Health care utilization and costs associated with direct-acting antivirals for patients with substance use disorders and chronic hepatitis C

Xinyi Jiang, PhD; Scott Martin Vouri, PhD, PharmD; Vakaramoko Diaby, PhD; Weihsuan Lo-Ciganic, PhD; Robert Parker, PhD; and Haesuk Park, PhD

What is already known about this subject

- Clinical trials have reported that patients with substance use disorders (SUD) and chronic hepatitis C virus (HCV) who were treated with all-oral direct-acting antivirals (DAA) achieved equally high sustained virologic response rates compared with patients with HCV but without SUD.
- Access to DAA for patients with SUD and chronic HCV has been limited, and the known barriers to DAA access among these patients include, but are not limited to, payers' restrictions and providers' concerns regarding limited resources and the risk of reinfection due to continued high-risk behaviors.
- Untreated patients with chronic HCV are more likely to develop advanced liver disease (decompensated cirrhosis and hepatocellular carcinoma), which result in higher health care costs.

What this study adds

- Among patients with SUD and chronic HCV, the use of DAA therapy resulted in significant reductions in liver-related costs without increasing SUD-related and all-cause costs in this disadvantaged population, regardless of cirrhosis status.
- Among patients with SUD and chronic HCV without cirrhosis, the use of DAA therapy resulted in significant reductions in SUD-related emergency department and long-term care visits, suggesting the extra benefit of early treatment in addition to reduced liver-related health care utilization and costs.

Author affiliations

Xinyi Jiang, PhD, Department of Pharmaceutical Outcomes & Policy, College of Pharmacy, University of Florida, Gainesville. Scott Martin Vouri, PhD, PharmD; Vakaramoko Diaby, PhD; Weihsuan Lo-Ciganic, PhD; and Haesuk Park, PhD, Department of Pharmaceutical Outcomes & Policy, Center for Drug Evaluation and Safety (CoDES), College of Pharmacy, University of Florida, Gainesville. Robert Parker, PhD, Department of Biostatistics, College of Public Health & Health Professions, College of Medicine, University of Florida, Gainesville.

AUTHOR CORRESPONDENCE:
Haesuk Park, 352.273.6261;
HPark@cop.ufl.edu

J Manag Care Spec Pharm.
2021;27(10):1388-402

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ABSTRACT

BACKGROUND: Patients with substance use disorders (SUD) and chronic hepatitis C virus infection (HCV) have limited access to direct-acting antivirals (DAAs) due to multilevel issues related to providers (eg, concern about reinfection); patients (eg, refusal); payers (eg, prior authorization); and health system structure, although clinical guidelines recommend timely DAA treatment for patients with SUD and HCV. Effects of DAAs on real-world

health care utilization and costs among these patients is unknown.

OBJECTIVE: To compare changes in medical service utilization and costs related to liver, SUD, and all-cause morbidity in patients with SUD and HCV treated with DAAs (DAA group) vs not treated with DAAs (non-DAA group).

METHODS: We conducted a retrospective cohort study using MarketScan Commercial and Medicare Supplemental Claims databases (2012-2018) for newly diagnosed HCV

treatment-naïve adults with SUD. We used difference-in-differences analyses, stratified by cirrhosis status, to determine the adjusted ratio of rate ratio (RoRR) to assess the difference in the relative changes from the pre- to posttreatment periods between the 2 groups.

RESULTS: 6,266 patients with SUD and HCV were identified. Of these patients who also had cirrhosis (n=607), 49% (n=298) initiated DAA therapy for HCV, whereas of those without cirrhosis (n=5,659), 22% (n=1,219)

initiated DAAs. For patients with cirrhosis ($n=607$), the liver-related costs decreased by \$6,213 (95% CI = -\$8,571, -\$3,856) for the DAA group and \$1,585 (95% CI = -\$4,659, \$1,490) for the non-DAA group. The relative decreases in the rate of liver-related costs were larger for the DAA group than for the non-DAA group, and the relative changes between groups were significantly different (RoRR=0.37, 95% CI=0.19-0.73). There was no difference in the relative changes after DAAs in the rate of SUD-related visits/costs or all-cause costs between the 2 groups. For patients without cirrhosis ($n=5,659$), a similar association was observed. Besides, the relative decreases in the rate of SUD-related emergency department (ED) visits (RoRR=0.54, 95% CI=0.38-0.77); SUD-related long-term care visits (RoRR=0.30, 95% CI=0.13-0.73); all-cause ED visits (RoRR=0.75, 95% CI=0.64-0.88); and all-cause long term-care visits (RoRR=0.36, 95% CI=0.18-0.72) were larger in the DAA group than in the non-DAA group.

