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MAJOR ARTICLE

Prevalence and Correlates of Hepatitis C Viremia Among People With Human Immunodeficiency Virus in the Direct-Acting Antiviral Era

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Background. National US data on the burden and risks for hepatitis C virus (HCV) infection in people with human immunodeficiency virus (HIV) during the direct-acting antiviral (DAA) era are limited. These data are important to understand current progress and guide future efforts toward HCV microelimination.

Methods. We evaluated (1) HCV prevalence (2011–2013, 2014–2017, 2018–2022) using a serial cross-sectional design and (2) correlates for HCV viremia (2018–2022) in adult people with HIV (PWH) within the Centers for AIDS Research Network of Integrated Clinic Systems (CNICS) cohort using multivariable adjusted relative risk regression. The most recent data from each time period were used for calculations and models.

Results. In the CNICS cohort, HCV viremia prevalence was 8.7% in 2011–2013, 10.5% in 2014–2017, and 4.8% in 2018–2022. Disparities in prevalence across demographic groups defined by age, gender, and race/ethnicity were smaller in 2018–2022 than earlier time periods. In relative risk regression, female gender, detectable HIV RNA, higher proportion of missed visits (last 18 months), higher FIB-4 score, higher depressive symptom severity, and current use of methamphetamine and illicit opioids were associated with HCV viremia in 2018–2022.

Conclusions. The prevalence of HCV viremia during the DAA era in this US-based national cohort of PWH improved over time and across demographic subgroups but remains higher than those without HIV. Our findings highlight the continued importance of prioritizing HCV care in all PWH, especially in certain key, less-reached groups. Proactive, comprehensive efforts to care engagement, substance use, mental health, and other social determinants will be crucial to improve reach, prevention, and treatment to achieve HCV elimination goals.

Keywords. DAA; direct-acting antiviral; health equity; hepatitis C; HIV/HCV coinfection.

Hepatitis C virus (HCV) infection occurs more frequently in people with human immunodeficiency virus (HIV) than in the general population and is a leading cause of liver-related morbidity and mortality [1]. The introduction and expansion of highly efficacious interferon (IFN)–free direct-acting antiviral (DAA) regimens enabled the possibility of more widespread HCV cure, prompting the World Health Organization, the United States (US), and other countries to propose comprehensive HCV plans with the goal of eliminating HCV within specific populations (microelimination) [2, 3] and overall by 2030 [4, 5]. Population-level data on HCV infection are crucial for understanding current progress and directing future efforts. Although many data exist on HCV infection burden in non-HIV populations [6–8], to our knowledge, US-based national data on epidemiology of HCV/HIV coinfection with up-to-date clinical and behavioral determinants are limited in the DAA era. Most studies among people with HIV (PWH) have been limited to single-center or regional samples [9, 10], administrative or claims data [5], non-US-based studies [1],

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or the pre-DAA era [11, 12]. Characterizing the burden of and understanding correlates for HCV infection in the DAA era among PWH will provide key information on current progress and guide efforts toward HCV microelimination.

We evaluated HCV viremia prevalence among PWH in clinical care in the US in 3 distinct time periods in the DAA era (2011–2013, 2014–2017, 2018–2022) and examined correlates of HCV viremia in the current DAA era (2018–2022). The population with HCV viremia represents the ideal unit of study given their risk for HCV transmission and liver-related complications if untreated. Because HCV viremia reflects the sum of infection (initial and recurrent) and clearance (treatment with cure, natural clearance, death), understanding HCV viremia prevalence provides an important practical benchmark and insight on our elimination efforts. This study aims to assess population-level HCV viremia overall and within key populations among PWH and to clarify risk factors and barriers for PWH to HCV prevention and treatment in the current DAA era in the US.

METHODS

Study Setting, Data Source, and Participants

The Centers for AIDS Research Network of Integrated Clinic Systems (CNICS) is a prospective observational cohort study of adult PWH in clinical care at 10 academic institutions across the US [13]. Patient-reported outcome (PRO) assessments, administered every 4–6 months, and comprehensive clinical data including diagnoses, laboratory results, and medications are collected through electronic medical records and institutional data systems. All data undergo rigorous quality assessment and harmonization in a central repository updated quarterly.

