Curr Treat Options Infect Dis (2019) 11:92–102
DOI 10.1007/s40506-019-00184-7

Hepatitis C (J Raybould, Section Editor)

Barriers to Treatment of Hepatitis C Virus in the Direct-Acting Antiviral Era

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Published online: 13 April 2019

This article is part of the Topical Collection on *Hepatitis C*

Keywords Hepatitis C (HCV) · People who Inject Drugs (PWID) · Barriers · Direct Acting Antivirals (DAA)

Abstract

Purpose of review Hepatitis C Virus (HCV) is a major public health problem in the USA, accounting for more deaths than any other infectious disease. New infections have been on the rise in recent years because of increased parenteral transmission related to injection drug use and the opioid epidemic. Curative treatment for HCV is now available; however, many barriers to treatment still exist.

Recent findings Direct-acting antiviral (DAA) treatments have been available since 2011 in combination with interferon, and since 2014, as part of interferon-free regimens, and have greatly improved both safety and efficacy and made the prospects of HCV elimination possible. However, due to the initially high cost of these medications, factors related to younger individuals infected through injection drug use, and concerns about adherence and reinfection, access to treatment has been limited. Recent studies have documented barriers along the care continuum and have attempted to address these barriers to make treatment more widely available.

Summary HCV is a curable infection, and an opportunity exists to dramatically reduce the spread and consequences of this chronic infection with highly effective and well-tolerated treatment. Systemic, provider-related, and patient-related barriers have been identified; however, increased education, policy and advocacy, and innovative models of care may address these barriers. Expansion of HCV treatment efforts will need to be sensitive to these barriers.

Introduction

Hepatitis C virus (HCV) infection represents a major public health threat in the USA, with an estimated 2 to 4 million prevalent infections, and more than 40,000 new infections per year [9]. Curative treatment decreases morbidity and mortality via reductions in decompensated cirrhosis, hepatocelllular carcinoma (HCC), and liver-related death [32, 35]. Since their introduction in 2014, direct acting antivirals (DAAs) have transformed the field of Hepatitis C treatment. DAAs now achieve sustained virological response (SVR) rates of greater than 95% with only 8–12 weeks of treatment, have vastly improved tolerability profiles compared to prior interferon-based therapies, and can be used in a broad array of patients who were previously ineligible or very difficult to treat (e.g., patients with decompensated cirrhosis, mental illness, below age 18, patients with hemodialysis). Although in the interferon-era treatment was largely confined to specialty offices, the ease and safety of DAAs has allowed significant task sharing of HCV with primary care and advanced practice providers (APP).

Concurrent with this leap forward in HCV treatment, and thanks to significant decreases in price and availability of these therapies in lower- and middle-income countries, the World Health Organization (WHO) has called for the elimination of viral hepatitis as a public health threat by 2030 [37]. Defined as a reduction in new HCV infections of 90% and a decrease in HCV-related mortality of 65%, this bold proposition will require large-scale screening and linkage to care initiatives such that 80% of those with chronic HCV infection were diagnosed, linked to care, and provided access to curative treatment. In the USA, the Department of Health and Human Services published a report outlining the current landscape of viral hepatitis epidemiology, diagnostic, and treatment challenges [34]. Following this, the National Academies of Sciences, Engineering, and Medicine mapped out a strategy to address barriers in order to achieve elimination in the USA [29]. This plan seeks to achieve a treatment goal of 90% of the estimated HCV-infected population, or an estimated 3.15 million individuals, by 2030. The US strategy acknowledges significant challenges with drug pricing, the need for increases in testing including smart screening strategies, the outsized contribution of injection drug use to new infections, and the key role of the corrections system to ongoing HCV transmission.

In order to achieve these lofty goals, the community of HCV treaters must identify these and other barriers and deploy effective countermeasures to mitigate them. Informed by the published literature, policy disputes, and frontline clinical experience, we outline and describe barriers to HCV treatment and prevention services in the following categories: systemic/policy, provider-related, and patient-related barriers.

