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Psychosocial Obstacles to Hepatitis C Treatment Initiation Among Patients in Care: A Hitch in the Cascade of Cure

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There are limited data examining the relationship between psychosocial factors and receipt of direct-acting antiviral (DAA) treatment among patients with hepatitis C in large health care organizations in the United States. We therefore sought to determine whether such factors were associated with DAA initiation. We analyzed data from an extensive psychological, behavioral, and social survey (that incorporated several health-related quality of life assessments) coupled with clinical data from electronic health records of patients with hepatitis C enrolled at four health care organizations during 2017-2018. Of 2,681 patients invited, 1,051 (39.2%) responded to the survey; of 894 respondents eligible for analysis, 690 (77.2%) initiated DAAs. Mean follow-up among respondents was 9.2 years. Compared with DAA recipients, nonrecipients had significantly poorer standardized scores for depression, anxiety, and life-related stressors as well as poorer scores related to physical and mental function. Lower odds of DAA initiation in multivariable analysis (adjusted by age, race, sex, study site, payment provider, cirrhosis status, comorbidity status, and duration of follow-up) included Black race (adjusted odds ratio [aOR], 0.59 vs. White race), perceived difficulty getting medical care in the preceding year (aOR, 0.48 vs. no difficulty), recent injection drug use (aOR, 0.11 vs. none), alcohol use disorder (aOR, 0.58 vs. no alcohol use disorder), severe depression (aOR, 0.42 vs. no depression), recent homelessness (aOR, 0.36 vs. no homelessness), and recent incarceration (aOR, 0.34 vs. no incarceration). *Conclusion:* In addition to racial differences, compared with respondents who initiated DAAs, those who did not were more likely to have several psychological, behavioral, and social impairments. Psychosocial barriers to DAA initiation among patients in care should also be addressed to reduce hepatitis C-related morbidity and mortality. (*Hepatology Communications* 2021;5:400-411).

Public health prevention and control of hepatitis C entails identification of infected persons through universal testing, followed by linkage to clinical services and ensuring that persons linked to care receive and complete effective treatment.[1-5] On an individual level, eradication of hepatitis C virus (HCV) infection eliminates the possibility of HCV transmission to others and reduces morbidity and mortality from HCV-attributable hepatic and extrahepatic disease among persons who no longer engage in transmission-associated behaviors.[4] Despite radical improvement in the treatment of HCV infection since the release of second-generation direct-acting antiviral (DAA) medications, uptake of these drugs in many U.S. general health care

Abbreviations: aOR, adjusted odds ratio; AUDIT-C, Alcohol Use Disorders Identification Test; CHeCS, Chronic Hepatitis Cohort Study; DAA, direct-acting antiviral; GAD-7, Generalized Anxiety Disorder-7 scale; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; PHQ8, Patient Health Questionnaire 8 questions; SF-8, Short Form 8; WPAI, Work Productivity and Activity Impairment Questionnaire.

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systems has been low.[6-8] Investigators have identified a variety of sociodemographic and clinical factors associated with reduced likelihood of treatment, including younger age, non-White race, Medicaid coverage, lower annual income, lesser degrees of liver fibrosis, and ongoing or recent drug/alcohol use or mental health disorders.[6-11] However, even in settings in which individuals infected with HCV have largely unrestricted access to DAAs, uptake can be suboptimal and nonsustained.[9,12,13] Under these conditions, studies have identified patient factors related to reduced uptake, such as skepticism about treatment effectiveness and tolerability, limited engagement and negative experiences with providers and health care systems, a lack of perceived urgency for treatment, and competing situational priorities and demands.[12-15]

Few studies have directly examined, using validated psychometric instruments, the psychosocial impediments to treatment initiation among identified patients with hepatitis C who receive integrated clinical care in large U.S. health care organizations. A recent study that classified reasons for DAA noninitiation based on clinical record review found that psychosocial issues were the principal barriers to hepatitis C treatment in an urban academic medical practice.[16] In an earlier study in the pre-DAA era, we found a high degree of physical and psychological impairment among patients in our hepatitis C cohort based on responses to a survey that incorporated several quality of life measures as well as information on employment status, drug/alcohol/tobacco use, recent psychological stressors, and levels of social support.[17] To examine whether these factors were associated with receipt of treatment in the DAA era, we repeated this survey during 2017-2018. Our objective in this analysis was to compare the psychological, behavioral, and social characteristics of patients with diagnosed hepatitis C who initiated DAAs with those who did not initiate DAAs.

