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Patient Engagement is the Predominant Barrier to Completing Hepatitis C Virus Treatment in the Pan-Genotypic Direct-Acting Antiviral Era

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Abstract

Background: Data regarding real-world barriers patients encounter along the hepatitis C (HCV) care continuum is limited since the availability of pan-genotypic direct-acting antivirals (DAA). We sought to evaluate the HCV cascade of care during the pan-genotypic DAA era at an academic health system with multiple hospital and clinic sites in a large, diverse urban population.

Methods: We conducted a retrospective cohort study of adult patients with chronic HCV at a single, academic health system between January 1, 2017 to September 30, 2019. The primary outcome evaluated was completion of DAA. Secondary outcomes included successful progression through each stage of the HCV care continuum from diagnosis to cure.

Results: 1215 patients were included. The average age was 61.5 years old and 62% were men. 84.5% had public insurance. All patients were referred to an HCV treatment provider. 550 patients (45.3%) met with an HCV treatment provider. 189 patients (15.6%) completed DAA. Active intravenous drug use, a mental health disorder, being referred by the emergency room or inpatient setting were associated with HCV treatment not being completed. Treatment by hepatology and infectious diseases and living closer to the treatment clinic was associated with treatment completion. Undergoing fibrosis staging, resistance testing, receiving medication education, and attending more clinic visits during the treatment course was also associated with treatment completion. Virologic response at 12 and 24 weeks was inconsistently obtained.

Conclusion: In a predominantly under-represented minority, urban population with public insurance, significant barriers to HCV treatment with pan-genotypic DAAs continue to exist.

Keywords: Hepatitis C virus; viral hepatitis; Care cascade; Care continuum; Direct-acting antivirals

Introduction

The release of pan-genotypic direct-acting antiviral (DAA) agents in 2016-2017 have allowed all patients with chronic hepatitis C virus (HCV) potential access to a cure.[1] While expensive, DAA oral availability, low side effect profile, cost-effectiveness, and reduction in HCV-related morbidity and mortality make them ideal.[2,3,4]

While scientific discovery and availability of DAA therapy were the first and biggest steps towards eradicating HCV, practical aspects regarding

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patient linkage to care and progression along the HCV care cascade remain the most important in achieving real-world success.[5] Studies have emerged over the years describing where patients fall off the HCV care cascade. These studies have been relatively small, lack granularity, and/or were performed outside the United States.[6,7,8] The most robust data available were obtained prior to the availability of pan-genotypic DAAs, had strict treatment criteria, or followed patients through the cascade based on where patients were initially diagnosed as opposed to how treatment was attempted.[9,10]

We sought to evaluate the HCV cascade of care at a single academic center with multiple hospital and clinic sites in a large, diverse urban population and determine the efficacy of various pathways based on the types of clinics and patient-provider relationships.

Methods and Materials

Study Design and Population

We conducted a retrospective cohort study of patients receiving care at a single, academic health system comprised of 3 major hospitals with affiliate primary and specialty clinics in Bronx, New York. Data was collected from January 1, 2017 to September 30, 2019. The starting date of data collection was selected as this was the time that pan-genotypic DAAs were readily available to patients in this geographic region. Patients included in the analysis were adults ≥18 years old and had an HCV diagnosis defined by seropositivity and detectable RNA by HCV PCR, which is reflexive by protocol within our laboratory, during the study period. Patients already receiving treatment at the time of identification were excluded from the study. The study was approved by the Institutional Review Board of the study center. It was conducted in compliance with the Unite States Health Insurance Portability and Accountability Act.

Outcomes and Definitions

The primary outcome evaluated was completion of treatment, which was confirmed either by end of treatment (EOT) blood testing with HCV PCR or documentation within the electronic health records (EHR) of the patient completing treatment by a healthcare provider. Treatment completion was chosen over sustained virologic response at 12 (SVR12) or 24 weeks (SVR24) as cure rates for HCV are very high once treatment is completed, and compliance with SVR24 testing can be poor. Secondary outcomes included successful progression through each stage of the HCV care cascade from diagnosis to treatment completion and confirmation of a cure with SVR24 HCV PCR testing (Table 1).