Trends in US HCV epidemiology

Two competing epidemiologic trends are at play in the HCV epidemic in the USA: while the cumulative number of individuals seeking treatment and cure continues to grow, new infections—particularly among young people who use drugs—are increasing. Curative treatments are now available with the potential to eradicate HCV infection, decrease ongoing transmission, and potentially eliminate the disease. Many patients, especially those aware of their diagnoses and previously "warehoused" by their clinicians in order to await newer therapies have sought out treatment by specialists, and the vast majority have achieved SVR. Although in the interferon-era, small cadres of hepatologists, gastroenterologists, and infectious disease specialists offered treatment, increasingly, non-traditional treaters such as internists, family practitioners, and APPs are providing treatment in primary care or other settings. Likewise, screening programs—both various methods of birth cohort screening, as well as targeted community-based screening in at-risk groups—are identifying new infections and linking to care.

Despite this progress, several reports suggest that mortality related to HCV infection, particularly in older patients who have long been infected, is

significant and increasing. A report published in 2016 showed that as of 2013 HCV-related mortality has exceeded that of all other 60 infectious diseases tracked by the CDC [27].

Conversely, several populations are seeing increasing rates of infection, largely driven by needle sharing during IV opioid abuse. The "syndemics" of mental illness, poverty, opioid and other drug addiction and blood-borne pathogens such as HIV, HCV, and hepatitis B infection have had far-reaching effects across the USA. The Centers for Disease Control in fact reported an increase in the number of new HCV infections by 3.5 times from 2010 to 2016 [9]. Unlike their "warehoused" counterparts, these younger, recently infected patients are less likely to have advanced liver fibrosis and are more likely to face significant barriers as outlined below. As calls for HCV elimination grow in urgency, it will be essential to identify and address these barriers in order to truly realize the potential of HCV DAAs [14, 26].

Systemic barriers

In order to take on a holistic view of the HCV landscape, from diagnosis through treatment and cure, many authors have used the care continuum or care cascade model first described by Gardner et al. in the context of the HIV epidemic [12]. This model not only provides a snapshot of many aspects of HCV screening, linkage, and treatment; it also readily displays the relative contribution of barriers along the way to drop-offs along the cascade and ideally facilitates the deployment of countermeasures to address these barriers. One of the most comprehensive analyses of the HCV care continuum was described by Yehia et al. and is shown in Fig. 1 [38]. Based on a systematic review of the published literature, this serves as a useful baseline of the care continuum before the DAA era. The figure illustrates major drop-offs at various steps along

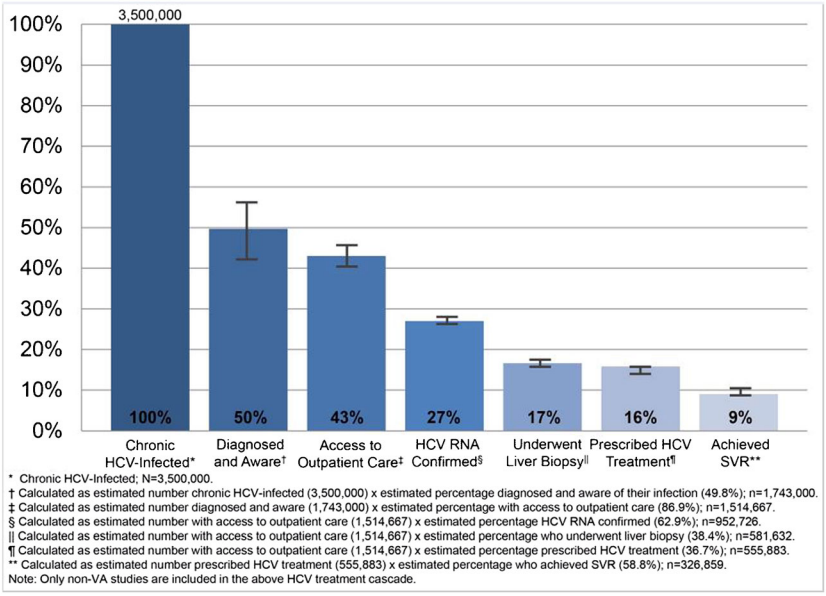

Fig. 1. HCV care continuum in the USA (Permissions Received from [38]).