Patients and Methods

STUDY POPULATION

We analyzed data collected from adults with chronic HCV infection in the Chronic Hepatitis Cohort Study (CHeCS), an observational study of patients who receive integrated health care services at four sites: Geisinger Health System in Danville, PA; Henry Ford Health System in Detroit, MI; Kaiser Permanente Northwest in Portland, OR; and Kaiser Permanente Hawaii in Honolulu, HI. The criteria for cohort inclusion and analytic methods involved in its derivation have been described in detail.[18,19] The cohort was created based on analysis of electronic health records and administrative data (supplemented with individual chart review) of approximately 2.7 million patients aged ≥18 years who had at least one clinical service visit (i.e., outpatient or inpatient, emergency department, or laboratory test) from January 1, 2006, to December 31, 2013. Patients who met a combination of laboratory-based (i.e., positive HCV RNA) and International Classification

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of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)-based criteria identifying them as having chronic HCV infection were included.[18] Among these patients, prospective follow-up data were available through December 31, 2018. The study protocol was reviewed by an Institutional Review Board and approved by the Office for Human Research Protections at each participating study site. The CHeCS investigation follows the guidelines of the U.S. Department of Health and Human Services regarding the protection of human subjects. The CHeCS study protocol was approved and is renewed annually by the institutional review board at each participating site.

DERIVATION OF THE SURVEYED COHORT

To determine the patient population available for survey invitation, we excluded from the CHeCS hepatitis C cohort those who had died, those who had achieved sustained virologic response (SVR) from any hepatitis C treatment before 2014, and those without contact information. All patients prescribed all-oral second-generation DAA regimens after January 1, 2014, and before survey invitation and had not undergone liver transplant were invited from March through November 2017 to participate. A sample of CHeCS DAA-untreated chronic hepatitis C intended control patients with evidence of continuing care in the previous 5 years (approximately 1:1 untreated to treated at the time of invitation), matched by sex and 5-year birth year range at each site, were also invited to participate in the survey. Patients were sent an invitation letter by U.S. mail at three of the study sites and through the medical record portal at one site (Portland, OR). The letter explained the survey and provided a unique access code for online completion and offered a $25 incentive for participation. If no response was received after 6 weeks, telephone recruiters made up to five attempts to offer the survey as an in-person interview and to encourage online completion of the survey if an interview was declined.

DATA COLLECTED BY ELECTRONIC HEALTH RECORDS AND SURVEY

We collected demographic information from electronic health records, including age, sex, race/ethnicity, mean annual household income (by census tract geocode), and study site. Clinical data collected included HCV genotype, cirrhosis status, Charlson comorbidity score, and duration of CHeCS follow-up. Cirrhosis was defined according to any of the following criteria: a) fibrosis-4 score >5.88[20]; b) liver biopsy equivalent to Metavir F4 or transient elastography results >12.5; or c) ICD-9-CM/ICD-10-CM and Current Procedural Terminology codes consistent with cirrhosis or hepatic decompensation (Supporting Material Appendix S1).[21] Charlson comorbidity scores were calculated from diagnosis codes (excluding liver-related comorbidities) and were used to categorize patients into scores of 0, 1, or ≥2, where a score of 0 indicated no listed comorbidities, 1 indicated a single comorbidity, and a score of 2 or higher indicated multiple comorbidities.[22] Receipt of and start dates for DAA regimens were confirmed based on individual chart review data for all invited participants.

From the survey, we collected information on access to health care, smoking history, drug and alcohol use, employment and work productivity, the presence of affective and anxiety disorders, and life events and social support. Access to health care assessment included questions about difficulty in getting medical appointments, the time and mode of travel required to get to appointments, and the use of the Department of Veterans Affairs health system for hepatitis C care. The survey also incorporated several health-related quality of life instruments, including the Alcohol Use Disorders Identification Test (AUDIT-C),[23] the Work Productivity and Activity Impairment Questionnaire (WPAI),[24] the Patient Health Questionnaire 8 questions (PHQ8) instrument for depression,[25] the Generalized Anxiety Disorder-7 (GAD-7) scale,[26] a validated stressful life events scale adapted from Holmes and Rahe stress scale,[27-28] Short Form 8 (SF-8) physical and mental components,[29,30] and an abbreviated Medical Outcomes Study Social Support Survey.[31,32] Details and scoring methods of these instruments can be found in Supporting Material Appendix S2.

