The use of all-oral direct-acting antivirals in hepatitis C virus-infected patients with substance use disorders

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What is already known about this subject

- Clinical trials reported that hepatitis C virus (HCV)-infected patients with substance use disorders (SUDs) who were treated with all-oral direct acting antivirals (DAA) achieved equally high sustained virologic response rates compared to HCV-infected patients without SUDs.
- The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America recommends timely DAA treatment for all patients with HCV, including patients with SUDs.
- High drug costs have led insurers to restrict access to DAA treatments, requiring patients to meet specific prior authorization approval (e.g., abstinence from drug or alcohol use).

What this study adds

- Only one-third of newly diagnosed patients with chronic HCV filled their prescription for DAA therapy following their HCV diagnosis regardless of SUD status.
- After adjusting for demographics and clinical characteristics, HCV-infected patients with SUDs were significantly less likely to initiate DAA treatments compared to those without SUDs (24% vs. 34%, $P < 0.01$).
- Once patients initiated DAA therapy, the overall discontinuation rate was low (3%) and there was no difference in discontinuation of DAA treatment between those with and without SUDs (4% vs. 3%).

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J Manag Care Spec Pharm.
2021;27(7):873-81

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ABSTRACT

BACKGROUND: There is evidence that barriers exist for the initiation of direct-acting antiviral (DAA) treatment for hepatitis C virus (HCV) for those with substance use disorders (SUDs). However, real world clinical evidence of DAA treatment initiation following receipt of a prescription and continuation among those with SUDs and HCV is lacking.

OBJECTIVES: To (1) compare HCV treatment initiation (prescription fill) rates and early discontinuation rates between HCV-infected patients with and without SUDs in the DAA era, and (2) identify patient-level factors associated with HCV treatment initiation and early discontinuation in patients with SUDs.

METHODS: A retrospective cohort analysis of the MarketScan databases (January 2012-December 2018) was conducted for

newly diagnosed treatment naïve HCV-infected patients (age ≥ 18) with and without SUDs. We used multivariable Cox regression to estimate adjusted hazard ratios (aHRs) with 95% confidence intervals of treatment initiation and early discontinuation in those with SUDs versus those without.

RESULTS: We identified a total of 29,228 newly diagnosed HCV-infected patients (6,385 with SUDs and 22,843 without SUDs).

Overall, DAA treatment initiation for patients with SUDs was significantly lower than that for those without SUDs (24% vs 34%; $P < 0.01$). After adjusting for demographics and clinical characteristics, patients with SUDs were less likely to initiate DAA treatments than those without SUDs (aHR, 0.87 [0.82-0.92]). There was no difference in discontinuation of DAA treatment between those with and without SUDs (4% vs 3%; aHR, 1.13 [0.81-1.60]). Among patients with SUDs ($n = 6,385$), lower rates of initiating DAA treatment was associated with younger age, and comorbidities including alcoholic liver disease (ALD; aHR, 0.44 [0.33-0.57], chronic kidney disease (CKD) (aHR, 0.52 [0.36-0.75]), and hepatitis B virus (HBV; aHR, 0.64 [0.44-0.92]). DAA treatment discontinuation was associated with younger age, ribavirin (RBV) therapy (aHR, 3.78 [2.21-6.47]), and cirrhosis diagnosis (aHR, 2.42 [1.21-4.84]) but not SUD treatment (aHR, 0.68 [0.34-1.34]).

CONCLUSIONS: HCV-infected patients with SUDs had significantly lower treatment initiation rates, especially in young females and those with ALD, CKD, and HBV. No difference was found in DAA discontinuation. However, younger patients with RBV treatment and/or cirrhosis were more likely to stop treatment. Interventions directed towards these groups are needed to enhance DAA initiation and treatment maintenance among HCV-infected patients with SUDs.

Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States. The high-risk behavior of injection drug use in this country accounts for a disproportionately large burden of HCV infection (~75% of newly acquired cases and ~50% of cases of chronic infection).^{1,2} According to data from the Centers for Disease Control and Prevention, the number of cases of acute HCV infection has more than tripled between 2010 and 2016, following significant increases in substance use disorders (SUDs) driven by increased intravenous injection of illicit drugs, abuse of prescription opioids among young persons, and concomitant use of alcohol and illicit drugs.³⁻⁶

The vast majority of HCV-infected patients with SUDs have not received interferon-based therapy for their HCV infection due to concerns about influenza-like symptoms and neuropsychiatric adverse events associated with interferon-based therapy.⁷⁻⁹ Fortunately, in recent years, HCV treatment has taken a major step forward with the introduction of highly efficacious, interferon-free, all-oral direct-acting antiviral (DAA) treatments, providing therapeutic efficacy in more than 95% of patients, including patients with SUDs, within 8-12 weeks.¹⁰ HCV-infected patients with SUDs who were treated with DAAs achieved equally high sustained virologic response rates as treated patients without SUDs.¹¹ These new DAA therapies opened up treatment options for HCV-infected patients with SUDs. Nevertheless, high drug costs have led insurers to restrict

access to these medications, requiring patients to meet specific prior authorization approvals (eg, abstinence from drug or alcohol use).^{12,13} Thus, patients with SUDs continue to face barriers to treatment.¹⁴

To explore how large the gap is for the rates of DAA treatment initiation and DAA treatment discontinuation between HCV-infected patients with SUDs and without in the real world, we aimed to compare the DAA treatment initiation and early discontinuation rates between the two groups. Additionally, we examined the factors associated with HCV treatment initiation and early discontinuation, particularly SUD status.

Methods

DATA SOURCE

We conducted an exploratory retrospective cohort study using the Truven Health Analytic MarketScan Commercial and Medicare Supplemental databases which includes complete claims for retirees with Medicare supplemental insurance paid by employers but not those who only receive Medicare as their primary insurance (2012-2018).¹⁵ Truven is a nationwide administrative claims database containing person-level information for diagnoses, procedures, and prescriptions across all settings including physician outpatient office visits, hospital stays, and pharmacy claims for over 80 million individuals in the commercial dataset and six million individuals in the Medicare Supplement database. Institutional review board approval was obtained from the University of Florida.

STUDY POPULATION

Identification of Newly Diagnosed Chronic HCV-Infected Patients and Comorbidities. We established the newly diagnosed chronic HCV cohort using October 2013 to December 2018 Truven data as described above while data from October 2012 to September 2013 were used to ensure at least one year of claims prior to HCV diagnosis. We identified patients aged ≥ 18 years with newly diagnosed chronic HCV using the *International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification* (ICD-9-CM) codes and ICD-10-CM codes ([Supplementary Table 1](#), available in online article). A patient was determined to have chronic HCV if they had one inpatient chronic HCV diagnosis or two outpatient diagnoses of chronic HCV on separate days within one year.¹⁶ Patients were included if they were continuously enrolled in their health plan one year before and 6 months after their first HCV diagnosis. We excluded patients who had decompensated cirrhosis, hepatocellular carcinoma, or liver transplantation or who had undergone

HCV therapy including interferon-based or DAA-based treatments during the 1-year period prior to the first HCV diagnosis to make the cohort homogeneous. Patients were followed from the first HCV diagnosis until at the end of their health insurance enrollment or December 31, 2018, whichever came first. In addition, selected comorbidities were also identified by ICD-9-CM/ICD-10-CM codes ([Supplementary Table 1](#)).

Identification of HCV-Infected Patients with SUD. The chronic HCV-infected patients were further categorized based on a diagnosis/treatment of SUD (HCV with SUD or HCV without SUD) recorded between one year before and 6 months after the first HCV diagnosis. By adapting a previously validated algorithm,¹⁷ patients were considered to have an SUD if they met 1 of 2 criteria: (1) had at least one inpatient or one outpatient claim of drug or alcohol use disorders using ICD-9-CM/ICD-10-CM codes ([Supplementary Table 1](#)); or (2) had a record of methadone, buprenorphine, acamprosate, or naltrexone for opioid use disorder or alcohol use disorder.^{18–20}

DAA Treatment Initiation Rate. We defined DAAs using the National Drug Codes according to the US Food and Drug Administration (FDA) and American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) definitions for treatment-naïve patients during the time period of interest ([Supplementary Table 2](#), available in online article). We grouped DAA treatment into two groups: DAA only or DAA with ribavirin (RBV).