CONCLUSIONS: DAAs are associated with a significant decrease in the rate of SUD-related ED visits and liver-related costs without increasing the rate of all-cause costs among patients with SUD and HCV, suggesting that the benefits of DAAs extended beyond liver-related outcomes, especially in this disadvantaged population.

In the United States, approximately 4.1 million persons were infected with hepatitis C virus (HCV) during 2013–2016.¹ Due in part to the opioid epidemic and associated injection drug use, the number of acute HCV infections increased approximately 2.9-fold from 2011 to 2018.² As a result, patients with substance use disorders (SUD) have a high risk for the contraction and transmission of HCV.^{3,4} Approximately 60%–90% of individuals with SUD may contract HCV during their lifetime,^{3–6} and more than half of all HCV infections become chronic HCV infections.^{7,8} However, before the advent of direct-acting antiviral agents (DAAs) in 2013, more than 90% of patients with SUD and chronic HCV were not treated for HCV because of the concerns regarding adverse effects and contraindications associated with the use of injectable interferon, a mainstay of previous HCV treatment.⁹ As such, untreated patients with SUD and chronic HCV frequently suffer from advanced liver disease, including decompensated cirrhosis (DCC) and hepatocellular carcinoma (HCC), which result in high health care costs.¹⁰

In late 2013, treatment for HCV changed significantly with the advent of DAAs. After the introduction of DAAs, treatment for HCV evolved into all-oral, interferon-free DAA regimens taken for only 8 to 24 weeks.^{5,11–16} These new DAA treatment regimens provide sustained virologic response (SVR) rates of greater than 95%, even for patients with SUD, as evidenced by data from clinical trials and real-world retrospective/prospective studies.^{17–23} As a result, the American Association for the Study of Liver Diseases

(AASLD) and the Infectious Diseases Society of America (IDSA) recommend timely DAA treatment for all patients with HCV, including patients with SUD.^{24,25}

Despite these recommendations, access to DAAs for patients with SUD and chronic HCV has still been limited.^{26–29} This divergence from the AASLD/IDSA clinical guidelines for patients with SUD and chronic HCV may reflect concerns of payers and providers.^{29–31} Concerns regarding high prescription DAA costs have led private and public payers to restrict access to these medications, requiring that patients meet specific prior authorization approvals.^{32–34} Although some restriction criteria (eg, patient liver disease stage) have been eased, current illicit substance and/or alcohol use still pose as restrictions to accessing DAA.^{35,36} However, a recent study reported that among the untreated patients with chronic HCV, those with an SUD had a significantly higher risk of end-stage liver diseases compared with those without an SUD.³⁷

In addition, the results of 2 prospective clinical trials suggested that DAAs may provide a critical opportunity to reduce risky behaviors (eg, alcohol and drug use, injecting behavior) in high-risk patients with SUD and chronic HCV,^{35,38} which suggests that the benefits of DAAs may extend beyond liver-related outcomes.

Little is known about the effect of DAA treatment on health care utilization and expenditures for patients with SUD and chronic HCV in real-world clinical practice.³⁷ Our purpose was to assess and compare the changes in liver-related, SUD-related, and all-cause medical service utilization and costs after DAA treatment among patients with SUD and chronic HCV treated with DAAs vs those without DAAs.

Methods

DATA SOURCE

We conducted a retrospective cohort study using the IBM MarketScan Commercial Claims and Encounters Database (>80 million unique beneficiaries) and Medicare Supplemental and Coordination of Benefits Database (>6 million unique beneficiaries), which include complete claims for retirees with Medicare supplemental insurance paid by employers but not those who only receive Medicare as their primary insurance, from January 2012 to December 2018. These nationwide administrative claims databases contain person-level information on diagnoses, procedures, and prescriptions across all settings, including physician outpatient office visits, hospital stays, and outpatient pharmacy claims. Health care is provided for covered employees, their spouses, and dependents, representing US individuals

TABLE 1 Baseline Characteristics for Patients With SUD and Chronic HCV Infection After Stabilized IPTW, 2013-2018