Data Collection

All data were obtained from the EHR system utilized at our health system. Patient sociodemographic characteristics were collected at the time of diagnosis, including age, sex, shortest driving distance from home to the referred HCV clinic, preferred language, need for interpreter service, and primary insurance. Information regarding the characteristics of HCV infection were also collected: history of prior treatment, genotype, HCV RNA quantification at the time of diagnosis, fibrosis staging, and evidence of cirrhosis and decompensation. The DAA regimen and duration taken by patients was also recorded. Medical co-morbidities, specifically substance use disorder, tobacco use disorder, and mental health disorders, were noted.

Patients' completion (or lack thereof) of every stage along the HCV care cascade was recorded. Specific dates were recorded (date of referral, date of the decision by the treatment provider to proceed with prior authorization application to the insurance company, and date of insurance approval). Other dates were omitted due to the inconsistent recording of events. Additional information, such as the specialty of the initial referring provider, whether the referring provider was within our health system or not, the medical specialty of the HCV treating provider, the type of treating provider (attending physician, housestaff, or advanced practice provider), testing performed prior to submitting prior authorization for treatment , number of office visits with the treating provider prior to submitting prior authorization, number of office visits during treatment, testing performed during treatment were collected. For patients who did not meet a treating provider after being diagnosed, notes were reviewed to see if a reason could be identified for not seeking treatment.

Statistical Analysis

For each step of the HCV care cascade, the proportion of patients completed was calculated. Categorical variables were expressed as number of patients and percentage and compared using Chi square test or Fisher's exact test. Continuous variables were expressed as mean, median, standard deviation (SD), and interquartile range (IQR) and compared using two-sample t-test or Wilcoxon rank sum test. A p-value of < 0.05 was deemed statistically significant. All analyses were performed with SAS version 9.4.

Results

Patient Characteristics

During the study period, 1215 patients were identified to have HCV Ab positivity with detectable HCV PCR and were not already receiving DAA (Table 2). The average age was 61.5 years old and 62% were men. The majority of patients (84.5%) had public insurance and 30.6% had secondary insurance. 13.6% of patients had prior treatment exposure (9.1% with interferon and ribavirin, 4.5% with DAAs). About half of patients had unknown stage of fibrosis. For those with known fibrosis stage, the distribution of patients was: stage

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0 = 9.7%, stage 1 = 8.6%, stage 2 = 8.7%, stage 3 = 6.7%, stage 4 =14.4%). Distribution was similar between those who completed DAA therapy and those who did not.

Active intravenous drug use was associated with HCV treatment not being completed (8.5% completed vs. 16.0% not completed, p=0.01). A mental health disorder noted in the history was also associated with treatment not being complete 33.3% completed vs. 36.6% not completed, p=0.0004), though the details of mental health disorders was not further defined (type of disorder, severity of disorder, whether disorders were under treatment or treatment-controlled).

HCV Care Cascade

All 1215 patients were referred to an HCV treatment provider. Their progression along the HCV care cascade is summarized in Figure 1. The plurality of patients was identified and referred by primary care providers (30.4%), followed by emergency room and inpatient hospital settings (10.8%), hepatology (4.9%), infectious disease (3.9%), gastroenterology (2.2%), and then self-referred (0.7%). 12.3% of patients were referred by other providers, of which the majority were in solid organ or bone marrow transplant or oncology. For the largest group of patients (34.8%), it was unclear who diagnosed and referred the patients for treatment. Being referred by the emergency room, inpatient hospital setting, an "other" provider not within the above listed specialties, or "unknown" provider was associated with treatment not being completed (p<0.0001).