Initiation rate for all-oral DAA therapy was defined as the rate of the first DAA prescription without interferon using pharmacy claims, per 1,000 person-months during the study period. For each individual, the person-months of follow-up were calculated from the first HCV diagnosis date to the first DAA prescription, end of enrollment, or December 31, 2018, whichever came first.

DAA Treatment Discontinuation Rate. Of the HCV-infected patients who initiated DAA therapy, patients were excluded from the discontinuation rate analyses if they disenrolled from their health plan during treatment, switched to another DAA therapy, or had zero days' supply of DAA medication. Patients were considered to have discontinued early if the observed treatment duration (summing the number of days from the filling of the first prescription to the end date of the last prescription claim fill date plus days' supply) was shorter than the expected treatment duration (a 30-day gap was allowed as discussed in prior studies).^{21–23} The expected treatment duration was based on the 2017 AASLD/IDSA HCV treatment guidelines accounting for baseline cirrhosis diagnosis.²¹ For example, we used 8 weeks for sofosbuvir/

ledipasvir among patients without cirrhosis and a 12-week treatment of the other all-oral therapy with and without cirrhosis.

The DAA therapy discontinuation rate (per 1,000 person-months) was defined as time to the earliest date of a 30-day gap prior to the completion of therapy from the first DAA prescription date.

STATISTICAL ANALYSIS

Baseline characteristics (one year before the first HCV diagnosis) were compared between HCV-infected patients with and without SUDs using t-tests for continuous variables and chi-square tests for categorical variables.

To compare DAA initiation or discontinuation between HCV-infected patients with and without SUDs, chi-square tests were used. We used multivariable Cox proportional hazards regression models to estimate adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) of treatment initiation and early discontinuation in those with SUDs versus those without (the proportional hazard assumption was not violated based on the Schoenfeld residual). Additionally, the other multivariable Cox regressions were separately used to identify factors associated with DAA initiation/early discontinuation in patients with SUDs or those without, controlling for covariates measured one year before the DAA initiation date (the covariates are listed in [Supplementary Table 3](#), available in online article). Because the 8-week regimen for sofosbuvir/ledipasvir among patients without cirrhosis was not recommended by guidelines until 2016, we performed a sensitivity analysis for discontinuation using 12-week sofosbuvir/ledipasvir during 2013–2015 and 8-week sofosbuvir/ledipasvir during 2016–2018 for patients without cirrhosis. We assessed for multicollinearity using a variance inflation factor (VIF) with a cutoff of either 5 or 10. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

PATIENT CHARACTERISTICS

Of 29,228 patients newly diagnosed with HCV, 22% (n=6,385) had SUDs while 78% (n=22,843) did not have SUDs ([Supplementary Figure 1](#) and [Supplementary Table 1](#), available in online article). HCV-infected patients with SUDs were more likely to be younger (mean age 43±17 vs 56±11 years), more likely male (63% vs 58%), have cirrhosis (2.8% vs 2.4%), and were more likely to have depression, schizophrenia/bipolar, epilepsy, and be pregnant compared to HCV-infected patients in the non-SUD group (all P values

<0.001). Of HCV-infected patients with SUDs, 56% had an opioid use disorder, 60% had other drug-related disorders, and 48% had an alcohol use disorder. Approximately one-third of individuals with SUDs received some form of medication for SUD.