This study included PWH in CNICS with ≥1 encounter (clinical visit, HIV RNA, or CD4 result) in 2011–2013 (IFN-based DAA era), 2014–2017 (early DAA era), or 2018–2022 (current DAA era) from 9 CNICS sites with available data: Case Western Reserve University (Cleveland, Ohio); Fenway Community Health Center/Harvard University (Boston, Massachusetts); Johns Hopkins University (Baltimore, Maryland); University of Alabama at Birmingham; University of California, San Diego; University of California, San Francisco; University of North Carolina at Chapel Hill; University of Washington, Seattle; and Vanderbilt University (Nashville, Tennessee). DAA eras were based on evolution of DAA formulations and access: DAAs were initially used with IFN in 2011–2013 [12]; IFN-free DAA regimens became available in 2014 though with significant national access restrictions that were widely lifted starting around 2018 allowing for more universal DAA treatment [10, 14]. Given the serial cross-sectional nature of the study, participants could only contribute data once for each DAA era but could contribute to multiple different DAA eras. All clinical, laboratory, demographic, health utilization, and PRO assessment data used for covariates, calculations, and models were determined using the most recent values on/before a participant's HCV laboratory test or latest patient encounter if a participant had no available HCV laboratory tests. Each site's institutional review board approved the CNICS study protocol.

Measures

HCV viremia, our primary outcome of interest, was defined as a detectable HCV RNA or genotype during a specific DAA era. "Current or prior HCV infection," a secondary outcome of interest, was defined as a detectable or reactive HCV antibody, RNA, or genotype during a specific DAA era. We defined current or prior HCV infection to be inclusive of these HCV laboratory types to provide a comprehensive denominator and context for HCV viremia prevalence.

We considered age, self-identified gender, and self-identified race/ethnicity as key demographic factors to report prevalence for comparability [7, 8] and in models based on known disparities [7, 8, 10, 12, 15]. We used the term "demographic group" here as a subgrouping of 1 of these 3 demographic factors or categories (eg, transgender group is part of the gender category or factor). The transgender group included both transgender men and women to be inclusive given the overall small number identifying as transgender; almost all individuals in the transgender group identified as transfeminine [16].

For the multivariable analysis in the current DAA era, we determined an a priori set of demographic, clinical, and behavioral correlates based on known risk factors and disparities for HCV [7, 8, 10, 12, 15, 17]. Demographic factors in multivariable analysis were the same as those used for reporting HCV viremia prevalence with the addition of geographic location (CNICS site). HIV detectability (HIV factors) was defined as HIV RNA ≥50 copies/mL. The proportion of missed visits in the previous 18 months, our measure for care engagement, was calculated as the number of missed HIV primary care visits divided by total scheduled visits from a participant's HCV laboratory test or latest patient encounter (if no HCV laboratory results) [9]. We assessed liver fibrosis using the FIB-4 score [18]. Behavioral factors including current substance use (AUDIT-C [for alcohol] [19, 20], ASSIST [for other drugs [21–23]) and depressive symptom severity (PHQ-9 [24, 25]) were based on PRO assessment. Referents within different covariates were selected based on largest group size (eg, gender, race/ethnicity, alcohol use, among others) for statistical power stability or comparability if the covariate had escalating doses (eg, FIB-4).

Data Analysis

We determined the overall prevalence of HCV viremia and current or prior HCV infection in a serial cross-sectional design using laboratory results for each DAA era (2011–2013, 2014–2017, 2018–2022). We also ascertained HCV viremia

prevalence by demographic group (age, gender, race/ethnicity) within each DAA era. Given possible effects of loss to follow-up and death, we completed a sensitivity analysis for HCV viremia prevalence adjusting for these factors using inverse probability of censoring weighting.