COMPARISONS OF SURVEY RESPONDENTS VERSUS NONRESPONDENTS AND OF RESPONDENTS WHO INITIATED VERSUS DID NOT INITIATE DAAs

Among CHeCS patients with hepatitis C invited to participate in the survey, we compared survey respondents with nonrespondents according to data derived

from electronic health records alone, which included demographics, study site, and clinical characteristics (HCV genotype, cirrhosis status, Charlson comorbidity score, receipt of DAAs, and duration of CHeCS follow-up). Among patients who responded to the survey, we compared characteristics of those who initiated DAA treatment before their survey response date with those who had not initiated DAAs before their survey response. We compared characteristics among respondents with respect to the aforementioned data from electronic health records as well as survey-derived data elements that pertained to access to health care, smoking history, drug and alcohol use, employment and work productivity, the presence of affective and anxiety disorders, and life events and support. Among respondents who did not initiate DAAs, we examined responses to survey questions that addressed access to care issues, including the specialty care referral experience and self-reported reasons for not starting treatment.

STATISTICAL ANALYSIS

Analyses were conducted using SAS 9.4 (Cary, NC). For univariable analysis, the two-sided chi-square test and *t* test were used to compare differences for categorical and continuous variables, respectively; we considered $P < 0.05$ statistically significant. To examine factors associated with DAA initiation among survey respondents, we also conducted multivariable logistic regression analysis, controlling (selected *a priori*) for age, race, sex, study site, insurance status, cirrhosis status, Charlson comorbidity score, and duration of follow-up.

Results

STUDY POPULATION AND DERIVATION OF SURVEYED COHORT

Of 20,349 patients in the chronic hepatitis C cohort, 2,361 had achieved SVR before 2014 and 4,103 had died or had no contact information, leaving 13,885 eligible for the survey. Of these, 2,681 were invited during March through November 2017 to participate; invitees included all 1,408 patients who had been prescribed all-oral second-generation DAA regimens in CHeCS on or after January 1, 2014, and before survey invitation and 1,273 intended control patients (i.e., who had not received DAA before survey invitation), matched by age, sex, and study site. With the passage of time between survey invitation and response, however, 410 (32.2%) of the intended control patients had received DAAs before their date of response to the survey, leaving in effect a final survey-invited sample of 1,818 patients treated with DAA and 863 patients not treated with DAA (n = 2,681).

COMPARISON OF SURVEY RESPONDENTS WITH NONRESPONDENTS

Of these 2,681 patients invited to participate, 1,051 (39.2%) responded to the survey. Compared with survey nonrespondents, respondents were more likely to be non-Hispanic White, aged 51-70 years, and have annual income ≥$30,000, Medicaid or Medicare plus supplemental insurance coverage, and a Charlson comorbidity score ≥1 (Table 1).

COMPARISON OF SURVEY RESPONDENTS WHO INITIATED VERSUS DID NOT INITIATE DAAs

Among the 1,051 patients who responded to the survey, we excluded 126 respondents with characteristics that could affect the receipt of DAAs: previous clinical trial participation (n = 30), hepatitis B virus coinfection (n = 16), human immunodeficiency virus (HIV) coinfection (n = 27), and liver transplant between survey selection and completion date (n = 62). We excluded an additional 31 patients who reported DAA receipt on the survey but for whom we could not confirm a DAA prescription or fill order from electronic health records. With respect to analysis of characteristics associated with receipt of DAAs, the final cohort comprised 894 survey respondents, of whom 690 (77.2%) initiated and 204 (22.8%) did not initiate DAAs. Among these 894 respondents, the mean follow-up in the CHeCS was 9.2 years; patients who did not initiate DAAs had significantly more follow-up than those who did (11.2 vs. 8.6 years, $P < 0.001$).

In the univariable analysis, compared with respondents who received DAAs, those not receiving DAAs

TABLE 1. DEMOGRAPHICS AND CLINICAL FACTORS OF PATIENTS WITH CHRONIC HEPATITIS C INVITED TO PARTICIPATE IN THE 2017-2018 SURVEY, ACCORDING TO RESPONSE (CHeCS)