DAA TREATMENT INITIATION RATE

Among 29,228 patients with a new diagnosis of HCV, 68% of HCV-infected patients (n=19,874) did not receive any HCV treatment. The remaining 32% (n=9,354) of HCV-infected patients received all-oral DAA treatment (Table 1). Overall, of the treated patients, 81% received DAA only and 19% received DAA plus RBV. Among the HCV-infected patients with SUDs, 24% initiated DAA therapy, which was significantly lower compared to the initiation rate of 34% of HCV-infected patients without SUDs (13 vs 18 per 1,000 person-months; $P < 0.001$). After adjusting for covariates, chronic HCV-infected patients with SUDs were less likely to initiate all-oral DAAs than those without SUDs (adjusted hazard ratio [aHR], 0.87 [0.82–0.92]; Table 2).

FACTORS ASSOCIATED WITH DAA TREATMENT INITIATION

Among patients with SUDs (n=6,385), factors associated with a significantly lower probability of initiating DAAs included: being younger [18–35 years old (aHR, 0.85 [0.73–0.99]) and 36–50 years old (aHR, 0.80 [0.68–0.95]) vs 51–64 years old]; being female (aHR, 0.81 [0.72–0.91]); having a Health Maintenance Organization (HMO; aHR, 0.80 [0.67–0.96]) when compared to a Preferred Provider Organization. Having hepatitis B virus (aHR, 0.64 [0.44–0.92]), mental disorders (aHR, 0.69 [0.62–0.77]), cardiovascular disease (aHR, 0.78 [0.66–0.92]), chronic kidney disease (aHR, 0.52 [0.36–0.76]), alcoholic liver disease (aHR, 0.44 [0.33–0.57]), and being pregnant (aHR, 0.58 [0.40–0.86]) were associated with a significantly lower probability of initiating DAAs (Supplementary Table 4, available in online article). In contrast, patients having cirrhosis were more likely to initiate DAA treatment (aHR, 2.68 [2.32–3.10]). However, receiving medication for an SUD was not associated with DAA initiation (aHR, 0.91 [0.80–1.04]). Similar factors were observed among patients without SUDs (n=22,843; Supplementary Table 4, available in online article).

TREATMENT DISCONTINUATION

Among the 9,354 HCV-infected patients who initiated DAA treatment, 3% (n=262) of patients discontinued their DAA treatment. Among the SUD group (n=1,529), 4% (n=61) discontinued their treatment (of which, 52% discontinued DAA treatment only and 48% discontinued DAAs in combination with RBV treatment) providing a crude incidence rate

TABLE 1 Baseline Characteristics for HCV-Infected Patients in Substance Use Disorders (SUD) and Non-SUD Groups^a

Characteristic	SUD group (n=6,385)	Non-SUD group (n=22,843)	P value
Age (mean; SD)	43 (17)	56 (11)	<0.001
18–35	2,566 (40.2)	1,327 (5.8)	
36–50	884 (13.8)	3,432 (15.0)	
51–64	2,590 (40.6)	15,034 (65.8)	
≥ 65	345 (5.4)	3,050 (13.4)	
Gender (male)	4,029 (63.1)	13,146 (57.6)	<0.001
Region			<0.001
Northeast	1,346 (21.1)	4,652 (20.4)	
North central	1,564 (24.5)	3,992 (17.5)	
South	2,581 (40.4)	9,850 (43.1)	
West	838 (13.1)	4,100 (18.0)	
Unknown	56 (0.9)	249 (1.1)	
Type of insurance			0.002
PPO	3,471 (54.4)	12,492 (54.7)	
HMO	827 (13.0)	3,215 (14.1)	
COMP	690 (10.8)	2,122 (9.3)	
POS	457 (7.2)	1,618 (7.1)	
Others ^b	940 (14.7)	3,396 (14.9)	
Comorbidities			
CKD	208 (3.3)	1,183 (5.2)	<0.001
COPD	941 (14.7)	2,603 (11.4)	<0.001
CVD ^c	762 (11.9)	3,175 (13.9)	<0.001
Depression	2,293 (35.9)	2,365 (10.4)	<0.001
Diabetes	807 (12.6)	4,389 (19.2)	<0.001
Dyslipidemia	1,221 (19.1)	7,070 (31.0)	<0.001
Epilepsy	171 (2.7)	191 (0.8)	<0.001
HIV	118 (1.9)	561 (2.5)	<0.001
Hypertension	2,139 (33.5)	10,075 (44.1)	<0.001
Pregnancy	209 (3.3)	250 (1.1)	<0.001
Schizophrenia/bipolar	733 (11.5)	346 (1.5)	0.004
Other liver disease			
Alcoholic liver disease	146 (2.3)	80 (0.35)	<0.001
Non-alcoholic liver disease	204 (3.2)	694 (3.0)	0.52
Hepatitis A virus	23 (0.4)	49 (0.2)	0.038
Hepatitis B virus	63 (1.0)	409 (1.8)	<0.001