Of the 1215 patients identified, 550 patients (45.3%) met with an HCV treatment provider. HCV treatment providers were available at different clinics: primary care, infectious disease, hepatology, gastroenterology, other (often transplant clinics), and unspecified. Ultimately only 189 (15.6%) of patients completed treatment. Patient progression through the HCV care cascade based on the type of treatment provider was similar amongst the various specialties.

Being treated by hepatology and infectious diseases specialty clinics and living closer to the treatment clinic (3.2 vs. 3.7 miles, p=0.01) was associated with treatment completion (Table 3). Patients who completed treatment more often underwent fibrosis staging (86.2% of treatment completed vs. 57.9% of treatment not completed, p<0.0001), resistance testing (42.3% of treatment completed vs. 30.3%

Table 1: HCV Care Continuum: Definitions

Stage	Definition	Exclusion
Diagnosis	Patient had HCV antibody detection and detectable HCV RNA.	Patient was already progressing through the HCV care continuum at the time of lab identification
Referred	Evidence of one of the following: - Patient was provided a referral to see an HCV provider (electronically or scanned paper referral) - Documentation of a discussion with between patient and referring provider that the patient should see an HCV treatment provider	No referral available or no documentation of discussion for patient to see a provider.
Initial Assessment	Patient presented for the first clinic visit with an HCV provider	Patient never met an HCV provider
Agreement to Pursue Treatment	Documentation that HCV provider and patient agree to proceed with HCV treatment pending any necessary testing	Documentation that the patient declines HCV treatment after meeting HCV provider
Prior Authorization (PA) Submission	Documentation from HCV provider that a PA was submitted to the insurance	Documentation from HCV provider PA submission will not be pursued
Medication Approval	Documentation that DAA was approved by the insurance	Documentation that DAA was not approved by the insurance
Treatment Completed	Confirmed administration of the entire prescribed treatment based on patient or family reporting	Evidence of one of the following: - Treatment was discontinued for any reason - Patient lost to follow-up
End of Treatment (EOT) Response	Undetectable HCV RNA at the completion of therapy	Evidence of one of the following: - Treatment failure defined as detectable HCV RNA - Patient lost to follow-up
Sustained Virologic Response at 12 weeks (SVR12)	Undetectable HCV RNA at 12 weeks following completion of therapy	Evidence of one of the following: - Treatment failure defined as detectable HCV RNA - Patient lost to follow-up
Sustained Virologic Response at 24 weeks (SVR24)	Undetectable HCV RNA at 24 weeks following completion of therapy	Evidence of one of the following: - Treatment failure defined as detectable HCV RNA - Patient lost to follow-up

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Table 2: Baseline characteristics of patients with chronic HCV