We estimated prevalence ratios (PRs) using relative risk regression adjusted for an a priori set of demographic, clinical, and behavioral correlates for HCV viremia in 2018–2022 to better understand potential HCV risk factors and key groups to target efforts in the current DAA era. We serially adjusted for different sets of factors to more comprehensively evaluate their associations with HCV viremia. In Model 1, we adjusted for demographic factors; Model 2 adjusted for demographic, HIV detectability, and care engagement factors; Model 3 adjusted for demographic, liver fibrosis, and behavioral factors; and Model 4, our comprehensive main model, incorporated all of these factors. We also conducted a sensitivity analysis stratifying the comprehensive model (Model 4) by individuals with known diagnosis of HCV viremia before (had a detectable HCV RNA or genotype and clinical visit in 2011–2017) and after 2018 (first detectable HCV RNA or genotype in 2018 or later) to explore potential differences in risk factors. We considered individuals with HCV viremia before and on/after 2018 to be persistently viremic given data constraints to evaluate reinfections and mixed data on reinfection rates in different populations [26–28]. Missing values underwent multiple imputation with chained equations (m = 50). Statistical analyses were completed with Stata version 18 software (StataCorp, College Station, Texas).

Table 1. Prevalence of Hepatitis C Viremia Among People With Human Immunodeficiency Virus in the United States by Direct-Acting Antiviral Era and Demographic Group[a,b]

Characteristic	IFN-Based DAA Era 2011–2013 (n = 22 445)	Early DAA Era 2014–2017 (n = 25 161)	Current DAA Era 2018–2022 (n = 25 314)
Overall (HCV viremia[b])	1953 (8.7%)	2634 (10.5%)	1204 (4.8%)
Age, y			
<30	77 (3.0%)	98 (3.5%)	54 (3.2%)
30–39	259 (5.8%)	333 (6.6%)	267 (5.2%)
40–49	672 (9.2%)	654 (10.4%)	271 (5.2%)
50–59	748 (12.1%)	1073 (13.8%)	395 (5.4%)
≥60	197 (10.0%)	476 (14.4%)	217 (3.7%)
Gender			
Male	1509 (8.5%)	2021 (10.1%)	923 (4.6%)
Female	401 (9.3%)	557 (11.9%)	253 (5.4%)
Transgender	43 (13.0%)	56 (13.1%)	28 (5.6%)
Race/ethnicity			
White	856 (8.7%)	1064 (10.1%)	557 (5.6%)
Black	860 (9.8%)	1200 (11.8%)	448 (4.3%)
Hispanic	166 (5.9%)	242 (7.5%)	132 (3.9%)
Other	71 (7.4%)	128 (10.3%)	67 (4.8%)

Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; IFN, interferon.

[a]For each cell, n is the number of tests with detectable HCV RNA or genotype, and % is the proportion of tests with detectable HCV RNA or genotype within a cell's group (eg, n = 77 or 3.0% of <30-year-old participants had a detectable HCV RNA or genotype on their last test in 2011–2013).

[b]HCV viremia was defined as a detectable HCV RNA or genotype during a specific DAA era. All data were based on the most recent laboratory values in a specific DAA era. Participants could only contribute data once for each DAA era but could contribute to multiple different DAA eras.

RESULTS

Within this national US-based cohort of PWH in care, the overall prevalence of HCV viremia was 8.7% in the IFN-based DAA era (2011–2013, n = 22 445), rose to 10.5% in the early DAA era (2014–2017, n = 25 161), and dropped to 4.8% in the current DAA era (2018–2022, n = 25 314) (Table 1). HCV viremia prevalence was higher in all demographic groups from the IFN-based DAA to the early DAA era but decreased in the current DAA era. Although HCV viremia prevalence in the age groups <30 years and 30–39 years followed this general trend, prevalence largely remained stable over the 3 DAA eras (3.0%–3.5% range for <30 years and 5.2%–6.6% range for 30–39 years). In the IFN-based DAA era, older individuals aged 50–59 (12.1%) or ≥60 years (10.0%), identifying as transgender (13.0%) or cisgender female (9.3%), and reporting Black (9.8%) or White (8.7%) race had the highest HCV viremia prevalence within their respective demographic categories (Table 1). Although the same demographic groups generally continued to have the highest HCV viremia prevalence in early and current DAA eras as those in the IFN-based DAA era, the disparities among demographic groups were smaller in the current DAA era compared to earlier time periods (overall range across all 3 demographic categories by time period: 3.0%–13.0% [IFN-based DAA]; 3.5%–14.4% [early DAA]; 3.2%–5.6% [current DAA]). HCV viremia prevalence adjusted for loss to follow-up and death did not differ substantially from unadjusted estimates overall and within each group among age, gender, and race/ethnicity categories (Supplementary Table 1). Overall prevalence of current or prior HCV infection remained generally stable across DAA treatment eras (IFN-based DAA: 18.9%, early DAA: 18.4%, current DAA: 17.9%).

