

Hepatitis C Within a Single Health System: Progression Along the Cascade to Cure Is Higher for Those With Substance Misuse When Linked to a Clinic With Embedded Support Services

J. E. Sherbuk,^{1,0} K. A. McManus,¹ E. T. Rogawski McQuade,¹ T. Knick,¹ Z. Henry,² and R. Dillingham¹

¹Division of Infectious Diseases and International Health and ²Division of Gastroenterology and Hepatology, University of Virginia, Charlottesville, Virginia

Background. Hepatitis C is now curable for most individuals, and national goals for elimination have been established. Transmission persists, however, particularly in nonurban regions affected by the opioid epidemic. To reach goals of elimination, barriers to treatment must be identified.

Methods. In this open cohort of all individuals diagnosed with active hepatitis C from 2010 to 2016 at a large medical center, we identified patient and clinic characteristics associated with our primary outcome, sustained virologic response (SVR). We performed a subgroup analysis for those with documented substance misuse.

Results. SVR was achieved in 1544 (41%) of 3790 people with active hepatitis C. In a multivariable Poisson regression model, SVR was more likely in individuals diagnosed outpatient (incident rate ratio [IRR], 1.7; 95% confidence interval [CI], 1.5–2.0), living in close proximity to the medical center (IRR, 1.2; 95% CI, 1.1–1.3), with private insurance (IRR, 1.1; 95% CI, 1.0–1.3), and with cirrhosis (IRR, 1.4; 95% CI, 1.3–1.5). Achieving SVR was less likely in those qualifying as indigent (IRR, 0.8; 95% CI, 0.8–0.9) and those with substance misuse (IRR, 0.8; 95% CI, 0.7–0.9). In the subgroup analysis of those with substance misuse, SVR rates were higher in those linked to the infectious diseases clinic, which has embedded support services, than those linked to the gastroenterology clinic, which does not (IRR, 1.4; 95% CI, 1.1–1.9).

Conclusions. Social determinants of health including proximity to care and poverty impacted achievement of SVR. Those with substance misuse, a high-priority population for treatment of hepatitis C, had better outcomes when receiving care in a clinic with embedded support services.

Keywords. hepatitis C cascade of care; hepatitis C virus; social determinants of health; substance abuse.

Due to treatment advances, chronic hepatitis C virus (HCV) infection is now curable for most of those infected [1–3], and the elimination of HCV as a public health problem by 2030 is an established goal [4, 5]. Unfortunately, national targets for elimination are not being met, with acute HCV incidence and HCV-related mortality exceeding goal rates [6]. People living with untreated chronic HCV remain at risk for the morbidity, mortality, and high health care costs associated with HCV complications [7, 8].

The rising incidence of HCV in the United States creates a significant challenge in making progress toward elimination

Open Forum Infectious Diseases®

[9]. The opioid epidemic is driving ongoing HCV transmission through injection drug use [9]. Nonurban regions, including Appalachia, have been disproportionately affected by opiates and HCV [10–12]. Existing literature on the HCV care cascade in the United States focuses primarily on urban populations [13], and the Department of Health and Human Services has identified further research on HCV and injection drug use in nonurban areas as a key strategy to promote the reduction of viral hepatitis due to drug use behaviors [14].

The HCV cascade of care, adapted from widespread use in the care of people living with HIV, defines the steps required to care for those with HCV, including diagnosis, linkage to care, treatment, and cure [15]. Among the estimated 3.2 million people living with HCV in the United States, only 50% are aware of their diagnosis [16, 17] and fewer than 10% have been cured [15, 16]. Moving toward the goal of elimination requires identification and mitigation of patient, health system, and treatment-related barriers along the cascade [18].

The management of HCV has undergone a remarkable change in recent years. Treatment has shifted from the poorly tolerated and prolonged course of interferon-based therapies to the

Received 10 April 2018; editorial decision 9 August 2018; accepted 13 September 2018. Correspondence: Jacqueline E. Sherbuk, MD, Division of Infectious Diseases and International Health, University of Virginia, PO Box 801379, Charlottesville, VA 22908 (jes2nk@virginia.edu).

[©] The Author(s) 2018. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/ by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com D0I: 10.1093/ofid/ofy202

well-tolerated, efficient, and more expensive era of direct-acting antivirals (DAAs). The cost of DAAs has led to a rapidly shifting landscape of treatment availability, as private insurance and government-funded plans have limited eligibility through restrictions on prescribers, severity of liver damage, and patient sobriety [19]. Although restrictions have slowly loosened to widen access to DAAs, eligibility remains limited across the country [19]. In our state, Medicaid continues to require a specialty physician prescriber for HCV treatment [19].