Variables	N (%)	Responded n (%)	Did Not Respond n (%)	*P* Value
Total	2,681	1,051 (39.2)	1,630 (60.8)	–
Sex				
Male	1,614 (60.2)	608 (57.8)	1,006 (61.7)	
Female	1,067 (39.8)	443 (42.2)	624 (38.3)	0.048
Race				
Non-Hispanic White	1,498 (55.9)	654 (62.2)	844 (51.8)	
Non-Hispanic Black	942 (35.1)	311 (29.6)	631 (38.7)	
Other	241 (9.0)	86 (8.2)	155 (9.5)	<0.001
Age (years) on Jan 1, 2017				
≤30	60 (2.2)	17 (1.6)	43 (2.6)	
31-40	106 (4.0)	32 (3.0)	74 (4.5)	
41-50	130 (4.8)	45 (4.3)	85 (5.2)	
51-60	665 (24.8)	276 (26.3)	389 (23.9)	
61-70	1,469 (54.8)	601 (57.2)	868 (53.3)	
>70	251 (9.4)	80 (7.6)	171 (10.5)	0.005
Insurance status (6 missing)				
None	95 (3.6)	23 (2.2)	72 (4.4)	
Private	1,110 (41.5)	385 (36.6)	725 (44.6)	
Medicaid	376 (14.1)	175 (16.7)	201 (12.4)	
Medicare	911 (34.1)	287 (27.3)	624 (38.4)	
Medicare + supplement	183 (6.8)	181 (17.2)	2 (0.1)	<0.001
Annual income (88 missing)				
<$30K	701 (27.0)	245 (24.0)	456 (29.0)	
$30-<50K	1,065 (41.1)	424 (41.5)	641 (40.8)	
≥$50K	827 (31.9)	352 (34.5)	475 (30.2)	0.009
Study Site				
Portland, OR	274 (10.2)	141 (13.4)	133 (8.2)	
Honolulu, HI	149 (5.6)	70 (6.7)	79 (4.8)	
Detroit, MI	1,645 (61.4)	579 (55.1)	1,066 (65.4)	
Danville, PA	613 (22.9)	261 (24.8)	352 (21.6)	<0.001
Genotype (412 missing)				
Genotype 1	1,859 (81.9)	771 (82.8)	1,088 (81.3)	
Genotype 2	199 (8.8)	82 (8.8)	117 (8.7)	
Genotype 3	159 (7.0)	59 (6.3)	100 (7.5)	
Genotype 4-6	45 (2.0)	16 (1.7)	29 (2.2)	
Genotype mixed	7 (0.3)	3 (0.3)	4 (0.3)	0.780
Cirrhosis status				
Decompensated	321 (12.0)	142 (13.5)	179 (11.0)	
Compensated	734 (27.4)	288 (27.4)	446 (27.4)	
None	1,626 (60.6)	621 (59.1)	1,005 (61.7)	0.128
Charlson comorbidity score				
0	1,730 (64.5)	639 (60.8)	1,091 (66.9)	
1	363 (13.5)	168 (16.0)	195 (12.0)	
2+	588 (21.9)	244 (23.2)	344 (21.1)	0.002
Mean years (SE) CHeCS follow-up	9.71 (0.11)	9.62 (0.18)	9.77 (0.14)	0.340

more likely were aged ≤40 and >70 years (marginally, P = 0.049), had Medicaid and Medicare (i.e., standard Medicare without a Medicare Advantage plan or a supplemental Medigap plan [e.g., Part E, F]) coverage, had annual income <$50,000, were affiliated with the Pennsylvania study site, and had

no cirrhosis. For access to care, substance use, and quality of life scores, those not receiving DAAs were more likely to report the following compared with those who received DAAs: difficulty obtaining medical treatment in the preceding year, dependence on others (including public transportation) to attend clinic appointments, current smoking, a history of drug injection in the preceding 6 months, and having received substance use disorder treatment. Patients who did not receive DAAs were also more likely in the preceding year to have had legal problems, been homeless, and to have been incarcerated. Compared with DAA recipients, those not receiving DAAs more likely had AUDIT-C scores consistent with alcohol use disorder (Table 2), had a higher mean percentage of time that hepatitis C affected general activities, had higher (i.e., worse) mean PHQ8 depression and GAD-7 anxiety scores, had lower (i.e., worse) mean SF-8 mental and physical function scores, and had higher mean scores on the abbreviated Holmes and Rahe stress scale (Table 3). There were no differences according to sex, HCV genotype, Charlson comorbidity score, travel time necessary to access care, history of military service, employment status, and a noncurrent history of smoking or drug use.

In the logistic regression analysis adjusted for age, race, sex, study site, insurance status, cirrhosis status, Charlson comorbidity score, and duration of follow-up, characteristics associated with lower odds of receiving DAAs included non-Hispanic Black race (adjusted odds ratio [aOR], 0.59 compared with non-Hispanic White race), affiliation with the Pennsylvania site (aOR, 0.59 compared to the Michigan site), difficulty getting medical care in the preceding year (aOR, 0.48 compared with no difficulty), injection drug use in the preceding 6 months (aOR, 0.11 compared with no recent injection), positive AUDIT-C score (aOR, 0.58 compared with negative score), PHQ8 score consistent with severe depression (aOR, 0.42 compared with no depression), homelessness in the preceding year (aOR, 0.36 compared with not homeless), and incarceration in the preceding year (aOR, 0.34 compared with no incarceration) (Table 2). Patients with compensated cirrhosis had greater odds of receiving DAAs (aOR, 1.77 compared with no cirrhosis).