In the current DAA era, current methamphetamine use (adjusted PR [aPR], 2.68 [95% confidence interval {CI}, 2.28–3.14]), current illicit opioid use (aPR, 1.91 [95% CI, 1.40–2.60]), and elevated FIB-4 score relative to FIB-4 <1.45 (FIB-4 1.45–3.25: aPR, 2.68 [95% CI, 2.28–3.14]; FIB-4 >3.25: aPR, 4.78 [95% CI, 3.87–5.89]) had the strongest associations with HCV viremia in the comprehensive model (Model 4, Table 2). Additional factors associated with higher risk of HCV viremia in the comprehensive model included female gender, detectable HIV RNA, higher proportion of missed visits in last 18 months, higher depressive symptom severity, and no current alcohol use relative to nonhazardous alcohol use. Conversely, Black race and Hispanic ethnicity (relative to

Table 2. Demographic, Clinical, and Behavioral Correlates of Hepatitis C Viremia[a] Among People With Human Immunodeficiency Virus in the Current Direct-Acting Antiviral Era (2018–2022)

	Model 1[b] Demographic Factors			Model 2[b] Demographic and HIV Factors			Model 3[b] Demographic, Liver, and Behavioral Factors			Model 4[b] (Comprehensive) Demographic, HIV, Liver, and Behavioral Factors		
Adjustment Factors	PR	(95% CI)	*P* Value	PR	(95% CI)	*P* Value	PR	(95% CI)	*P* Value	PR	(95% CI)	*P* Value
Age (per 10 y)	0.92	(.88–.96)	<.001	1.00	(.95–1.04)	.9	0.78	(.74–.84)	<.001	0.82	(.77–.87)	<.001
Gender (Ref: male)												
Female	1.30	(1.12–1.50)	<.001	1.22	(1.06–1.41)	.007	1.30	(1.11–1.51)	.001	1.24	(1.06–1.45)	.006
Transgender	1.08	(.74–1.58)	.7	1.00	(.68–1.46)	1.0	1.22	(.82–1.83)	.3	1.17	(.78–1.73)	.5
Race/ethnicity (Ref: White)												
Black	0.76	(.67–.88)	<.001	0.68	(.59–.78)	<.001	0.83	(.72–.97)	.02	0.77	(.66–.90)	.001
Hispanic	0.55	(.45–.67)	<.001	0.56	(.46–.69)	<.001	0.65	(.53–.81)	<.001	0.65	(.53–.80)	<.001
Other	0.68	(.53–.88)	.003	0.70	(.54–.91)	.007	0.86	(.66–1.13)	.3	0.84	(.64–1.11)	.2
HIV RNA ≥50 copies/mL	…	…		1.92	(1.69–2.18)	<.001	…	…		1.40	(1.22–1.61)	<.001
Missed visits in last 18 mo (per 25% missed)	…	…		1.58	(1.49–1.68)	<.001	…	…		1.30	(1.19–1.41)	<.001
FIB-4 score (Ref: <1.45)												
1.45–3.25	…	…		…	…		2.88	(2.45–3.38)	<.001	2.68	(2.28–3.14)	<.001
>3.25	…	…		…	…		5.70	(4.59–7.07)	<.001	4.78	(3.87–5.89)	<.001
Current methamphetamine use	…	…		…	…		2.41	(1.80–3.22)	<.001	2.02	(1.48–2.77)	<.001
Current cocaine use	…	…		…	…		1.15	(.86–1.54)	.4	1.04	(.77–1.39)	.8
Current illicit opioid use	…	…		…	…		2.15	(1.58–2.91)	<.001	1.91	(1.40–2.60)	<.001
Current marijuana use	…	…		…	…		0.88	(.68–1.14)	.3	0.7	(.67–1.12)	.3
Alcohol use[c] (Ref: nonhazardous use)												
None	…	…		…	…		1.37	(1.07–1.76)	.01	1.33	(1.04–1.70)	.02
Hazardous use	…	…		…	…		0.98	(.69–1.38)	.9	0.95	(.68–1.34)	.8
Depressive symptoms severity (PHQ-9 score, per 5 points)	…	…		…	…		1.16	(1.07–1.26)	.001	1.13	(1.04–1.22)	.006

Abbreviations: CI, confidence interval; DAA, direct-acting antiviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PHQ-9, Patient Health Questionnaire-9; PR, prevalence ratio.