Within our health system, HCV care is provided into 2 specialty clinics, infectious diseases and gastroenterology. The infectious diseases clinic, which treats both HIV/HCV-coinfected and HCV-mono-infected individuals, is co-located within the Ryan White HIV clinic. For people living with HIV, the Ryan White HIV/AIDS program (RWHAP) has overcome barriers to treatment by providing wraparound services for uninsured or underinsured individuals, including co-located access to services such as mental health services, substance use counseling, and case management [20, 21]. Individuals co-infected with HIV and HCV have successfully achieved HCV cure at high rates within the RWHAP model [22]. The gastroenterology clinic is in the same complex and serves the same catchment area but does not have co-located support services.

We aimed to determine patient and HCV clinic characteristics associated with achievement of sustained virologic response (SVR) in a large academic medical center serving a predominately nonurban population. Given the impact of substance misuse on ongoing transmission, we also examined the subset of patients with documented substance misuse.

METHODS

Study Population

The study population is an open cohort defined as all adults age 18 years or older within the University of Virginia Health System (UVAHS) who had a positive hepatitis C laboratory test, either antibody or RNA viral load, between January 1, 2010, and December 31, 2016. This study was approved by the University of Virginia Health Sciences Research Institutional Review Board. The UVAHS is an academic, tertiary medical center serving the western half of Virginia, including the southwestern Appalachian region.

Data Collection

The Clinical Data Repository (CDR), a UVAHS data warehouse, was used to identify individuals meeting inclusion criteria and to collect demographic and clinical data. Demographic data, including age, sex, race, residence location, insurance, and financial status were obtained from the patient visit associated with the initial diagnostic laboratory test. If demographic information was not available for the first visit, the second visit associated with a hepatitis C laboratory test was used. Proximity to the UVAHS was defined as residence within

the city of Charlottesville, where the UVAHS is located, and within surrounding counties. Definitions from Virginia's State Rural Health Plan defined rural vs urban residence [23]. For financial status, the UVAHS determination of "indigent" status, based on patient-reported financial information including household income and assets, was used. Health insurance status is not included in the determination. ICD9/ICD10 codes documented in the chart within 1 year before or after the initial laboratory test were used to determine relevant medical comorbidities including cirrhosis, hepatocellular carcinoma, hepatitis B, and HIV. The year of diagnosis was determined based on an initial positive HCV laboratory result. Patient location, either inpatient or outpatient, at the time of diagnosis was collected. HCV laboratory results including HCV antibody tests, HCV RNA levels, and HCV genotypes were collected through December 2017 to determine achievement of SVR. This time course allowed at least 1 year from time of diagnosis to potential cure. In our clinical experience, 1 year provides sufficient time to link to care, complete required laboratory and imaging evaluations, and complete a treatment course, including 12 weeks for follow-up laboratory testing. Data were collected on appointments scheduled with either HCV specialty clinic. Chart review was performed for HCV RNA levels and for prescription of hepatitis C treatments, as the CDR did not contain all the information. Additionally, manual chart review was performed for a random sampling of 10% of individuals to confirm accuracy of the information collected from the CDR relative to the diagnosis of substance misuse.

Study Outcomes

The primary study outcome was SVR, defined as a nondetectable viral load following treatment by December 31, 2017. An analysis of the health system–wide steps in the treatment cascade was also completed. Cascade steps were (1) any positive HCV test, (2) measurement of an HCV viral load, (3) active HCV, defined by a positive viral load, (4) linkage to care, defined as a scheduled appointment with an HCV specialty clinic, (5) medication prescribed through the electronic medical record, and (6) SVR, defined as a nondetectable viral load after treatment.

Data Analysis

Univariate analysis used the Student t test for continuous variables and chi-square analysis or Fisher exact test if indicated for categorical variables. We used multivariable Poisson regression to estimate the associations of patient characteristics with SVR during the variable follow-up period of 1–7 years after diagnosis. The follow-up period was defined to be from the date of diagnosis until either the end of study follow-up or time of death. Basic demographic variables, including age, race, and gender, were placed in a multivariate Poisson regression model, along with factors significant in univariate analysis and medical comorbidities that may impact treatment decisions to determine incident rate ratios (IRRs) and 95% confidence intervals

(CIs) for achieving SVR during a variable follow-up period of 1–7 years. Statistical analyses were performed in Stata 15.0 (StataCorp LLC, College Station, TX).