the cascade, with the most significant being from an estimated 3.5 million with chronic HCV, to only 50% of these individuals being diagnosed. From a systems perspective, this indicates inadequacy of HCV testing and linkage to care efforts. Likewise, failure to confirm chronic infection with HCV RNA, failure to achieve linkage to and HCV-treating provider, and even despite referral, and failure to obtain HCV treatment, result from significant systemic, provider-related, and patient-related barriers. Although certainly not the case anymore, a major barrier in the pre-DAA era was the lack of availability of safe, effective treatments for HCV, which prompted many patients to defer treatment. Other systemic barriers encompassed in this care cascade include poor access to insurance coverage, geographic maldistribution of HCV specialists limiting access to care, and burdensome prior authorization approval processes, which have discouraged clinics from offering more widespread HCV treatment.

Overlying these pragmatic barriers is the complexity of insurance coverage and individual plan policies on access to DAAs. Soon after the introduction of DAAs in 2014, health systems and payers struggled to balance access with the high cost of DAAs and developed policies that restricted access by degree of fibrosis, prescribing specialist, and demonstration of sobriety from drugs or alcohol. These policies collectively served and continue to serve as major barriers to HCV treatment access and are highly variable depending on geography and payer type [7, 8]. The best characterized maps of these policy restrictions on a state-by-state level have been compiled by the Center for Health Law and Policy Innovation of the Harvard Law School (CHLPI) and the National Viral Hepatitis Roundtable (NVHR) and are depicted in Figs. 2, 3, and 4 [17].

Disease Severity

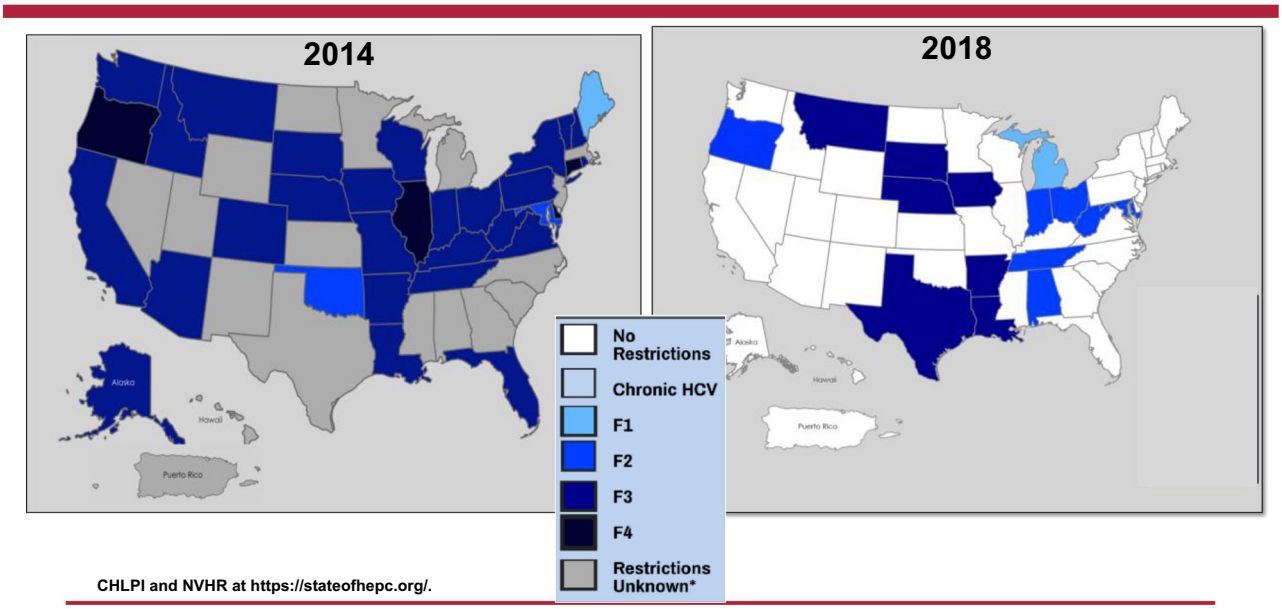

Fig. 2. (Permissions Received from [17]).