[a]HCV viremia was defined as a detectable HCV RNA or genotype in 2018–2022. All data were based on the most recent laboratory values or patient-reported outcome assessment (behavioral factors) in 2018–2022 before an individual's latest HCV laboratory test or patient encounter (if no HCV laboratory test available).

[b]Model adjusted for Centers for AIDS Research Network of Integrated Clinic Systems site and listed covariates in column.

[c]Nonhazardous alcohol use defined as Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) score 1–4 in men and 1–3 in women. Hazardous alcohol use defined as AUDIT-C score >4 in men and >3 in women.

White race) as well as older age were associated with lower risk of HCV viremia.

Estimates for demographic factors generally did not substantially change across the 4 models even after accounting for other clinical, HIV, and behavioral factors (Table 2). For the other correlates, in contrast, estimates for detectable HIV RNA, missed visits in the last 18 months, FIB-4 score, current methamphetamine use, and current illicit opioid use all attenuated more substantially when combined into the same model (Model 4) compared to those of models with only HIV and care engagement factors (Model 2) or with only liver and behavioral factors (Model 3). Associations for current alcohol use and depressive symptom severity (PHQ-9) remained statistically significant but did not substantially change between Models 3 and 4.

In the stratified sensitivity analysis exploring correlates with HCV viremia in the current DAA era among PWH diagnosed before and after 2018, a total of 630 PWH were diagnosed with HCV before 2018 and 574 were diagnosed in 2018 or later (Supplementary Table 2). Associations of FIB-4, current methamphetamine use, and current illicit opioid use with HCV viremia were substantially higher in PWH newly diagnosed with HCV in 2018 or later compared to those with known diagnosis of HCV in 2018, whereas the association between cisgender female identity and HCV viremia was substantially higher among PWH diagnosed before 2018 than on/after 2018 (Supplementary Table 3). Other estimates were similar between strata or did not reach statistical significance.

DISCUSSION

Overall HCV viremia prevalence decreased from 8.7%–10.5% in earlier time periods to 4.8% in the current DAA era within this US-based national cohort of PWH in care. The increase in overall HCV viremia prevalence between IFN-based and early DAA eras may be related to secular trends or increased testing with the initial availability of DAAs [29–31]. We also observed reductions in HCV viremia prevalence and disparities in prevalence across age, gender, and race/ethnicity groups in the current DAA era compared to earlier time periods. To our knowledge, our study reports the latest national HCV viremia prevalence data among PWH in the US. These developments likely reflect DAAs' high effectiveness and reduced barriers to DAA access [14, 32], among other factors frequently available in US HIV care settings. Despite advancements, our analysis indicates significant work remains to be done, especially among many key populations, to achieve HCV microelimination among PWH.

In the current DAA era, we found that current substance use, especially methamphetamine and illicit opioid use, and younger age were associated with HCV viremia among PWH in the US. This is consistent with current HCV trends in the general US population in which most HCV infections occur in younger individuals using substances, especially those who inject drugs [29]. Recently, greater fentanyl and methamphetamine use likely contributed to HCV viremia risk due to their impacts on substance use patterns and sexual behaviors [33–35]. These factors may also explain the general stability of HCV viremia prevalence over the 3 DAA eras among adult PWH aged <40 years despite decreases in other age groups [29, 36]. Additionally, substance use and depressive symptoms, behavioral factors that often occur together, could lead to suboptimal engagement in HCV treatment/care [37]. The large attenuation of estimates for several substances and HIV and care engagement factors after combining all into the same model (Model 4) suggests possible shared (eg, mental health, homelessness) or sequential (eg, substance use leading to suboptimal engagement) factors to explain their relationships with HCV viremia [15, 17, 37]. We also found an inverse relationship between alcohol use and HCV viremia that could suggest differences in choice of substance and route (eg, people who use more alcohol may not use much methamphetamine or inject drugs); reflect the "sick-quitter" hypothesis, in which individuals abstain from alcohol due to ill health (eg, HCV infection) [38]; or PRO collection timing relative to decision on DAA treatment, among other potential explanations. More investigation, especially longitudinal and intersectional, is needed to clarify these relationships.