Subgroup Analysis

A subgroup analysis was performed restricted to individuals with substance misuse based on ICD9/ICD10 codes who linked to care to evaluate the impact of the specialty clinic on this population. We used a multivariable Poisson regression analysis that included the same covariates as the primary analysis, with the addition of the specialty clinic. For this subgroup, we analyzed the association of the specialty clinic with completion of cascade steps, including rates of medication prescribing among those linked to care and SVR among those prescribed treatment.

RESULTS

Cohort Description

We identified 4846 individuals with a positive HCV test from 2010 to 2016. Of these, a viral load was measured in 4510 (93%), with a nondetectable viral load in 720 (16%) demonstrating viral clearance. Active HCV infection was confirmed in 3790 individuals. Among the 3790 people with active HCV, 3092 (82%) linked to care, 1931 (51%) were prescribed medication, and 1544 (41%) achieved SVR (Figure 1). Manual chart review of a random 10% of individuals with active HCV identified that the electronic medical record text was concordant with the CDR-coded diagnosis of substance misuse in 100% of those coded for substance misuse. Additionally, manual chart review demonstrated that 13% of those without a diagnosis of substance misuse in the electronic medical record text. Given the overall high rate of concordance between the CDR and electronic medical

record text, the CDR definition of substance misuse was used for analyses.

The active HCV population was predominately male (n = 2347, 62%), white (n = 2795, 74%), qualified as "indigent" (2314 of 3610, 64%), and lived in rural regions (2349 of 3610, 65%). On univariate analysis for the primary outcome, those achieving SVR were older (mean [SD], 52 [11] years vs 49 [12] years; P < .001), more likely to live in close proximity to the health system (46% vs 36%, P < .001), and more likely to have private health insurance (32% vs 21%, P < .001) or cirrhosis (42% vs 37%, P = .001) (Table 1). Those failing to achieve SVR were more likely to be male (63% vs 60%, P = .04), qualify as indigent (69% vs 57%, P < .001), and have hepatocellular carcinoma (9% vs 7%, P = .02) or substance misuse (21% vs 14%, P < .001). Diagnosis in the outpatient setting (89% vs 72%, P < .001) and a recent diagnosis were more common in those achieving SVR.

Multivariable Analysis

Of those with active HCV, the adjusted rates of SVR were higher among those residing in close proximity to the health system (IRR, 1.2; 95% CI, 1.1–1.3), with private insurance (IRR, 1.1; 95% CI, 1.0–1.3), diagnosed as an outpatient (IRR, 1.7; 95% CI, 1.5–2.0), diagnosed more recently (IRR, 5.6; 95% CI, 4.9–6.4, for those diagnosed in 2016 compared with those diagnosed in 2010), and with cirrhosis (IRR, 1.4; 95% CI, 1.3–1.5) (Table 2). Rates of SVR were lower in those qualifying as indigent (IRR, 0.8; 95% CI, 0.8–0.9) and with a history of substance misuse (IRR, 0.8; 95% CI, 0.7–0.9).

Subgroup Analysis

A subgroup analysis was performed on the 682 individuals (18%) with active hepatitis C who had a documented history

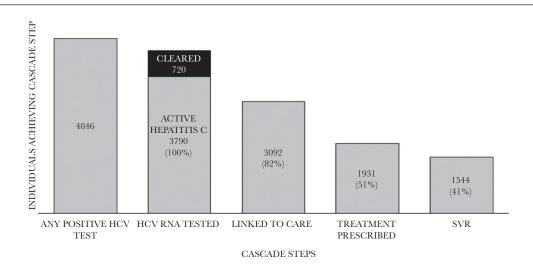


Figure 1. Hepatitis C cascade of care. Steps in the hepatitis C cascade of care were defined to be (1) any positive HCV test, (2) measurement of HCV viral load, (3) active HCV, defined by a positive viral load, (4) linkage to care, defined as a scheduled appointment with an HCV specialty clinic, (5) medication prescribed through the electronic medical record, and (6) SVR, defined as a nondetectable viral load after treatment. The cascade includes all individuals with a positive HCV test within the University of Virginia Health System between 2010 and 2016 who completed cascade steps by December 31, 2017. Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response.