Characteristics	Overall (n=1215)	Treatment completed (n=189)	Treatment not completed (n=1026	p-value
Age (years), mean (SD)	61.5 (12.8)	60.6 (11.7)	61.6 (13)	0.29
Sex, no. (%)				
Male	751 (62)	124 (65.6)	627 (61.3)	0.26
Female	461 (38)	65 (34.4)	396 (38.7)	
Primary insurance, no. (%)				
Medicare	474 (39.4)	80 (42.3)	394 (38.9)	
Managed Medicare	70 (5.8)	6 (3.2)	64 (6.3)	
Medicaid	466 (38.8)	64 (33.9)	402 (39.7)	0.1
Managed Medicaid	6 (0.5)	1 (0.5)	5 (0.5)	
Private	167 (13.9)	36 (19.1)	131 (12.9)	
None	19 (1.6)	2 (1.1)	17 (1.7)	
Preferred language				
English	1058 (87.2)	153 (81.0)	905 (88.3)	
Spanish	139 (11.5)	32 (16.9)	107 (10.4)	0.02
Other	17 (1.4)	4 (2.1)	13 (1.3)	
Requires a language interpreter	148 (12.2)	32 (16.9)	116 (11.3)	0.03
Alcohol use disorder, no. (%)				
None	836 (68.8)	132 (69.8)	704 (68.6)	
Active	199 (16.4)	32 (16.9)	167 (16.3)	0.78
Former	156 (12.8)	23 (12.2)	133 (13.0)	
Unknown	24 (2.0)	2 (1.1)	22 (2.1)	
Intravenous drug use, no. (%)				
None	548 (45.1)	85 (45.0)	463 (45.1)	
Active	180 (14.8)	16 (8.5)	164 (16.0)	0.01
Former	467 (38.4)	87 (46.0)	380 (37.0)	
Unknown	20 (1.7)	1 (0.5)	19 (1.9)	
Tobacco use, no. (%)				
Never	283 (23.3)	50 (26.5)	233 (22.7)	
Active	543 (44.7)	79 (41.8)	464 (45.2)	0.68
Former	366 (30.1)	57 (30.2)	309 (30.1)	
Unknown	23 (1.9)	3 (1.6)	20 (2.0)	
Mental health disorder, no. (%)	438 (36.1)	66 (33.3)	375 (36.6)	0.0004
Referring provider, no. (%)				
Primary care	369 (30.4)	113 (59.8)	256 (25.0)	
Infectious disease	47 (3.9)	17 (9.0)	30 (2.9)	
Gastroenterology	27 (2.2)	8 (4.2)	19 (1.9)	
Emergency room/hospital	131 (10.8)	14 (7.4)	117 (11.4)	<0.0001†
Self-referral	8 (0.7)	5 (2.7)	3 (0.3)	
Hepatology	60 (4.9)	20 (10.6)	40 (3.9)	
Other	149 (12.3)	10 (5.3)	139 (13.6)	
Unknown	423 (34.8)	2 (11)	421 (41.1)	

SD, standard deviation; no., number; †p<0.00001 when the “unknown” category is excluded

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of treatment not completed, p=0.01), and trended towards more non-fibrosis liver imaging (62.7% vs. 53.7%, p=0.06). Furthermore, patients were more successful when provided medication education prior to the taking DAA (80.9% vs. 62.5%, p=0.001) and attending more clinic visits during the treatment course (2 visits vs. 1 visit, p<0.0001).

Virologic response was poorly tracked (Table 4). The vast majority of patients had EOT testing performed (n=137, 72.5% of the treated cohort) and all had undetectable viral loads. Only 68 patients had SVR12 and 60 patients had SVR24 testing (30.6% and 11.6% of the treated cohort, respectively). Of the patients who completed treatment and were tested, 22 patients did not achieve SVR 24 (11.5% of the treated cohort). There was no statistical difference in virologic response tracking or achieving SVR24 amongst the different clinics.

Patients Who Did Not Seek HCV Treatment

432 (35.5%) did not follow-up with any treatment provider and 233 (19.2%) had told their referring provider they were uninterested in treatment. Of the patients who met with a HCV treatment provider, an additional 100 patients (8.2%) opted to not proceed with treatment. More granular data about the reasons for not seeking treatment were difficult to obtain.

Patients Who Did Not Have a Prior Authorization Submitted

Additional analysis was performed to identify any sociodemographic and clinical factors that differentiated patients who successfully proceeded along the care cascade to have a prior authorization submitted versus those who did not (Supplemental Table 1). Patients with active intravenous drug use were less likely to have a prior authorization submitted (16.8% vs. 8.4%). On the other hand, patients with former intravenous drug use were more likely to proceed along the care cascade and have a prior authorization submitted (47.4% vs. 35.7%). Patients with prior HCV treatment more often completed testing and clinic visits in order to have a prior authorization submitted (20.8% vs. 11.8%, p=0.0001). The type of provider who initially identified and referred the patient for treatment also had an impact on whether patients reached the stage of a prior authorization submitted.

