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

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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 [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
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-co-infected 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 (RWHP) 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 RWHP 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 by CDR coding had evidence 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
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
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

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

| Patient Characteristics | Incidence Rate Ratio (95% CI) | \( P \) |
|-------------------------|-------------------------------|-------|
| 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   |
| 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 |
| 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.
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)

| Diagnosis characteristics | Incidence Rate Ratio (95% CI) | P    |
|---------------------------|------------------------------|------|
| 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, RWHP serves populations with multiple social determinants of poor health [33], including vulnerable populations with high rates of poverty and racial minorities [21]. The RWHP 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 RWHP 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 RWHP-funded clinic. As noted above, the RWHP 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 RWHP 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 covariates 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 supported 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.

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