Among respondents who did not initiate DAAs, we examined responses to survey questions that addressed access to care issues, including the specialty care referral experience and self-reported reasons for not starting treatment. Among those who had not received specialty care, 34.5% said they were never referred, 11.9% did not know whether or why they had not been referred, 10.7% had more pressing medical issues, 8.3% reported they "did not feel sick," 6.0% were unable to pay for additional care visits, 4.8% lacked transportation, and 15.5% had some "other reason." Among respondents referred but not treated, 19.5% reported that the provider said they were "not sick enough," 13.3% were not sure why they were not treated, 11.6% were denied insurance coverage, 5.2% reported other medical conditions, 4.7% reported cost, 3.3% reported alcohol or drug use, 2.8% reported more urgent personal issues, 1.4% were waiting for better treatment options, 0.9% did not want to start DAAs, 0% said they did not start because of a history of nonadherence, 22.1% said it was for "other reasons." (Note: percentages do not add to 100 because blank responses were not included.)

Discussion

To determine patient characteristics associated with receipt of DAAs, we examined responses to an extensive psychosocial survey coupled with electronic health records of approximately 900 patients with chronic hepatitis C enrolled in four large health care organizations in the United States. These patients had a mean follow-up of approximately 9 years. Survey-derived data in univariable analysis revealed that those who did not initiate DAAs were more likely to report adverse behavioral, psychological, and social conditions compared with patients who received treatment. These included perceived difficulties accessing health care providers and dependence on others to get to health care appointments as well as recent injection drug use, alcohol use disorder, current smoking, higher depression and anxiety scores, homelessness, and legal difficulties and incarceration. Compared with patients who received DAAs, those who did not reported significantly higher levels of stress, more hepatitis C-attributed impairment of daily activities, lower levels of physical and mental function, and lesser degrees of social support. Findings were similar in the multivariable

TABLE 2. CHARACTERISTICS AND SURVEY RESPONSES OF PATIENTS WITH CHRONIC HEPATITIS C ASSOCIATED WITH INITIATION OF DAAS (CHECS, 2017-2018)

				Univariable	Multivariable†	
Variables	n (%)	DAA Before Survey n (%)	No DAA Before Survey n (%)	*P* Value*	aOR of DAA Before Survey (95% CI)	*P* Value
Total	894	690 (77.2)	204 (22.8)	–		
Sex						
Male	508 (56.8)	399 (57.8)	109 (53.4)	0.300	ref	
Female	386 (43.2)	291 (42.2)	95 (46.6)		1.00 (0.69-1.46)	0.992
Race						
Non-Hispanic White	555 (62.1)	437 (63.3)	118 (57.8)	0.081	ref	
Non-Hispanic Black	266 (29.8)	193 (28.0)	73 (35.8)		0.59 (0.36-0.98)	0.040
Other	73 (8.2)	60 (8.7)	13 (6.4)		0.82 (0.41-1.65)	0.579
Age (years) on Jan 1, 2017						
≤30	16 (1.8)	9 (1.3)	7 (3.4)	0.049	ref	
31-40	28 (3.1)	16 (2.3)	12 (5.9)		1.18 (0.33-4.26)	0.801
41-50	38 (4.3)	30 (4.3)	8 (3.9)		3.16 (0.81-12.28)	0.097
51-60	240 (26.8)	187 (27.1)	53 (26.0)		1.90 (0.64-5.61)	0.246
61-70	505 (56.5)	397 (57.5)	108 (52.9)		2.16 (0.73-6.42)	0.166
>70	67 (7.5)	51 (7.4)	16 (7.8)		1.95 (0.53-7.10)	0.312
Insurance status						
None	19 (2.1)	12 (1.7)	7 (3.4)	<0.001	ref	
Private	338 (37.8)	280 (40.6)	58 (28.4)		1.53 (0.44-5.31)	0.501
Medicaid	154 (17.2)	107 (15.5)	47 (23.0)		0.90 (0.25-3.17)	0.868
Medicare	236 (26.4)	170 (24.6)	66 (32.4)		0.90 (0.26-3.15)	0.873
Medicare + supplement	147 (16.4)	121 (17.5)	26 (12.7)		2.32 (0.61-8.78)	0.216
Annual income (27 missing)						
<$30K	212 (24.5)	151 (22.6)	61 (30.7)	<0.001	ref	
≥$30-<50K	359 (41.4)	265 (39.7)	94 (47.2)		0.94 (0.60-1.48)	0.785
≥$50K	296 (34.1)	252 (37.7)	44 (22.1)		1.69 (0.98-2.90)	0.057
Study site						
Portland, OR	130 (14.5)	109 (15.8)	21 (10.3)	<0.001	1.63 (0.80-3.32)	0.179
Honolulu, HI	62 (6.9)	55 (8.0)	7 (3.4)		1.74 (0.72-4.23)	0.222
Detroit, MI	467 (52.2)	366 (53.0)	101 (49.5)		ref	
Danville, PA	235 (26.3)	160 (23.2)	75 (36.8)		0.59 (0.36-0.96)	0.033
Cirrhosis status						
Decompensated	79 (8.8)	67 (9.7)	12 (5.9)	0.005	1.63 (0.78-3.42)	0.196
Compensated	243 (27.2)	201 (29.1)	42 (20.6)		1.77 (1.13-2.78)	0.013
None	572 (64.0)	422 (61.2)	150 (73.5)		ref	
Difficulty getting medical treatment in the past year (5 missing)						
No	802 (90.2)	634 (92.4)	168 (82.8)	<0.001	ref	
Yes	87 (9.8)	52 (7.6)	35 (17.2)		0.48 (0.27-0.83)	0.009
Mode of travel to health care provider (7 missing)						
Drive self	628 (70.8)	505 (73.6)	123 (61.2)	0.005	ref	
Friend/family member drives	172 (19.4)	118 (17.2)	54 (26.9)		0.63 (0.40-1.02)	0.059
Take public transportation	80 (9.0)	57 (8.3)	23 (11.4)		0.66 (0.35-1.25)	0.206
Walk or ride bicycle	7 (0.8)	6 (0.9)	1 (0.5)		1.32 (0.14-12.29)	0.806
Current smoker						
No	424 (58.5)	341 (61.7)	83 (48.3)	0.003	ref	
Yes	301 (41.5)	212 (38.3)	89 (51.7)		0.68 (0.44-1.03)	0.069