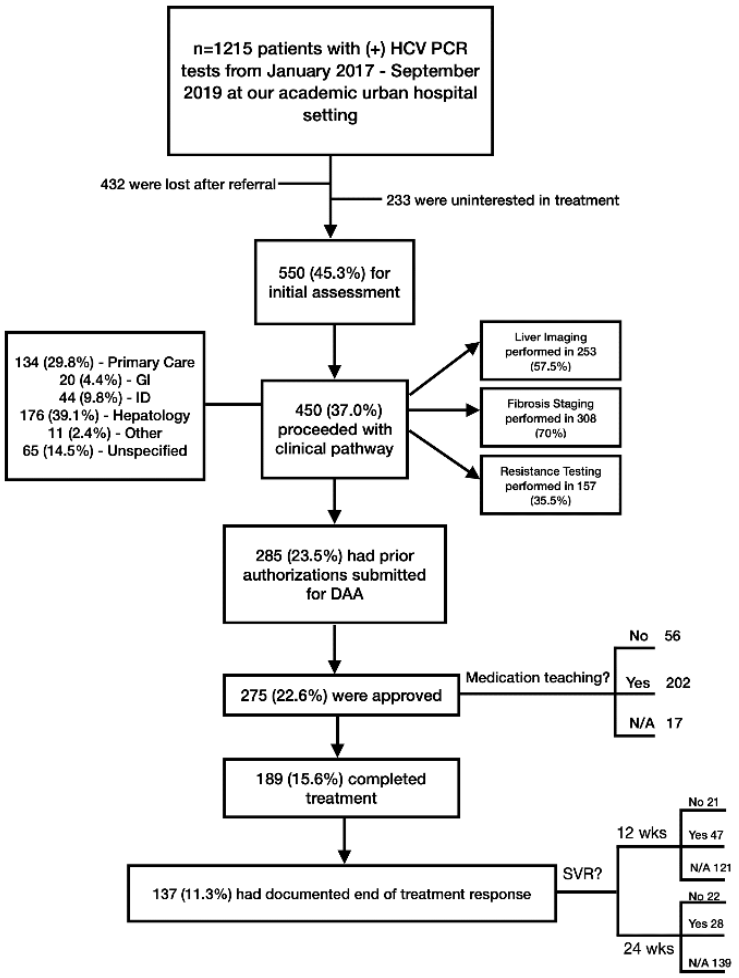

Figure 1: Patient progression along the HCV care cascade

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Table 3: Clinical pathway of HCV patients agreeing to proceed with HCV treatment

Characteristics	Overall (n=450)	Treatment completed (n=189)	Treatment not completed (n=261)	p-value
Clinic setting, no. (%)				
Primary care	134 (29.8)	60 (31.8)	74 (28.4)	
Gastroenterology	20 (4.4)	11 (5.8)	9 (3.5)	
Infectious disease	44 (9.8)	27 (14.3)	17 (6.5)	<0.0001‡
Hepatology	176 (39.1)	83 (43.9)	93 (35.6)	
Other	11 (2.4)	7 (3.7)	4 (1.5)	
Unknown	65 (14.5)	1 (0.5)	64 (24.5)	
Distance from home to treatment provider (miles), median (IQR)	3.5 (2.5.4)	3.2 (1.5.1)	3.7 (2.2-5.5)	0.01
Liver imaging performed prior to treatment, no. (%)	253 (57.5)	116 (62.7)	137 (53.7)	0.06
Fibrosis staging performed prior to treatment, no. (%)	307 (70.0)	162 (86.2)	146 (57.9)	<0.0001
Resistance testing performed prior to treatment, no. (%)	157 (35.5)	80 (42.3)	77 (30.3)	0.01
No. of visits prior to PA submission, median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	0.48
Time from initial visit to PA submission (days), median (IQR)	74 (22-227)	93 (17-204)	72 (22-227)	0.87
Reasons for delay in PA submission, no. (%)				
Patient compliance	18 (5.1)	11 (5.9)	7 (4.2)	
Testing incomplete	92 (26.2)	59 (31.7)	33 (20.0)	
Patient co-morbidities	27 (7.7)	8 (4.3)	19 (11.5)	
Patient hospitalization	6 (1.7)	2 (1.1)	4 (2.4)	0.01
Other	39 (11.1)	14 (7.5)	25 (15.2)	
Multiple	3 (0.9)	2 (1.1)	1 (0.6)	
No delay	166 (47.3)	90 (48.4)	76 (46.1)	
Time from PA submission to medication approval (days), median (IQR)	27 (156.5)	27 (12-56)	27 (12-66)	0.92
Approved regimen, no. (%)				
Elbasvir/grazoprevir	16 (6.0)	11 (5.9)	7 (6.0)	
Glecaprevir/pibrentasvir	164 (54.3)	99 (53.2)	65 (56.0)	
Ledipasvir/sofosbuvir	55 (18.2)	34 (18.3)	21 (18.1)	
Daclatasvir/sofosbuvir	2 (0.7)	2 (1.1)	0 (0.0)	0.97
Paritaprevir/ritovir/ombitasvir/dasabuvir	0 (0.0)	0 (0.0)	0 (0.0)	
Daclatasvir/sofosbuvir	0 (0.0)	0 (0.0)	0 (0.0)	
Sofosbuvir/velpatasvir	62 (20.5)	39 (21.0)	23 (19.8)	
Sofosbuvir/simepravir	1 (0.3)	1 (0.5)	0 (0.0)	
Medication teaching performed, no. (%)	271 (74.3)	152 (80.9)	65 (62.5)	0.001
No. of visits during treatment, median (IQR)	2 (1-3)	2 (1-3)	1 (1-2)	<0.0001