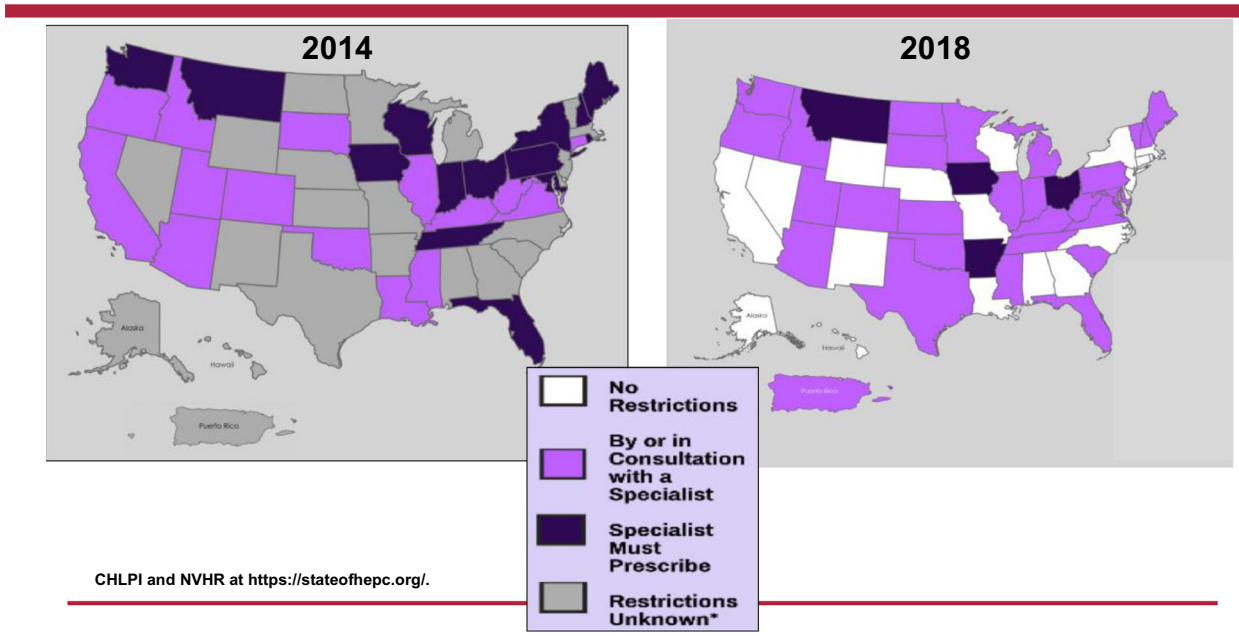

Fig. 3. (Permissions Received from [17]).

These barriers to HCV treatment are broken down into three categories: disease severity restrictions, provider restrictions, and sobriety restrictions. As