Characteristic	Patients with SUD and HCV with cirrhosis			Patients with SUD and HCV without cirrhosis		
	DAA treatment (n=298)	No treatment (n=309)	Standardized difference	DAA treatment (n=1,219)	No treatment (n=4,440)	Standardized difference
Number of subjects (weighted)	287	311	NA	1,218	4,440	NA
Age, years, n (%)						
18-35	24 (8.36)	26 (8.36)	-0.004	534 (43.84)	1,930 (43.47)	0.009
36-50	41 (14.29)	58 (18.65)		149 (12.23)	619 (13.94)	
51-64	199 (69.34)	188 (60.45)		476 (39.08)	1,673 (37.68)	
≥ 65	22 (7.67)	39 (12.54)		59 (4.84)	218 (4.91)	
Sex, n (%)						
Male	209 (72.82)	228 (73.31)	0.016	464 (38.10)	1,688 (38.02)	0.001
Female	78 (27.18)	83 (26.69)		754 (61.90)	2,752 (61.98)	
Comorbidity, n (%)						
Diabetes	65 (22.65)	74 (23.79)	0.031	165 (13.55)	576 (12.97)	-0.018
Hypertension	158 (55.50)	177 (56.91)	0.040	450 (36.95)	1,629 (36.69)	-0.005
Dyslipidemia	82 (28.57)	92 (29.58)	0.023	285 (23.40)	1,006 (22.66)	-0.018
CVD ^a	66 (23.00)	74 (23.79)	-0.004	170 (13.96)	608 (13.69)	-0.012
Chronic kidney disease	13 (4.53)	14 (4.50)	0.001	37 (3.04)	130 (2.93)	-0.004
COPD	69 (24.04)	73 (23.47)	-0.02	193 (15.85)	695 (15.65)	-0.004
HIV	^b	^b	NA	29 (2.38)	99 (2.23)	-0.008
Schizophrenia/bipolar, n (%)	18 (6.27)	18 (5.79)	-0.015	118 (9.69)	426 (9.59)	-0.004
Depression	105 (36.59)	110 (35.3%)	-0.024	527 (43.27)	1,955 (44.03)	0.015
Epilepsy	16 (5.57)	15 (4.82)	-0.026	41 (3.37)	160 (3.60)	0.012
Pregnancy	^b	^b	NA	55 (4.52)	185 (4.17)	-0.018

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covered by commercial health insurance.³⁹ The University of Florida Institutional Review Board approved this study.

STUDY COHORT

Identification of Patients with SUD and Chronic HCV.

We identified patients aged at least 18 years with a newly diagnosed chronic HCV infection using the *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* (ICD-9/10-CM) codes ([Supplementary Table 1](#), available in online article). Patients were determined to have chronic HCV if they met the criteria of a previously validated algorithm of 1 inpatient or 2 outpatient chronic HCV infection diagnoses on separate days within 1 year.⁴⁰ We used the 2013-2018 data to establish the cohort and used the 2012 data to ensure that patients had at least 1 year as

a baseline period before the first chronic HCV diagnosis. Patients were required to be HCV treatment naive (not having interferon-based or DAA-based treatments) before the first chronic HCV diagnosis and to be continuously enrolled in the health plan 1 year before and 6 months after the first chronic HCV diagnosis.

We further required patients to have a diagnosis of an SUD either within 1 year before or 6 months after the first chronic HCV diagnosis using the following criteria: (1) at least 1 inpatient or outpatient claim for a drug use or alcohol use disorder defined by the presence of specific ICD-9/10-CM codes ([Supplementary Table 1](#)) or (2) a claim for methadone, buprenorphine (limited to formulations approved by the US Food and Drug Administration [FDA] for opioid use disorder treatment), acamprosate, or naltrexone

TABLE 1 Baseline Characteristics for Patients With SUD and Chronic HCV Infection After Stabilized IPTW, 2013-2018 (continued)