Table 1. Characteristics of People Living With Active Hepatitis C at the Time of Diagnosis

	Prima	ary Outcome					
Individual Characteristics	Achieved SVR n = 1544 No. (%)	Did Not Achieve SVR n = 2246 No. (%)	P				
				Demographic characteristics			
				Age, mean (SD), y	52.0 (10.6)	48.9 (11.7)	<.001
Male sex	926 (60)	1421 (63)	.04				
Race			.4				
White	1147 (74)	1648 (73)					
Black	334 (22)	489 (22)					
Asian	8 (1)	6 (0.3)					
Hispanic	5 (0.3)	5 (0.2)					
Native American	3 (0.2)	4 (0.2)					
Other	47 (3)	94 (4)					
Residence location							
Close proximity to medical center ^a	713 (46)	816 (36)	<.001				
Rural ^b	971 (66)	1378 (65)	.6				
Financial characteristics							
Indigent per payment scale ^c	855 (57)	1459 (69)	<.001				
Private insurance ^d	486 (32)	437 (21)	<.001				
Medical comorbidities							
Cirrhosis	655 (42)	830 (37)	.001				
HIV	55 (4)	82 (4)	.9				
Hepatitis B	37 (2)	71 (3)	.2				
Hepatocellular carcinoma	101 (7)	192 (9)	.02				
Substance misuse	209 (14)	473 (21)	<.001				
Diagnosis factors							
Outpatient diagnosis	1372 (89)	1626 (72)	<.001				
Year of diagnosis			<.001				
2010	254 (16)	399 (18)					
2011	211 (14)	363 (16)					
2012	186 (12)	324 (14)					
2013	167 (11)	327 (15)					
2014	224 (15)	296 (13)					
2015	275 (18)	288 (13)					
2016	227 (15)	249 (11)					
Hepatitis C genotype ^e			.02				
1	802 (80)	900 (77)					
2	120 (12)	123 (11)					
3	76 (8)	137 (12)					
4	2 (0.2)	3 (0.3)					
Mixed	5 (0.5)	5 (0.4)					

Abbreviation: SVR, sustained virologic response.

^aData missing for 3 (0.2%) who achieved SVR and 8 (0.4%) who did not.

^bData missing for 62 (4%) who achieved SVR and 118 (5%) who did not.

^cData missing for 35 (2%) who achieved SVR and 145 (6%) who did not.

^dData missing for 48 (3%) who achieved SVR and 136 (6%) who did not.

^eData missing for 539 (35%) who achieved SVR and 1078 (48%) who did not.

of substance misuse. Within this subgroup, 543 (80%) linked to care, 292 (43%) were prescribed medication, and 209 (31%) achieved SVR. Among the 444 individuals with substance misuse linked to the gastroenterology clinic, 233 (52%) were prescribed medication and 168 (38%) achieved SVR (Figure 2). Of the 164 linked to the infectious diseases clinic, 103 (63%) were

prescribed medication and 70 (43%) achieved cure. Sixty-five individuals linked to both the gastroenterology and infectious diseases clinics. In a multivariate Poisson regression analysis of people who use substances, SVR was 1.4 times (95% CI, 1.1–1.9) more likely in those linked to infectious diseases compared with gastroenterology (Table 3). Rates of SVR were also higher

Table 2. Patient Characteristics Associated With Achieving SVR Among Those With Active Hepatitis C in a Multivariable Poisson Regression Model (n = 3495)

	Incidence Rate Ratio (95% CI)	Р
Individual characteristics		
Age ≤30 y	1.1 (0.9–1.2)	.3
Male sex	0.9 (0.9–1.0)	.2
White race	1.0 (0.9–1.1)	1.0
Close proximity to medical center	1.2 (1.1–1.3)	<.001
Indigent	0.8 (0.8–0.9)	.001
Private insurance	1.1 (1.0–1.3)	.01
Diagnosis characteristics		
Outpatient diagnosis	1.7 (1.5–2.0)	<.001
Diagnosis year		
2010	1 (ref)	
2011	1.1 (1.0–1.3)	.1
2012	1.3 (1.1–1.5)	<.001
2013	1.5 (1.3–1.8)	<.001
2014	2.3 (2.1–2.7)	<.001
2015	3.4 (3.0–3.8)	<.001
2016	5.6 (4.9–6.4)	<.001
Medical comorbidities		
Cirrhosis	1.4 (1.3–1.5)	<.001
Hepatocellular carcinoma	0.9 (0.8–1.0)	.1
HIV	1.1 (0.9–1.4)	.3
Hepatitis B	1.1 (0.8–1.3)	.7
Substance misuse	0.8 (0.7–0.9)	.001

Incidence rate ratios were adjusted for all other variables listed in this table

Abbreviations: CI, confidence interval; SVR, sustained virologic response.

in those diagnosed outpatient (IRR, 1.5; 95% CI, 1.1–2.1). On analysis of the individual cascade steps seen in Figure 2 using Poisson regression analysis, those linked to infectious diseases were more likely to be prescribed medication (IRR, 1.3; 95% CI, 1.1–1.6; P = .01) than those linked to gastroenterology; however, once prescribed medication, rates of SVR did not differ

between infectious diseases and gastroenterology (IRR, 1.1; 95% CI, 0.9-1.4; P = .3).