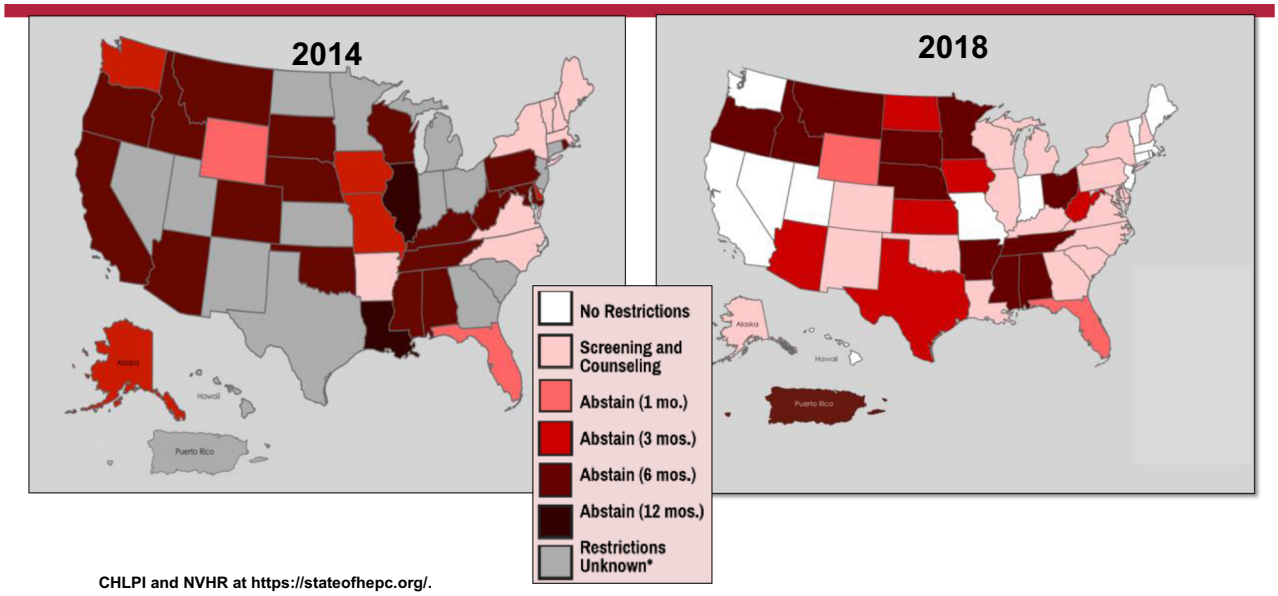

Fig. 4. (Permissions Received from [17]).

is noted in Figs. 2, 3, and 4, there have been reductions in these systemic barriers to care between 2014 and 2018, however, there still exist stark discrepancies in the ease of accessing HCV treatment based on geography and particular state Medicaid policy.

Although an in-depth state-by-state analysis of each of these barriers is beyond the scope of this article, each of the categories do warrant brief comment. Firstly, disease severity restrictions—that is withholding potentially curative DAA treatment from an individual infected with HCV because of the absence of significant liver fibrosis—have theoretical roots in the tradition of interferon-based HCV treatment, but in the DAA era, contradicts current AASLD/IDSA treatment recommendations [1]. In the interferon era, the prospect of a year-long treatment with a highly toxic, difficult to tolerate treatment with a poor safety profile meant that treatment was reasonably restricted to only those with the most severe liver fibrosis, and thus had the most proximate risk of death from liver disease. With vastly improved safety, this paradigm does not apply to the DAAs. Furthermore, evidence has accumulated demonstrating the benefits of HCV cure even at lower fibrosis stages [20].

Secondly, provider restrictions that only allow hepatologists, gastroenterologists, or infectious diseases specialists to prescribe DAAs fail to recognize the many successful examples of primary care-based treatment of HCV [10]. With appropriate support, such as via clinical consultation or via telehealth such as in the Project ECHO model, primary care-based treatment of HCV has been shown to achieve noninferior rates of cure while allowing patients to be treated closer to home in their own primary care clinics (Arora, Project ECHO: democratizing knowledge for the elimination of viral hepatitis, [3]) (Arora, Thornton, & Muruata, Outcomes for treatment for Hepatitis C virus infection by primary care providers, [4]) [23]. The US National Strategy acknowledges the success of this task sharing in recommendation 5-2 which calls on AASLD and IDSA to "build capacity to treat Hepatitis C in primary care" [29].

Finally, sobriety restrictions, namely those that require serial testing of urine toxicology screens prior to authorizing HCV treatment have no basis in the scientific literature. On the contrary, persons who inject drugs (PWID) are identified by the AASLD/IDSA guidelines as a population that is of greatest need of treatment as a way to reduce onward transmission in order to meet HCV elimination goals [1]. Modeling studies have in fact shown that treating only a modest percentage of PWID on an annual basis can result in significant reductions in incidence of new HCV infections [28]. Simply put, withholding treatment from the population of PWID significantly undermines HCV elimination efforts by perpetuating ongoing transmission.

Taken together, these three classes of restriction have served mainly to restrict access of patients to potentially life-saving interventions and shield payers from costs associated with covering DAA treatment. When challenged in court, they have uniformly been stricken down as unlawful, and their existence runs counter to our own US National Strategy for the Elimination of hepatitis C, which states in recommendation 4–5: "Public and Private health plans should remove restrictions that are not medically indicated and offer direct-acting antivirals to all chronic Hepatitis C patients" [29].