Characteristic	Patients with SUD and HCV with cirrhosis			Patients with SUD and HCV without cirrhosis		
	DAA treatment (n=298)	No treatment (n=309)	Standardized difference	DAA treatment (n=1,219)	No treatment (n=4,440)	Standardized difference
Other liver disease (1 year before DAA index date), n (%)						
Alcoholic liver disease	75 (26.13)	90 (28.94)	0.063	24 (1.97)	86 (1.94)	-0.004
Nonalcoholic liver disease	52 (18.12)	58 (18.65)	0.007	66 (5.42)	254 (5.72)	0.011
Hepatitis A virus	^b	^b	0.004	^b	29 (0.65)	0.010
Hepatitis B virus	11 (3.83)	14 (4.50)	0.033	20 (1.64)	82 (1.85)	0.015
Substance use disorders, n (%)						
Opioid	81 (28.22)	87 (27.97)	-0.005	711 (58.37)	2,615 (58.90)	0.010
Other drug-related	113 (39.37)	123 (39.55)	-0.001	763 (62.64)	2,769 (62.36)	-0.007
Alcohol	185 (64.46)	205 (65.92)	0.031	556 (45.65)	2,036 (45.86)	0.004
History of SUD-related hospitalization or ED visits, n (%)	37 (12.89)	45 (14.47)	0.038	330 (27.09)	1,205 (27.14)	0.000
Medication for opioid use disorder or alcohol use disorder, n (%)	46 (16.03)	50 (16.08)	0.002	414 (33.99%)	1,519 (34.21)	0.005
Pretreatment follow-up time,^c mean (SD), months	8.9 (9.74)	8.8 (12.97)	0.021	9.0 (10.2)	8.5 (9.9)	0.048
Posttreatment follow-up time,^d mean (SD), months	16.90 (12.70)	13.44 (5.27)	NA	15.40 (11.50)	13.09 (4.94)	NA

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

^bCell size <11.

^cPretreatment follow-up time was estimated from the date when patients were either first diagnosed with SUD or HCV, whichever came later, until the index date. If the first SUD diagnosis was after the index date, pretreatment follow-up time was estimated from the first HCV diagnosis until the index date.

^dPosttreatment follow-up was estimated from the index date to the end of insurance eligibility, or December 31, 2018.

COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease; DAA=direct-acting antiviral; ED=emergency department; HCV=hepatitis C virus; IPTW=inverse probability of treatment weighting; NA=not available; SUD=substance use disorder.

(oral and injectable) for either opioid use disorder or alcohol use disorder, as defined by the presence of the relevant National Drug Code (NDC) numbers or Current Procedural Terminology (CPT) codes ([Supplementary Table 2](#), available in online article).⁴¹⁻⁴⁴

We also stratified the patients with SUD and chronic HCV by baseline cirrhosis status because advanced fibrosis (cirrhosis) is one of the strongest predictors of DAA initiation and liver-related health care utilization and costs^{10,26,36,37}

Identification of Index Date. For patients with SUD and chronic HCV who received DAA treatment, we assigned the first DAA prescription date as the index date. We defined DAAs using NDC numbers according to the FDA and AASLD/IDSA definitions for treatment-naïve patients ([Supplementary Table 3](#), available in online article).

To avoid immortal-time bias, we assigned a hypothetical index date for each untreated patient through the use of a

prescription time-distribution matching approach based on the difference between the time of the first chronic HCV diagnosis and the dispensing time of the first DAA prescription for treated patients.^{45,46} We matched the overall distribution of time differences between the first HCV diagnosis and the index date of the untreated patients to that of the treated patients.

We excluded patients with a diagnosis of DCC or HCC or who had received a liver transplant during the year before the index date. We defined the baseline cirrhosis status as the diagnosis from at least 1 inpatient or 1 outpatient claim of ICD-9/10-CM codes for a cirrhosis diagnosis occurring 1 year before the index date ([Supplementary Table 1](#)).⁴⁷

We defined the pretreatment period as the time from the first SUD diagnosis or the first chronic HCV diagnosis, whichever came later, until the index date ([Supplementary Figure 1](#), available in online article). The posttreatment period started on the index date and continued until

TABLE 2 Adjusted Liver-Related, SUD-Related, and All-Cause Medical Service Utilization PPPY Before and After DAA Treatment in the Stabilized IPTW Patients With SUD and Chronic HCV With Cirrhosis (N = 607)^a