DISCUSSION

In this predominately nonurban cohort of almost 5000 patients, 41% of those diagnosed with active HCV achieved SVR. We identified that cure rates are higher among individuals with substance misuse when care is provided in a specialty clinic with embedded support services. We also identified social determinants of health to be associated with lower rates of progression through the cascade from diagnosis to cure, including proximity to care, poverty, and lack of private health insurance.

Among patient characteristics, cirrhosis was associated with a higher rate of SVR. Cirrhosis, or advanced liver fibrosis, has commonly been prioritized for prescription coverage, and treatment rates are higher in this group [24]. Men had lower SVR rates, consistent with prior studies [24, 25]. Disparities are often seen related to treatment outcomes of racial minorities [26, 27]; however, we did not see an impact of race on SVR. Additionally, young age, generally considered to be less than 30 years, has been associated with both higher [25, 28] and lower [29] rates of linkage to care but was not associated with outcomes in our cohort. Rates of SVR were higher in those diagnosed more recently, which is expected given the improved tolerability and availability of treatment. However, the proportion of individuals cured over the full time period was similar regardless of diagnosis date as those diagnosed earlier tended to have a longer time to treatment.

Diagnosis in the outpatient setting was strongly associated with cure. Those diagnosed with HCV in an outpatient setting have higher linkage to care rates than those diagnosed inpatient or in the emergency room [24, 29, 30]. In the inpatient setting, linkage to care for a new diagnosis of HCV may not be

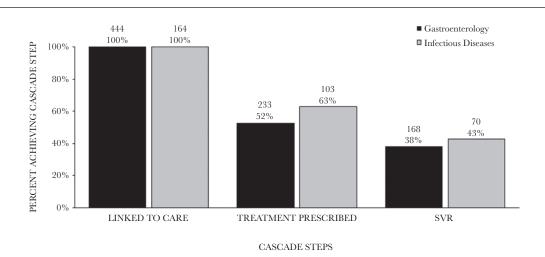


Figure 2. Cascade of care by hepatitis C specialty clinic among those with substance misuse linked to care. "Linked to care" is defined as a scheduled appointment with an HCV specialty clinic. To successfully complete the second step, "treatment prescribed," an HCV treatment course must be prescribed through the electronic medical record. To achieve the final step of "SVR," the individual must have a nondetectable viral load after treatment. Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response.

Table 3. Factors Associated With SVR in a Multivariable Poisson Regression Model Among Those With Substance Misuse Linked to Either Gastroenterology or Infectious Diseases Hepatitis C Specialty Clinic (n = 458)

	Incidence Rate Ratio (95% CI)	Ρ
Hepatitis C clinic		
Infectious diseases clinic	1.4 (1.1–1.9)	.01
Individual characteristics		
Age ≤30 y	1.1 (0.8–1.6)	.4
Male sex	1.1 (0.9–1.4)	.5
White race	0.9 (0.7–1.1)	.4
Close proximity to medical center	1.1 (0.9–1.4)	.5
Indigent	1.1 (0.7–1.6)	.8
Private insurance	1.3 (0.9–2.0)	.2
Diagnosis characteristics		
Outpatient diagnosis	1.5 (1.1–2.1)	.01
Diagnosis year		
2010	1 (ref)	na
2011	1.0 (0.7–1.4)	.8
2012	1.6 (1.2–2.3)	.003
2013	1.3 (0.9–1.9)	.2
2014	1.8 (1.2–2.5)	.003
2015	2.6 (1.8–3.8)	.000
2016	4.3 (2.3–8.1)	.000
Medical comorbidities		
Cirrhosis	1.1 (0.9–1.4)	.4
Hepatocellular carcinoma	1.4 (1.0–1.9)	.03
HIV	0.6 (0.3-1.2)	.1
Hepatitis B	1.1 (0.6–1.8)	.8

Incidence rate ratios were adjusted for all other variables listed in this table.

Abbreviations: CI, confidence interval; SVR, sustained virologic response.

considered a priority during the management of acute medical conditions. Furthermore, differentiating acute and chronic HCV infections can be difficult in the inpatient setting, and linkage to outpatient care is required to monitor for clearance of an acute infection as well as treatment of a chronic infection. A similar finding of relatively low linkage to care rates among inpatients newly diagnosed with HIV led to the development of interventions that successfully improved linkage to HIV care [31]. Therefore, there may be a role for developing linkage to care programs among those diagnosed with HCV in the acute care setting to improve progression along the cascade.