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TABLE 1 Baseline Characteristics for HCV-Infected Patients in Substance Use Disorders (SUD) and Non-SUD Groups^a (continued)

Characteristic	SUD group (n=6,385)	Non-SUD group (n=22,843)	P value
Liver severity			
Cirrhosis	181 (2.8)	538 (2.4)	0.029
Substance use disorder			
Opioid	3,579 (56.1)	NA	NA
Other drug-related	3,838 (60.1)	NA	NA
Cocaine, heroin	1,381 (21.6)	NA	NA
Sedatives, hypnotics, anxiolytics, tranquilizers, and barbiturates	936 (14.7)	NA	NA
Stimulants	665 (10.4)	NA	NA
Other (un) specified drug dependence and drug-induced mental disorders	3,037 (47.6)	NA	NA
Cannabis	1,289 (20.2)	NA	NA
Hallucinogens	87 (1.4)	NA	NA
Alcohol	3,059 (47.9)	NA	NA
Medication for opioid use disorder or alcohol use disorder			
Methadone	217 (3.4)	NA	NA
Buprenorphine	1,654 (25.9)	NA	NA
Naltrexone (including injectable naltrexone)	610 (9.6)	NA	NA
Acamprosate	64 (1.0)	NA	NA
Claims Dataset type			
Commercial	5,942 (93.1)	19,736 (86.4)	
Medicare Supplemental	443 (6.9)	3,107 (13.6)	
Follow-up time			
Mean (SD), months	22.4 (14.0)	25.6 (15.7)	<0.001

^aData are reported as numbers (percentages).

^bOthers included basic/major medical, Exclusive Provider Organization (EPO), non-Capitated Point-of-Service (POS) with capitation, CDHP (Consumer-Driven Health Plan), and HDHP (High Deductible Health Plan).

^cCVD includes cerebrovascular disease, coronary artery disease, and peripheral vascular disease.

CKD=chronic kidney disease; COMP=Comprehensive insurances; COPD=chronic obstructive pulmonary disease; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HMO=Health Maintenance Organization; NA=not available; POS=non-Capitated Point-of-Service; PPO=Preferred Provider Organization; SD=standard deviation; SUD=substance use disorders.

of 18 per 1,000 person-months. Among the non-SUD group (n=7,825), 3% (n=201) of patients discontinued their treatment (of which, 54% discontinued DAA treatment only and 46% discontinued DAAs in combination with RBV treatment) providing a crude incidence rate of 12 per 1,000 person-months. After adjusting for covariates, there was no difference in the hazard of discontinuation of DAA treatment for those with or without SUDs (aHR, 1.14 [0.81-1.60]; Table 3). Sensitivity analysis displayed the similar result (Table 3).

FACTORS ASSOCIATED WITH TREATMENT DISCONTINUATION

Among patients with SUDs who initiated DAA treatment (n=1,529), factors associated with a significantly higher probability of discontinuing DAA treatment included: taking DAAs in combination with RBV (aHR, 3.90 [2.27-6.70]); being 18-35 years old (aHR, 4.90 [2.15-11.16] vs 51-64 years old); having chronic kidney disease (aHR, 4.85 [1.28-18.47]); and having cirrhosis (aHR, 2.59 [1.29-5.18]). However, different types of SUDs or receiving medication for SUD were not associated with early discontinuation of DAA (Supplementary Table 5, available in online article). Among patients without SUD (n=7,825), factors associated with a significantly higher probability of discontinuing DAA treatment included: taking DAAs in combination with RBV (aHR, 3.77 [2.85-5.01]), and having cirrhosis (aHR, 2.53 [1.86-3.43]; Supplementary Table 5). Multicollinearity was not found in any of the models as all VIFs were found to be around 1.