IQR, interquartile range; PA, prior authorization, ‡p<0.00001 when the unknown category is excluded.

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Table 4: Virologic response among patients who completed HCV treatment

Virologic Response	Treatment completed (n=189)
End of treatment response, no. (%)	
Yes	137 (72.5)
No	0 (0.0)
Not checked	52 (27.5)
Sustained virologic response at 12 weeks, no. (%)	
Yes	47 (24.9)
No	21 (11.1)
Not checked	121 (64.0)
Sustained virologic response at 24 weeks, no. (%)	
Yes	28 (14.8)
No	22 (11.6)
Not checked	139 (73.5)

Discussion

The present real-world study demonstrates that in a predominantly under-represented minority, urban population with public insurance, significant barriers to HCV treatment with pan-genotypic DAAs continue to exist. While all patients with chronic HCV were identified by a healthcare provider and subsequently referred to an HCV treatment provider, only 15.6% successfully completed treatment. This is the largest study to date evaluating patients progressing through the HCV care cascade and the only to evaluate treatment since the advent of pan-genotypic DAAs.

All patients with HCV antibody detection were confirmed with HCV RNA polymerase chain reaction (PCR). 100% of patients found to have chronic HCV infection were electronically referred to an HCV treatment provider. Prior studies have reported lower levels of confirmatory testing and subsequent referrals. A recent study published in 2018 at a single US academic center cited only 79% of patients receiving confirmatory RNA testing. Other studies conducted at federally qualified health centers in Philadelphia had confirmatory testing rates between 84-95%.[9] Subsequent referrals rates ranged between 75-90%. Younger patients and those with active substance use disorders were less often referred.

At our health system, all age-appropriate patients are flagged in the inpatient and outpatient HER for HCV screening. Blood samples that test positive for HCV antibody reflex test for HCV RNA PCR. Abnormal results are subsequently flagged in the provider's inbox. These automated systems bypass several human steps needed to correctly identify patients with active infection and easily allow providers to submit electronic referrals for all patients regardless of sociodemographic factors. These interventions have allowed our system to have 100% care linkage to an HCV treatment provider and have proven highly beneficial in increasing HCV diagnosis and referrals other studies in the United States and abroad.[11,12]

The most common barriers to completing HCV treatment related to active patient engagement along the care çascade. The largest drop-off in patient engagement was getting patients to meet with an HCV treatment provider. While all patients were referred, 54.7% never came to an initial appointment with an HCV treatment provider. Patients referred from the inpatient setting were less likely to pursue and complete treatment. Granular details regarding this particular issue are lacking, though could be due to lack of patient education, poor patient-physician relationships, difficulty coordinating care between inpatient and outpatient settings, and/or to low priority of treating a chronic condition that is often asymptomatic.