Social determinants of health, including proximity to care, poverty, and insurance status, impacted the rates of SVR. Living in proximity to the medical center was positively associated with SVR. Our hospital system covers a wide geographic and predominantly rural area. Those living further from the HCV clinics in these rural areas may face challenges accessing the specialty care, laboratory tests, and medications required for treatment. Broader implementation and adaptation of models like the ECHO model in New Mexico, which has facilitated greater access to HCV care in rural areas in the Southwest United States, are needed [32]. Cure was also less likely in those living in poverty and those without private health insurance. Treatment must reach these vulnerable populations to move toward elimination. In the care of those living with HIV, RWHAP serves populations with multiple social determinants of poor health [33], including vulnerable populations with high rates of poverty and racial minorities [21]. The RWHAP has been able to navigate the complex roles social determinants of poor health play in caring for people living with HIV, resulting in improved outcomes [20, 33, 34] and decreased disparities in viral suppression [35]. The RWHAP may serve as a model in caring for vulnerable patients living with HCV.

In our cohort, SVR rates were lower in those with substance misuse, including injection drug use, opiate abuse, and alcohol use. These individuals comprise a population at high risk for personal and public health consequences of HCV if untreated, given that alcohol use can worsen liver disease [36] and injection drug use drives ongoing viral transmission. Historically, restrictions have been placed on treating those with ongoing substance misuse, though current guidelines recommend treatment of this population [2]. Increasing the number of people who inject drugs who are treated is cost-effective [37] and can reduce HCV transmission and prevalence [38]. The recent SIMPLIFY study demonstrated that even people with recent, or active, injection drug use can be treated successfully [39].

Our subanalysis of those with substance misuse demonstrated that those linked to infectious diseases were more likely to achieve SVR than those linked to gastroenterology. We identified a higher rate of prescribing medication to those with substance misuse in the infectious diseases clinic, even when adjusting for potential confounders, including HIV diagnosis, in a multivariate analysis. Once prescribed medication, SVR rates were similar across specialty clinics. These 2 specialty clinics are part of the same academic, tertiary health system and face the same barriers of insurance restrictions and challenges in prescribing. The central difference in the structure of these clinics is the co-location of the infectious diseases HCV clinic within an RWHAP-funded clinic. As noted above, the RWHAP supports a wraparound model of co-located care coordinators, substance use disorder counselors, and nursing support for PLWH. Although individuals with HCV mono-infection who received care at the infectious diseases HCV clinic did not benefit directly from services or staff solely dedicated to caring for PLWH, they may have benefited from receiving care in a clinic where staff are accustomed to delivering a comprehensive model of care, including on-site referrals for and coordination of substance use disorder counseling and mental health services. The infectious diseases clinic structure may also have contributed to an increased comfort level among providers in prescribing HCV treatment to those with substance use disorders, as the structure supports treatment of both HCV and substance use disorder. Given the importance of social determinants of health in HCV care and the success of HCV treatment in our RWHAP co-located clinic, these findings suggest a role for enhancing comprehensive services for those with HCV in

other clinical settings. This aligns with earlier studies demonstrating that elements of an interdisciplinary model such as care coordination and case management [40] or patient navigators can improve HCV outcomes [41].

The retrospective, observational nature of this study has inherent limitations. We identified a 41% SVR rate among those with diagnosed *active* HCV. This does not include the 7% (336) of the entire population with HCV antibody sero-positivity who never had an HCV viral load recorded and thus could not progress to the second step of the cascade. Therefore, our estimate is likely an overestimate of the cure rate for the entire HCV population within our health system. This highlights the importance of making HCV viral load testing more accessible, so that the direct and indirect costs associated with completing an HCV viral load test do not limit individuals' ability to progress along the cascade and so that a community's rate of progression toward HCV elimination is not falsely elevated.

Additionally, as an open cohort, patients may have received treatment and achieved SVR outside our health system. As there is not a process for standardized reporting of negative viral loads to health departments, we are unable to identify these individuals. The ever-changing eligibility restrictions impacted which individuals were able to access treatment at the time of diagnosis or linkage to care. To address this, we included covariables in our multivariable analysis, such as date of diagnosis and presence of cirrhosis. Our use of ICD codes to determine comorbidities relies on the accuracy and completeness of coding. We collected ICD codes documented within 1 year before and after the initial laboratory test to provide more complete information; however, this approach likely missed some diagnoses as we found that the use of ICD codes underestimated the prevalence of substance misuse. Linkage to care was defined to be a scheduled appointment with an HCV specialist. We were not able to identify whether the individual attended an appointment, so we may have overestimated linkage to care. Clinically, SVR was defined as a negative viral load at least 12 weeks after the completion of treatment. However, as we were unable to determine the exact dates of treatment from our available data, our negative viral loads used to define SVR may have been drawn before the 12-week point past treatment completion.