Discussion

This retrospective study using real world data has provided important information on DAA treatment initiation (prescription fill) and early discontinuation among chronic HCV-infected persons with and without SUDs. We found that overall, one-third of newly diagnosed patients with chronic HCV filled a prescription for DAA therapy following their HCV diagnosis regardless of SUD status. Second, fewer HCV-infected patients with SUDs filled their prescription for DAA therapy compared to those without SUDs (24% vs 34%) especially among HMO recipients. Thirdly, among those who initiated DAA therapy, the overall discontinuation rate was low (2.8%), and there was no difference in DAA discontinuation noted between those with or without SUDs or by claims datasets or type of insurance after we adjusted for demographics and clinical characteristics.

These significant findings demonstrate that despite the availability of highly effective treatment for chronic HCV and the receipt of a prescription, treatment initiation remains very low overall and among those with SUDs.

TABLE 2 Initiation Rates of All-Oral DAA Therapy for HCV-Infected Patients, Stratified by Presence of SUD

	No. of patients initiated DAA (%)	Person-months	Crude incidence/1,000 person-months	Adjusted HR ^a (95% CI)
Overall				
SUD group (n = 6,385)	1,529 (24) ^d	118,202	13	0.87 (0.82-0.92)
DAA only ^b	1,242 (20)		11	
DAA + ribavirin ^c	287 (4)		2	
Non-SUD group (n = 22,843)	7,825 (34) ^d	438,890	18	Reference
DAA only ^b	6,349 (28)		15	
DAA + ribavirin ^c	1,476 (6)		3	
Individuals with Medicare supplemental insurance				
SUD group (n = 443)	105 (24)	10,110	11	0.93 (0.75-1.14)
DAA only ^b	88 (20)		9	
DAA + ribavirin ^c	17 (4)		2	
Non-SUD group (n = 3,107)	863 (28)	68,600	13	Reference
DAA only ^b	754 (24)		11	
DAA + ribavirin ^c	109 (4)		2	
Individuals with commercial insurance				
SUD group (n = 5,942)	1,424 (24) ^d	108,093	13	0.86 (0.81-0.92)
DAA only ^b	1,154 (19)		11	
DAA + ribavirin ^c	270 (5)		2	
Non-SUD group (n = 19,736)	6,962 (35) ^d	370,290	19	Reference
DAA only ^b	5,595 (28)		15	
DAA + ribavirin ^c	1,367 (7)		4	

^aCox proportional hazard modeling was used to adjust for age, sex, region, health plan, insurance type, diabetes, cardiovascular disease (including cerebrovascular disease, coronary artery disease, and peripheral vascular disease), chronic kidney disease, mental disorders (including schizophrenia/bipolar, depression, and epilepsy), diabetes, pregnancy, alcoholic liver disease, non-alcoholic liver disease, hepatitis A virus, hepatitis B virus, human immunodeficiency virus, and cirrhosis.

^bDAA only included sofosbuvir, sofosbuvir/ledipasvir, paritaprevir/ritonavir/ombitasvir ± dasabuvir, elbasvir/grazoprevir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, and glecaprevir/pibrentasvir.

^cDAA + ribavirin (RBV) included sofosbuvir/ledipasvir + RBV, sofosbuvir + simeprevir + RBV, sofosbuvir + RBV, sofosbuvir + daclatasvir + RBV, paritaprevir/ritonavir/ombitasvir ± dasabuvir + RBV, elbasvir/grazoprevir + RBV, sofosbuvir/velpatasvir + RBV, sofosbuvir/velpatasvir/voxilaprevir + RBV, and glecaprevir/pibrentasvir + RBV.

^dCompared to the non-SUD group, the SUD group was significantly less likely to initiate DAA ($P < 0.001$ from chi-square test).