TABLE 2. *Continued*

Variables	n (%)	DAA Before Survey n (%)	No DAA Before Survey n (%)	Univariable *P* Value*	Multivariable† aOR of DAA Before Survey (95% CI)	Multivariable† *P* Value
Injected drugs in last 6 months						
No	412 (97.4)	311 (98.7)	101 (93.5)	0.008	ref	
Yes	11 (2.6)	4 (1.3)	7 (6.5)		0.11 (0.02-0.54)	0.006
Ever in drug treatment program (7 missing)						
No	588 (66.3)	474 (69.3)	114 (56.2)	<0.001	ref	
Yes	299 (33.7)	210 (30.7)	89 (43.8)		0.83 (0.55-1.25)	0.363
AUDIT-C score (13 missing)						
Negative	696 (79.0)	549 (80.7)	147 (73.1)	0.023	ref	
Positive	185 (21.0)	131 (19.3)	54 (26.9)		0.58 (0.38-0.90)	0.015
PHQ8 depression score categories (30 missing)						
Negative <10	629 (72.8)	501 (75.3)	128 (64.3)	0.007	ref	
Moderate 10-14	119 (13.8)	88 (13.2)	31 (15.6)		0.72 (0.42-1.24)	0.233
Moderate-severe 15-19	74 (8.6)	50 (7.5)	24 (12.1)		0.71 (0.38-1.33)	0.287
Severe ≥20	42 (4.9)	26 (3.9)	16 (8.0)		0.42 (0.20-0.90)	0.025
Legal problems in past year (10 missing)						
No	807 (91.3)	632 (92.4)	175 (87.5)	0.045	ref	
Yes	77 (8.7)	52 (7.6)	25 (12.5)		0.66 (0.35-1.23)	0.188
Homeless in past year (8 missing)						
No	858 (96.8)	671 (97.8)	187 (93.5)	0.005	ref	
Yes	28 (3.2)	15 (2.2)	13 (6.5)		0.36 (0.14-0.94)	0.037
Incarcerated in past year (9 missing)						
No	864 (97.6)	674 (98.3)	190 (95.5)	0.033	ref	
Yes	21 (2.4)	12 (1.7)	9 (4.5)		0.34 (0.12-0.94)	0.037

*Two-sided chi-square test.
†Multivariable logistic regression analysis adjusted for sex, race, age, insurance status, study site, cirrhosis status, Charlson comorbidity score, and length of follow-up.
Variables omitted from table for brevity and nonsignificance: time needed to travel, history of military service, planned to use VA for hepatitis C care, past smoker, injected drugs in the past, used needle exchange in the past, illicit drug use in the past, employment status.
Abbreviations: CI, confidence interval; ref, reference; VA, Veterans Affairs.