During the interferon era, poor attendance rates were observed with only 43-76% of patients attending their first appointment with an HCV treatment provider.[13,14,15] More recent studies that included patients during the early DAA era have reported similarly wide ranges of initial attendance rates between 33-70%.[16,17,18] Most studies with higher attendance rates studied fewer clinics within a narrow geographic region, included clinics of one or few medical specialties, and/or only included outpatient clinics. The largest study evaluating 885 chronically infected patients associated with federally qualified health centers in Philadelphia between 2012-2016 had an initial attendance rate of 69.4%.[9]

In this study, reasons patients declined to see an HCV treatment provider were poorly documented. More than one-third of these patients cited disinterest in pursuing treatment despite counseling received by the referring provider. Reasons, when documented, included concerns about the treatments themselves, the duration and commitment to treatment, the patients' view of their other co-morbidities,

and/or whether treatment would have an overall impact on their quality or quantity of life. Of the patients who presented for initial assessment with an HCV treatment provider, 18.1% (8.2% of all HCV patients) decided against further evaluation and testing for HCV treatment. For this group of patients, the decision, when documented, was often made by the patient and physician together and took into consideration issues of quality and quantity of life. Qualitative studies have tried to look at this patient perspective in further detail; however, their extremely small sample sizes and unique patient populations make it challenging to extrapolate for real-world application. [19,20,21] Larger, more inclusive studies are needed to better inform how to better engage patients to seek HCV treatment.

With the availability of pan-genotypic DAAs, genotype and resistance testing and fibrosis staging are often not required in order to prescribe therapy. At our health system, individual practitioners (regardless of their clinic affiliation) required different degrees of testing prior to submitted a prior authorization for DAA therapy. Testing requirements may be seen as a barrier to care for many patients. Yet in our study, patients who underwent fibrosis testing (with labs or imaging), resistance testing, and imaging were associated with treatment completion compared to those who did not. Furthermore, more clinic visits and medication teaching prior to initiating DAA therapy was also associated with treatment completion. These findings suggest that having patients engage with the health center and medical team may improve patient engagement and treatment completion.

Once DAAs were approved by insurance, there remained a large drop-off in patient follow-up to confirm treatment was completed (31% of patients were not confirmed to have completed treatment) and assess SVR. Similar loss of patients after treatment was prescribed and prior authorization approved has been seen in other studies, particularly in urban clinics.[9,10] It may be presumed that a proportion of these patients did ultimately complete treatment. Prior studies have not reached out to such patients to determine the ultimately treatment completion rate. However, the Telepass project reported that about 19% of recalled patients who were documented as having chronic HCV and not treated had actually successfully completed treatment.[22]

Many of the limitations to this study relate to its retrospective nature. Data as to why patient engagement was poor leading to failed progression along the care cascade are lacking. The HCV screening and treatment algorithms are highly variable among the different hospitals and clinics within the health system as well as among the individual referring and treatment providers. While our health system has a significant catchment area, the majority of the population served are urban, under-represented minority patients with public insurance; thus results may not be applicable broadly.

Despite scientific advancements that have allowed us to cure almost all patients with chronic HCV, the dissemination and completion of DAA treatment remain significant challenges. Pan-genotypics have not changed barriers to care linkage and patient progression along the HCV care cascade. Past studies have not informed current health systems how to successfully overcome identified breaks in the care cascade as our study shows that the vast majority of patients remain uncured. Further research and health system efforts must focus on how to increase patient engagement. Areas of interest should include improving care linkage between inpatient and outpatient settings, increasing patient education and awareness of HCV treatments, increasing interactions between medical providers and patients during the evaluation and treatment process.

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Conflicts of Interest: None

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