Given the national goal for elimination of HCV as a public health problem by 2030, HCV care must expand to treat the patients who remain chronically infected within the United States. Suggested models for treatment expansion include increased prescribing by primary care providers or a telehealth approach such as ECHO [32]. For treatment to reach all those living with HCV, strategies will also need to address the social determinants of health associated with lack of progression along the HCV care cascade. Finally, targeted efforts are needed to reach those with substance use disorders. Adapting strategies developed through the RWHAP for PLWH and people with HCV may be an effective approach to move toward elimination of HCV.

Acknowledgments

Financial support. This work was support by the National Institute of Allergy and Infectious Diseases (grant number T32 AI007046-41). This work was supported by the Translational Health Research Institute of Virginia (THRIV) through funding to Kathleen A. McManus.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

- Millman AJ, Nelson NP, Vellozzi C. Hepatitis C: review of the epidemiology, clinical care, and continued challenges in the direct acting antiviral era. Curr Epidemiol Rep 2017; 4:174–85.
- AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015; 62:932–54.
- European Association for Study of Liver. EASL recommendations on treatment of hepatitis C 2015. J Hepatol 2015; 63:199–236.
- World Health Organization. Global Hepatitis Programme. Combating hepatitis B and C to reach elimination by 2030, 2016. http://apps.who.int/iris/bitstream/10665/206453/1/ WHO_HIV_2016.04_eng.pdf?ua=1. Accessed 2 March 2018.
- National Academies of Sciences, Engineering, and Medicine. A National Strategy for the Elimination of Hepatitis B and C. Washington, DC: The National Academies Press; 2017.
- Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Progress toward viral hepatitis elimination in the United States, 2017. https://www.cdc.gov/hepatitis/policy/PDFs/NationalReport.pdf. Accessed 2 March 2018.
- Razavi H, Elkhoury AC, Elbasha E, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. Hepatology 2013; 57:2164–70.
- Backus LI, Belperio PS, Shahoumian TA, Mole LA. Direct-acting antiviral sustained virologic response: impact on mortality in patients without advanced liver disease. Hepatology. In press.
- Zibbell JE, Asher AK, Patel RC, et al. Increases in acute hepatitis C virus infection related to a growing opioid epidemic and associated injection drug use, United States, 2004 to 2014. Am J Public Health 2018; 108:175–81.
- Becka CM, Bryant ZE, Robertson D, Ratard R. Increase in hepatitis C diagnosis and opioid-related deaths in urban versus rural areas of louisiana from 2012 to 2015. Open Forum Infect Dis 2016; 3:455.
- Zibbell JE, Iqbal K, Patel RC, et al. Increases in hepatitis C virus infection related to injection drug use among persons aged ≤ 30 years - Kentucky, Tennessee, Virginia, and West Virginia, 2006-2012. 2015; 64:453–8.
- Suryaprasad AG, White JZ, Xu F, et al. Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006–2012. Clin Infect Dis 2014; 59:1411–9.
- Paquette CE, Pollini RA. Injection drug use, HIV/HCV, and related services in nonurban areas of the United States: a systematic review. Drug Alcohol Depend 2011; 188:239–50.
- US Department of Health and Human Services. Combating the silent epidemic of viral hepatitis: action plan for the prevention, care & treatment of viral hepatitis. https://www.hhs.gov/sites/default/files/action-plan-viral-hepatitis-2011.pdf. Accessed 17 July 2018.
- Yehia BR, Schranz AJ, Umscheid CA, Lo Re V 3rd. The treatment cascade for chronic hepatitis C virus infection in the United States: a systematic review and meta-analysis. PLoS One 2014; 9:e101554.
- Holmberg SD, Spradling PR, Moorman AC, Denniston MM. Hepatitis C in the United States. N Engl J Med 2013; 368:1859–61.
- Denniston MM, Klevens RM, McQuillan GM, Jiles RB. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001– 2008. Hepatology 2012; 55:1652–61.
- Mehta SH, Genberg BL, Astemborski J, et al. Limited uptake of hepatitis C treatment among injection drug users. J Community Health 2008; 33:126–33.
- National Viral Hepatitis Roundtable. Hepatitis C state of Medicaid access 2018. https://stateofhepc.org/. Accessed 17 July 2018.
- Diepstra KL, Rhodes AG, Bono RS, et al. Comprehensive Ryan White assistance and human immunodeficiency virus clinical outcomes: retention in care and viral suppression in a Medicaid nonexpansion state. Clin Infect Dis 2017; 65:619–25.
- Cahill SR, Mayer KH, Boswell SL. The Ryan White HIV/AIDS program in the age of health care reform. Am J Public Health 2015; 105:1078–85.