CI = confidence interval; DAA = direct-acting antiviral; HCV = hepatitis C virus; HR = hazard ratio; RBV = ribavirin; SUD = substance use disorders.

The low treatment initiation in the SUD population may be due to factors such as patients' refusal, physicians' concerns, and payer's rejection/rigid eligibility criteria which appears to be most relevant to those who

are in an HMO.^{9,10,12,24,25} Patient-level barriers include poor knowledge of HCV, stigma associated with having HCV, mental health issues, and general challenges with accessing the health care system.^{23,26} On the other

hand, it is noteworthy that the type of SUDs and the utilization of SUD treatment were not predictors for initiating DAA treatment. In fact, we found that among patients with SUD, factors associated with not initiating treatment included several non-modifiable factors of gender (female) and age (young), which suggests that there is concern about DAA treatment for young female patients with SUDs who are of childbearing age. The determination of when to treat HCV during pregnancy is an area of intense research at the present time, so there are no current recommendations.^{27,28} As such, we recommend that further research is needed to understand what are the barriers within HMO's that are precluding treatment initiation for those who do receive a prescription.

On the other hand, several potential modifiable factors were found to be predictors of not initiating DAA treatment among patients with SUDs. These factors included the type of insurance and certain comorbidities. We found that patients with plans with higher copays (COMP) or with more restrictive coverage (HMO) had lower DAA initiation rates. Such policies may hinder patients' ability to pay for all services, which would suggest that further refinement of cost sharing may be necessary if the goal of hepatitis elimination by the year 2030 is going to be reached.²⁹⁻³¹ In addition, comorbidities including alcoholic liver disease, chronic kidney disease, and hepatitis B virus were associated with lower rates of DAA initiations among patients with SUDs. More research is now needed to understand barriers to access to DAA treatment among those with the above clinical burdens.^{15,32}

A very promising finding was that only less than 3% of HCV-infected patients who started DAA treatment discontinued treatment regardless of having or not having an SUD, which

TABLE 3 Discontinuation Rates of All-Oral DAA Therapy for HCV-Infected Patients, Stratified by Presence of SUD (n = 9,354)

	No. of patients discontinued DAA (%)	Person-months	Crude incidence/1,000 person-months	Adjusted HR ^a (95% CI)
Main analysis				
SUD group (n = 1,529)	61 (4) ^d	3,400	18	1.14 (0.81-1.60)
DAA only ^b	32 (2)	2,663	12	
DAA + ribavirin ^c	29 (2)	738	39	
Non-SUD group (n = 7,825)	201 (3) ^d	17,389	12	Reference
DAA only ^b	108 (2)	13,463	8	
DAA + ribavirin ^c	93 (1)	3,926	24	
Sensitivity analysis of different treatment duration of sofosbuvir/ledipasvir				
SUD group (n = 1,529)	75 (5) ^e	3,586	21	1.08 (0.80-1.46)
DAA only ^b	46 (3)	2,848	16	
DAA + ribavirin ^c	29 (2)	738	39	
Non-SUD group (n = 7,825)	281 (4) ^e	18,676	15	Reference
DAA only ^b	188 (2)	14,750	13	
DAA + ribavirin ^c	93 (1)	3,926	24	
Individuals with Medicare supplemental insurance				
SUD group (n = 105)	3 (3)	243	12	1.90 (0.53-6.81)
DAA only ^b	1 (1)	200	5	
DAA + ribavirin ^c	2 (2)	43	47	
Non-SUD group (n = 863)	21 (2)	1,897	11	Reference
DAA only ^b	13 (2)	1,611	8	
DAA + ribavirin ^c	8 (1)	286	28	
Individuals with commercial insurance				
SUD group (n = 1,424)	58 (4)	3,158	18	1.07 (0.75-1.53)
DAA only ^b	31 (3)	2,463	13	
DAA + ribavirin ^c	27 (2)	695	39	
Non-SUD group (n = 6,962)	180 (3)	15,492	12	Reference
DAA only ^b	95 (2)	11,852	8	
DAA + ribavirin ^c	85 (1)	3,640	23	

^aCox proportional hazard modeling was used to adjust for age, gender, region, health plan, insurance type, diabetes, cardiovascular disease (including cerebrovascular disease, coronary artery disease, and peripheral vascular disease), chronic kidney disease, mental disorders (including schizophrenia/bipolar, depression, epilepsy), diabetes, pregnancy, alcoholic liver disease, non-alcoholic liver disease, hepatitis A virus, hepatitis B virus, human immunodeficiency virus, and cirrhosis.