TABLE 3. SURVEY RESPONSES OF PATIENTS WITH CHRONIC HEPATITIS C ACCORDING TO RECEIPT OF DAAS (CHeCS, 2017-2018)

Variables	Mean (SE)	DAA Before Survey, Mean (SE)	No DAA Before Survey, Mean (SE)	*P* Value
Total	894	690 (77.2)	204 (22.8)	–
Mean years of follow-up	9.22 (0.19)	8.63 (0.22)	11.20 (0.37)	<0.001
Mean hours of missed work in the past week due to hepatitis C (5 missing)	0.57 (0.21)	0.48 (0.20)	0.92 (0.67)	0.410
Mean percentage of the time hepatitis C affected activities	14.69 (1.18)	12.47 (1.26)	21.74 (2.79)	0.002
Mean percentage of the time hepatitis C affected work productivity	4.73 (0.82)	4.01 (0.85)	7.78 (2.30)	0.091
Mean PHQ8 depression score (30 missing)	6.21 (0.21)	5.79 (0.23)	7.61 (0.49)	<0.001
Mean GAD7 anxiety score in 2017 survey (not included in 2011-2012 survey) (26 missing)	5.62 (0.21)	5.26 (0.23)	6.83 (0.47)	0.003
Mean Stressful Life Events score (34 missing)	0.96 (0.04)	0.91 (0.04)	1.13 (0.09)	0.015
Mean SF-8 mental function score (26 missing)	46.66 (0.39)	47.38 (0.44)	44.23 (0.84)	<0.001
Mean SF-8 physical function score (26 missing)	43.94 (0.39)	44.45 (0.44)	42.20 (0.82)	0.012
Mean social support score (105 missing)	4.00 (0.13)	3.87 (0.15)	4.46 (0.28)	0.042

model; lower odds of DAA initiation were associated with perceived difficulties getting medical care, severe depression, alcohol use disorder, and recent injection drug use, homelessness, or incarceration. Unlike the univariable analysis results, non-Hispanic Black race was also associated with lower odds of DAA initiation in the multivariable model (as we found in an earlier uptake analysis of our cohort[8]).

Efforts to eliminate hepatitis C hinge foremost on the identification of infected persons and enabling their access to clinical care. However, considerable barriers to DAA initiation, which is a critical stage in the cascade of care, may remain even when a patient with identified hepatitis C is "in care." The steps needed to initiate DAAs may require a persistence and commitment that exceeds the capacity of persons with other more urgent and acute demands and priorities or of those afflicted with comorbid illness. For example, psychiatric conditions, such as severe depression, may impair one's ability to engage the medical system and pursue the often rigorous process of gaining payer approval for DAA treatment. Additional limitations involving social support, transportation to appointments, or concurrent problems related to employment, housing, and legal entanglements, may further complicate the pursuit of treatment. Multiple clinic visits for diagnostic assessment and drug testing, appointments with social workers and patient navigators, and numerous phone calls may be required to complete the preauthorization process; any of these might be impracticable or insurmountable for persons with ongoing psychosocial impairments.

Studies have examined interventions to alleviate barriers to various components of the hepatitis C care cascade. Measures to improve treatment initiation, the focus of this analysis, have included patient education and outreach, colocalization of services, nonspecialist hepatitis C treatment education and care delivery, use of telemedicine, patient navigation programs, and cost management approaches to help defray out-of-pocket expenses.[33-36] In recent years, government-affiliated health care systems, such as in the U.S. Department of Veterans Affairs, Cherokee Nation, and Alaskan Native Tribal Health Consortium, have demonstrated remarkable improvements in DAA access and uptake, illustrating the potential advantages of unified health delivery systems with relatively homogeneous patient populations.[37-40] In the private sector, specialty clinics embedded within large health care organizations also have demonstrated the capacity to improve DAA access. During 2014 through 2017, cumulative DAA uptake among Kaiser Permanente Northern California patients with HIV/HCV coinfection was 70%.[41] These patients received health care planning support from case managers and were prioritized for hepatitis C treatment, which was coordinated within each medical facility by a lead infectious disease clinician and a system-wide hepatitis C task force comprised of clinicians, researchers, and community-based advocates. Improving DAA uptake may be more challenging among a less unified hepatitis C population (i.e., not otherwise united by a shared clinical condition, such as HIV coinfection) in private sector health care organizations. For example, during the same time period, we found that approximately 33% of all CHeCS patients with active HCV infection initiated DAAs.[42] However, at the Kaiser Permanente Hawaii study site, nearly 45% initiated treatment. In 2003, this site established a dedicated hepatitis C clinic and began taking a proactive approach to hepatitis C management using a framework to prompt primary care providers to consider specialty care referral for assessment and treatment of patients infected with HCV at the time of diagnosis.[43] In contrast, patients with hepatitis C in more diffuse care networks, particularly those serving nonurban populations, may have challenges in accessing specialty care and DAAs.[44] This may in part explain why patients at the Pennsylvania study site, a network serving a sizable nonurban population, had lower odds of initiating DAAs than those at the other three sites.