- 22. Patel M, Rab S, Kalapila AG, et al. Highly successful hepatitis C virus (HCV) treatment outcomes in human immunodeficiency virus/HCV-coinfected patients at a large, urban, Ryan White clinic. Open Forum Infect Dis **2017**; XXX(X):XXX–XX.
- Virginia's state rural health plan: supporting rural health through community engagement and action, 2013. http://www.vdh.virginia.gov/content/uploads/ sites/76/2016/06/2013VSRHP-final.pdf. Accessed 2 March 2018.
- 24. Franco RA, Overton ET, Tamhane AR, et al. Characterizing failure to establish hepatitis C care of baby boomers diagnosed in the emergency department. Open Forum Infect Dis **2016**; XXX(X):XXX–XX.
- 25. Janjua NZ, Kuo M, Chong M, et al. Assessing hepatitis C burden and treatment effectiveness through the British Columbia Hepatitis Testers Cohort (BC-HTC): design and characteristics of linked and unlinked participants. PLoS One 2016; 11:e0150176.
- 26. Vutien P, Hoang J, Brooks L Jr, et al. Racial disparities in treatment rates for chronic hepatitis C: analysis of a population-based cohort of 73665 patients in the United States. Medicine (Baltimore) 2016; 95:e3719.
- 27. Sims OT, Guo Y, Shoreibah MG, et al. Short article: alcohol and substance use, race, and insurance status predict nontreatment for hepatitis C virus in the era of direct acting antivirals: a retrospective study in a large urban tertiary center. Eur J Gastroenterol Hepatol 2017; 29:1219–22.
- Strathdee SA, Latka M, Campbell J, et al; Study to Reduce Intravenous Exposures Project. Factors associated with interest in initiating treatment for hepatitis C virus (HCV) infection among young HCV-infected injection drug users. Clin Infect Dis 2005; 40(Suppl 5):S304–12.
- Young KL, Huang W, Horsburgh CR, et al. Eighteen- to 30-year-olds more likely to link to hepatitis C virus care: an opportunity to decrease transmission. J Viral Hepat 2016; 23:274–81.
- Assoumou SA, Huang W, Horsburgh CR Jr, et al. Relationship between hepatitis C clinical testing site and linkage to care. Open Forum Infect Dis 2014; XXX(X):XXX–XX.

- Kelen GD, Hsieh YH, Rothman RE, et al. Improvements in the continuum of HIV care in an inner-city emergency department. AIDS 2016; 30:113–20.
- Arora S, Thornton K, Murata G, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. N Engl J Med 2011; 364:2199–207.
- 33. Weiser J, Beer L, Frazier EL, et al. Service delivery and patient outcomes in Ryan White HIV/AIDS program-funded and -nonfunded health care facilities in the United States. JAMA Intern Med 2015; 175:1650–9.
- Bradley H, Viall AH, Wortley PM, et al. Ryan White HIV/AIDS program assistance and HIV treatment outcomes. Clin Infect Dis 2016; 62:90–8.
- Doshi RK, Milberg J, Jumento T, et al. For many served by the Ryan White HIV/ AIDS program, disparities in viral suppression decreased, 2010–14. Health Aff (Millwood) 2017; 36:116–23.
- 36. Safdar K, Schiff ER. Alcohol and hepatitis C. Semin Liver Dis 2004; 24:305-15.
- Martin NK, Vickerman P, Dore GJ, et al; STOP-HCV Consortium. Prioritization of HCV treatment in the direct-acting antiviral era: an economic evaluation. J Hepatol 2016; 65:17–25.
- Martin NK, Hickman M, Hutchinson SJ, et al. Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. Clin Infect Dis 2013; 57(Suppl 2):S39–45.
- Grebely J, Dalgard O, Conway B, et al; SIMPLIFY Study Group. Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use (SIMPLIFY): an open-label, single-arm, phase 4, multicentre trial. Lancet Gastroenterol Hepatol 2018; 3:153–61.
- Ho CJ, Preston C, Fredericks K, et al. A unique model for treating chronic hepatitis C in patients with psychiatric disorders, substance abuse, and/or housing instability. J Addict Med 2013; 7:320–4.
- Trooskin SB, Poceta J, Towey CM, et al. Results from a geographically focused, community-based HCV screening, linkage-to-care and patient navigation program. J Gen Intern Med 2015; 30:950–7.