Several studies have found that patients with Medicaid insurance are significantly less likely to be approved for treatment [36, 39, 40]. An analysis of progression through the cascade of care in a large academic medical center

system found that patients with Medicaid insurance were less likely to receive a complete evaluation and to receive treatment compared with non-Medicaid patients. [40]. Similarly, a recent analysis of patients with HCV in four large US health systems found that Medicaid insurance was associated with a 79% lower likelihood of receiving treatment compared to non-Medicaid patients [36]. This is particularly troubling given that Medicaid patients are particularly vulnerable and likely make of a substantial proportion of those infected with HCV in the USA.

Finally, there are still some small remaining populations for which clinical equipoise exists regarding the benefit of treatment. Although studies are ongoing, DAAs are not currently indicated in pediatric populations or in pregnant women. In addition, treatment of acute hepatitis C used to be done reluctantly or cautiously, only after repeat viral loads to see if clearance occurred within 6 months; however, given universal treatment recommendations, this may be changing as well [33].

Provider-associated barriers

In addition to the systemic issues regarding the maldistribution of specialty care, limited numbers of HCV-treating providers, and poor access of underserved and marginalized populations to specialists, provider bias and reluctance to treat certain patient populations have served as significant barriers to care for people living with HCV infection. In a survey of 108 HCV-treating providers (primarily hepatologists) conducted at the AASLD's annual Liver Meeting, investigators found that only 15% would be willing to treat patient who was actively injecting drugs [5]. 45% of respondents cited "Concerns about Adherence" as a major driver of their reluctance to treat, while 41% cited "Reinfection Risk.". In a survey of 925 primary care providers, a high proportion of respondents identified the following additional barriers: inadequate reimbursement (44%), too few hepatitis C patients (40%), difficulty in obtaining liver elastography (35%), lack of training (32%), and the perception that HCV treatment should be done by a specialist (30%) [21]. Indeed, a common theme identified in surveys of primary care providers is the reluctance to take on the burden of expanding scope of practice without additional training or support. [24].

Patients with mental health or substance-abuse disorders bear a disproportionate burden of provider reluctance to prescribe DAAs. A large survey of four health systems found that those with mental health or substance-abuse disorders were less likely to be treated than those without these conditions, in both the interferon and DAA era. Though the difference may be narrowing (54% less likely in interferon era vs. 37% less likely in the DAA era) ,it remains significant [19]. In addition, other studies of HCV treatment limited to the DAA era have also found alcohol and drug use to be negative predictors of receiving treatment [26]. A trend towards decreased provider reluctance to prescribe DAAs to patients with mental health and/or substance-abuse disorders may be related to an increasing evidence base of successful treatment of HCV in "difficult to treat" populations, as well as a lower-than-expected rate of reinfection among people who use drugs. A recently published systematic review and meta-analysis of 38 clinical trials of DAAs in patients on opioid agonist therapy (OAT) and those

with recent injection drug use showed summary estimates of SVR of 90.7% and 87.4% of study participants, respectively [15]. While these rates are just slightly lower than most registrational DAA trials, they do show that achieving high SVR rates in populations of people who inject drugs is possible. Further evidence that may be tamping down provider reluctance to treat people who inject drugs comes in the form of treatment as prevention, which has been shown in Australia's National Syringe exchange, where widespread availability of DAA treatments has dropped HCV prevalence in this registry from 43% in 2015 to 25% in 2017 [18]. Similar findings have been reported in Iceland, where a universal HCV treatment program called "TRAP Hep C," has resulted in an 82.3% drop in HCV prevalence among PWIDs [30]. Lastly, the emerging scientific literature on true reinfection risk has been surprisingly low in most studies. In a recently reported 3-year follow-up of the C-EDGE CoSTAR study, overall reinfection rate was 1.8/100 person-years, while in those who reported ongoing injection drugs use, the risk was only 2.8/100 person-years [13].

In summary, provider-associated barriers range from inadequate HCV-treating workforce, maldistribution, and poor access to specialists, to an anemic and reluctant primary care response to the great need for more treatment. Overarching these systemic provider-related challenges are lingering biases and misperceptions regarding HCV treatment success and reinfection rates, despite emerging evidence to the contrary.