Expanding the pool of health care professionals who can provide DAAs can also improve treatment uptake. Data demonstrate that hepatitis C treatment can be effectively delivered by primary care physicians, nurse practitioners, clinical pharmacy specialists, physician assistants, and registered nurses without compromising treatment efficacy or safety.[45,46] Accordingly, the American Association for the Study of Liver Diseases Hepatitis C Guidance Panel recently published simplified treatment algorithms for treatment-naive adults (without cirrhosis or with compensated cirrhosis).[2] These algorithms are designed to be used by any health care provider knowledgeable about hepatitis C, including those without extensive experience who have access to a specialist, and cover guidance on pretreatment assessment, on-treatment monitoring, assessment of response, and posttreatment management.

Although our surveyed population eligible for analysis consisted of approximately 900 respondents with long-term follow-up, our results may not be generalizable to the entire CHeCS hepatitis C cohort (as only 40% of invited patients responded), to other geographic settings, or to cohorts with different characteristics. Indeed, our surveyed population could be viewed as a unique subset of the complete CHeCS hepatitis C cohort as uptake within the surveyed cohort was approximately 77% compared to 33% for the overall hepatitis C cohort during 2014-2017.[42] Our analysis was limited, therefore, in that it was (unintentionally) heavily weighted with survey respondents who received DAAs, which may have hampered our ability to rely on survey responses to understand barriers to treatment in the overall survey-eligible cohort of nearly 14,000 patients. However, it is remarkable that the presence of psychosocial impairments was significantly more frequent among respondents who did not initiate DAAs compared with those who did, given that only 23% of respondents did not initiate DAAs. It is possible that these impairment differences were even more pronounced among the 60% of patients who did not respond to the survey. Also, given that only one sixth of our respondents were Medicaid recipients, it could be reasoned that treatment populations consisting of mostly patients with Medicaid might demonstrate even more pervasive degrees of psychosocial impairment.

Nonetheless, for some variables, such as recent injection drug use, the number of respondents who reported recent use was low (n = 11), so differences between treated and untreated respondents, although statistically significant, may have been underpowered to make definitive assessments. Our study was also limited by the absence of provider perspectives about barriers to DAA initiation, which reduced our capacity to explicate fully the associations between psychosocial impediments and initiation of treatment. For example, it is unknown whether patients who were severely depressed were less likely to seek treatment in the first place, if they were depressed because they had sought treatment but were denied it, or if they were offered treatment but declined to follow through with the process. We did, however, examine specific access to care issues among respondents who did not initiate DAA treatment. Almost half of these patients were not referred or were unsure whether they had been referred to specialty care. Of those who had been referred but not treated, approximately one third reported that either they were told they were "not sick enough" for treatment or were not told at all why they were not offered DAAs. Only small proportions of nontreated respondents explicitly noted an inability to pay for referral visits and medications, that they had been denied insurance coverage for them, or reported having more pressing medical or situational concerns. However, it was probable that some patients were not referred or offered treatment because of provider awareness of the futile nature of preauthorization constraints or because of "other reasons" not acknowledged by respondents; therefore, the low frequency of survey-reported financial and insurance barriers or of unacknowledged issues regarding nonadherence or substance use/mental health problems likely underestimated the true effect of these factors. For example, respondents with Medicaid and Medicare (without supplemental coverage) were less likely to receive DAAs in the univariable analysis. In Michigan, the location of our principal study site, Medicaid coverage for DAAs was delayed and fibrosis restrictions remained in place long thereafter.[47] A similar situation existed in Pennsylvania where another study site was located. The situation is less clear with our Medicare respondents, although there have been reports of difficulties with receipt of DAAs among Medicare recipients, particularly those lacking Part D coverage or with Part D coverage subject to high copays, or with Medicare/Medicaid dual coverage subject to state-specific Medicaid drug coverage rules.[48] Unfortunately, not all our study sites (each in a different state) collected information on Part D coverage, so we were not able to discern whether or to what degree this might be an issue.

Understanding such complex issues might be difficult to unravel with respect to causation, yet our identification of several adverse behavioral, psychological, and social qualities associated with noninitiation of DAAs among these patients in care suggests the presence of additional treatment barriers to be addressed by clinicians and programs dedicated to reducing the morbidity and mortality burden of hepatitis C and ultimately to its elimination as a public health threat.

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