research Institute (PCORI).

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KEY TAKEAWAYS

- A very high proportion of patients with HCV disease can be identified by screening in venues that provide health care to low-income individuals and where persons with substance use disorders congregate.
- Provider and patient education are paramount to increasing interventions related to HCV such as screening, linkage to care, and surveillance for hepatocellular carcinoma.
- Treatment of substance use disorders can increase rates of adherence to an HCV evaluation and retention in treatment.

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