^bDAA only included sofosbuvir, sofosbuvir/ledipasvir, paritaprevir/ritonavir/ombitasvir ± dasabuvir, elbasvir/grazoprevir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, and glecaprevir/pibrentasvir.

^cDAA + ribavirin (RBV) included sofosbuvir/ledipasvir + RBV, sofosbuvir + simeprevir + RBV, sofosbuvir + RBV, sofosbuvir + daclatasvir + RBV, paritaprevir/ritonavir/ombitasvir ± dasabuvir + RBV, elbasvir/grazoprevir + RBV, sofosbuvir/velpatasvir + RBV, sofosbuvir/velpatasvir/voxilaprevir + RBV, and glecaprevir/pibrentasvir + RBV.

^dCompared to the non-SUD group, the SUD group was significantly more likely to discontinue DAA (P = 0.002 from chi-square test).

^eCompared to the non-SUD group, the SUD group was significantly more likely to discontinue DAA (P = 0.014 from chi-square test).

CI = confidence interval; DAA = direct-acting antiviral; HCV = hepatitis C virus; HR = hazard ratio; RBV = ribavirin; SUD = substance use disorders.

was similar to other recent studies which also showed that among those with SUDs those that started treatment were highly likely to complete treatment and to obtain a cure.^{25,33,34} We found that those whose treatment regimens included RBV were almost four times as likely to discontinue therapy regardless of their SUD status as those who did not have RBV as part of their therapy. This finding partially explains why those with cirrhosis, regardless of their SUD status, were almost three times as likely to discontinue treatment. RBV is usually part of the treatment for those with cirrhosis but can cause serious adverse effects (eg, anemia), which may lead patients to stop the treatment earlier.³⁵⁻³⁷

LIMITATIONS

There are several limitations to this study as this was an analysis of administrative claims data using ICD-9/ICD-10 codes. However, a recent validation study reported that a coding algorithm including one inpatient or two outpatient ICD-9 codes for HCV and cirrhosis had high accuracy although using ICD-10 codes has not been validated yet.¹⁶ It is possible that incomplete, missing, or miscoded claims may impact study findings; however, coding errors are likely to be evenly distributed between the two groups. Another limitation is that we can only identify individuals who engaged the system and received a recorded diagnosis of an SUD or received treatment for an SUD. Thus, we may have underreported the numbers of HCV-infected patients with SUDs. It is also possible that former drug/alcohol use was under-reported which may have biased the HCV without SUDs group, since we were not able to differentiate between patients with former SUDs. Additionally, we cannot generalize our findings to those who are uninsured, Medicaid beneficiaries.

Despite these limitations, this study provides the first estimates of treatment rates and discontinuation rates for DAA therapy in a nationally representative cohort of commercially insured patients, not geographically limited or representing highly selected patients (eg, opioid treatment clinic).

Conclusions

Despite the availability of effective all-oral DAA therapies, the overall treatment initiation (prescription fill) rate was only 32% leaving 68% of patients with HCV untreated despite having insurance. This is a concerning finding as patients with delayed access to HCV therapy may experience continued progression of hepatic disease resulting in end-stage liver disease. Besides, HCV-infected patients with SUDs were less likely to fill their DAA prescription, but they were just as likely to complete treatment when compared to those without SUDs. Further research is needed to understand the barriers to treatment for those with SUDs who also have alcoholic liver disease, HBV, or CKD.

DISCLOSURES

Research reported in this publication was supported in part by the National Institute on Drug Abuse of the National Institutes of Health under award number K01DA045618 (to Park). The other authors have nothing to disclose that may present a potential conflict of interest.

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