Our sensitivity analysis found that methamphetamine use, illicit opioid use, and FIB-4 score were stronger correlates for HCV viremia in the current DAA era among PWH diagnosed with HCV on/after 2018 than those diagnosed before 2018. These findings likely reflect more recent substance use trends with higher rates of methamphetamine and fentanyl use as mentioned earlier [33–35]. FIB-4 risk estimates were more pronounced in those with HCV viremia on/after 2018, suggesting that many PWH with recently diagnosed HCV and advanced fibrosis have not been treated (due to delayed diagnosis or lapse in care) and need urgent prioritization. Also concerning, our findings indicate that PWH with HCV viremia before 2018 and advanced fibrosis remain untreated. Both groups of PWH with persistent HCV viremia represent missed opportunities for HCV care.

Our data suggest that HCV treatment efforts in the DAA era have made good progress on HCV viremia across several race/ethnicity and gender groups in this study. In our cohort of PWH in care, in contrast to the general US population [29], PWH of Black race and Hispanic ethnicity had lower HCV prevalence than those reporting White race in the current DAA era. The Ryan White HIV/AIDS program, including its AIDS Drug Assistance Program that frequently covers DAAs [39], and the integrated, medical home model with wraparound services in many HIV clinics provide significant support and infrastructure to reduce inequities that may be observed in

conventional care models and settings [9, 40, 41]. However, lower care engagement continues to be associated with untreated HCV in the current DAA era and HCV prevalence in PWH is still many times higher than in the general population overall and among many key groups, such as PWH who are cisgender female, use substances, or have advanced fibrosis. With near-universal access to DAAs currently in the US [14, 32, 39], the fact that certain key populations have been unreached indicates continued need to improve care engagement, simplification, and prioritization of HCV care. Data to care approaches can identify and concentrate efforts for key populations and gaps in HCV care within health clinics, systems, and jurisdictions [42]. Addressing social determinants of health such as housing, transportation, and family care [15] through close partnership with comprehensive social service providers; managing comorbid conditions such as substance use, including medications for opioid use disorder, and mental health in integrated, comprehensive approaches [37, 43]; and providing novel low-barrier care models with walk-in, co-location with social service providers, and/or mobile services [17, 44] are several approaches that have shown success improving access and engagement to HCV care. Tied with these, expansion of harm reduction education and supplies for substance use and sexual activity, HCV testing, and simplification of HCV treatment models will be important for HCV prevention and treatment success [45, 46]. Ultimately, multidisciplinary interventions acting at multiple care levels will be needed to reach key groups, improve health equity, and achieve elimination.

Strengths of our study include laboratory-confirmed HCV data over all recent eras of DAA therapy with up-to-date clinical and behavioral contextual information through PROs from a large, diverse cohort of PWH in clinical care. Prevalence estimates are conservative given that data are laboratory-confirmed and reflect those in care. The cross-sectional nature of analyses precludes conclusions on causal direction of associations. Additional limitations include lack of data on incident HCV infections and reinfections; inability to determine HCV acquisition risk factor; potential mismatch of PRO assessment timing with HCV treatment decisions; inability to assess higher-level structural, health system, and provider factors; and potential additional unmeasured confounders given the observational nature of study. For this study, CNICS included data from PWH in care at 9 geographically diverse academic HIV clinics with demographic and clinical characteristics similar to the general HIV population within clinical care in the US. Our findings may not generalize to all clinical settings and for PWH not in care or unaware of their HIV status. Despite these limitations, this study provides a practical population-level overview and approach for following current progress and areas of focus for HCV microelimination in PWH.

Our study found reductions in HCV viremia prevalence and disparities in prevalence among PWH in the current DAA era compared to earlier time periods. Although progress has been made in HCV care among PWH, our findings underscore the continued importance of prioritizing HCV testing and treatment in all PWH, especially in certain key groups. Proactive, comprehensive efforts to care engagement, substance use, mental health, and other social determinants as well as expansion of HCV care in novel settings will be crucial to improve reach, prevention, and treatment to achieve HCV elimination goals.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Patient consent. All CNICS participants provided written informed consent for study participation. Each site's institutional review board approved the CNICS protocol.

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