Patient-associated barriers

Perhaps the least-studied category of barriers facing people living with HCV are those relating to the patients themselves, their perceptions of risk, comorbidities, health-seeking behavior, engagement in care, and prioritization of HCV relative to various other health issues. Without question, the co-occurrence of poverty, mental health challenges, substance-abuse disorders, and other social determinants of health serve to decrease the likelihood of people living with HCV to seek out and engage in care [2]. However, many of the barriers that might be considered "patient-related" are in actuality caused, reinforced, or perpetuated by the larger systemic failures discussed earlier.

Given the largely asymptomatic nature of HCV infection, the treatment of those with early stage fibrosis has often been considered lower priority than those with advanced fibrosis [25, 26]. Medicaid and other insurance policies with fibrosis restrictions have contributed to the perception by patients that treating HCV must not be important if not permitted by their insurance carrier. Lack of awareness of the slow and insidious disease process contributes to a lack of urgency to seek out treatment and engage in care. A qualitative study of young PWIDs in the DAA era underscores these patient-related factors, and also suggests that systemic breakdowns in the HCV care continuum may themselves adversely affect patient readiness and willingness [31].

Similarly, a survey of 117 PWIDs conducted at a syringe exchange program in Philadelphia reveals patient-level perceptions that both interplay with and are derived from larger systemic failures. For example, the most commonly cited barrier from the patients' perspective was "Treatment will make me sick," a

rather accurate perception when the survey was conducted in 2013. However, the next most commonly cited barrier was "Fear of Judgement by a doctor" [11]. Indeed, this theme of avoiding or even resisting linkage to care with an HCV-treating provider was found in other qualitative studies of PWIDs and suggests a need for HCV treaters to approach these patients with more sensitivity and less judgment [6]. A harm reduction-oriented, judgment-free approach has been suggested as a model of care likely to be perceived favorably by PWIDs, and ultimately would likely result in more accessing care and prevention services [16].

Taken together, the systemic barriers preventing people living with HCV from accessing potentially life-saving DAA treatments, the remaining provider-related workforce challenges and biases, and the lingering disconnect between traditional care settings, and the needs of PWIDs call for innovative approaches to engage people living with HCV.

Conclusion and future directions

Currently in the USA, many barriers to effective treatment exist for people living with HCV. These can be broadly classified as systemic, provider-related, and patient-related, acknowledging that some barriers span several categories. In order to reach the goal of HCV elimination, each will require tailored and innovative approaches in order to overcome them. The scientific literature describing barriers and facilitators to HCV treatment is limited but growing. State Medicaid HCV treatment policies are rapidly evolving, with significant reductions in fibrosis, provider, and sobriety restrictions in the past 4 years. Although provider-related barriers such as geographic maldistribution, poor specialist access, stigma, adherence and reinfection concerns, and unfamiliarity with mental health and substance-abuse issues still pose significant challenges to universal access to treatment, a new generation of primary care-based HCV treaters are emerging to address these challenges. Likewise, evidence is building that successful HCV treatment of even "difficult populations" such as those who use drugs or who have mental health or social challenges is possible, and reinfection rates are relatively low.

The path forward towards HCV elimination will require a serious and sustained effort in order to overcome these barriers [22, 40]. The US National Strategy for the Elimination of Hepatitis C provides a roadmap to help overcome many of these challenges [29]. Many national, state, and local efforts have been launched to gather stakeholders to collaboratively address these issues. Numerous community-based treatment programs are experimenting with innovative treatment models to help address patient-related barriers such as unstable housing, transportation, low health literacy, mental health problems, and substance-abuse diagnoses.

These and other efforts are underway to decrease drop-offs in the HCV care and treatment cascade. In order to maximize benefit of DAAs to society, to avoid morbidity and mortality from cirrhosis, HCC, and to realize the promise of HCV elimination, barriers must continue to be identified and addressed.

Compliance with Ethical Standards

Conflict of Interest

Dr. Frenette reports personal fees from Gilead, personal fees from Abbvie, personal fees from Merck, personal fees from Bristol Meyers Squibb, outside the submitted work.
Dr. Ramers reports grants and personal fees from Gilead Sciences, personal fees from AbbVie, personal fees from Merck, outside the submitted work.
Dr. Liu declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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