	Mean adjusted pretreatment	Mean adjusted posttreatment	Mean adjusted difference from pre/post periods	RoRR for DAA vs non-DAA from pre/post periods
Liver-related medical service utilization				
Inpatient visits				
DAA (n = 298)	0.10	0.14	0.04 (−0.07, 0.14)	0.86 (0.29, 2.56)
Non-DAA (n = 309)	0.32	0.52	0.20 (−0.05, 0.44)	
ED visits				
DAA (n = 298)	0.02	0.04	0.02 (−0.01, 0.04)	1.55 (0.40, 6.06)
Non-DAA (n = 309)	0.06	0.06	0.01 (−0.04, 0.06)	
Office visits				
DAA (n = 298)	4.76	2.87	−1.89 (−2.51, −1.26)	0.75 (0.55, 1.02)
Non-DAA (n = 309)	1.90	1.53	−0.37 (−0.79, 0.05)	
Other outpatient visits				
DAA (n = 298)	6.11	4.77	−1.34 (−2.28, −0.41)	0.99 (0.72, 1.35)
Non-DAA (n = 309)	2.72	2.15	−0.57 (−1.15, 0.007)	
SNF/long-term care visits ^b				
DAA (n = 298)	2.14 × 10 ^{−9}	0.15	0.15 (−0.17, 0.47)	2.10 (0.45, 9.67)
Non-DAA (n = 309)	0.03	0.08	0.04 (−0.01, 0.10)	
SUD-related medical service utilization				
Inpatient visits				
DAA (n = 298)	0.36	0.18	−0.18 (−0.38, 0.02)	0.42 (0.17, 1.03)
Non-DAA (n = 309)	0.53	0.63	0.10 (−0.22, 0.43)	
ED visits				
DAA (n = 298)	0.07	0.10	0.04 (−0.06, 0.14)	1.27 (0.41, 3.89)
Non-DAA (n = 309)	0.13	0.16	0.03 (−0.04, 0.10)	
Office visits				
DAA (n = 298)	0.83	0.50	−0.33 (−0.65, −0.005)	0.73 (0.44, 1.22)
Non-DAA (n = 309)	1.24	1.02	−0.21 (−0.56, 0.13)	
Other outpatient visits				
DAA (n = 298)	6.98	3.17	−3.81 (−6.46, −1.16)	0.56 (0.24, 1.35)
Non-DAA (n = 309)	5.25	4.56	−0.69 (−3.23, 1.85)	
SNF/long-term care visits				
DAA (n = 298)	0.059	0.008	−0.05 (−0.12, 0.02)	0.66 (0.09, 5.07)
Non-DAA (n = 309)	0.194	0.038	−0.16 (−0.38, 0.07)	

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the end of insurance eligibility or December 31, 2018, whichever came first ([Supplementary Figure 1](#)).

STUDY OUTCOMES

Medical Service Utilization and Costs. We applied a standardized algorithm to obtain medical service utilization and related costs from inpatient and outpatient claims for the pretreatment and posttreatment periods separately.⁴⁸ The visit types included hospitalization, emergency department (ED), outpatient office, skilled nursing facility (SNF)/long-term care (eg, hospice and residential substance abuse facility), and other nonpharmacy outpatient services (eg, laboratory outpatient chemistry tests).

For medical service utilization, we calculated the average number of medical visits related to liver, SUD, and all-cause morbidity. Liver-related and SUD-related morbidities were identified via primary claims with any liver-related diagnosis or procedure (ie, HCV, cirrhosis, DCC, HCC, DCC-related procedure, and liver transplant) defined by the presence of the relevant ICD-9/10-CM/CPT codes or a primary diagnosis of SUD ([Supplementary Table 1](#)).^{40,47}

Medical costs were defined as the amounts that payers paid plus member cost sharing for services related to the same causes of morbidity. Given that the cost distribution was skewed with extreme values, we excluded patients with total pretreatment and posttreatment all-cause medical costs at or greater than the 99% percentile of the total costs outliers (ie, >\$642,898 per person; [Supplementary Figure 2](#), available in online article).^{49,50} We adjusted all costs to 2018 U.S. dollars using an annual 3% inflation rate.

STATISTICAL ANALYSIS

We used a multivariable logistic regression model to estimate the propensity

TABLE 2 Adjusted Liver-Related, SUD-Related, and All-Cause Medical Service Utilization PPPY Before and After DAA Treatment in the Stabilized IPTW Patients With SUD and Chronic HCV With Cirrhosis (N = 607)^a (continued)

	Mean adjusted pretreatment	Mean adjusted posttreatment	Mean adjusted difference from pre/post periods	RoRR for DAA vs non-DAA from pre/post periods
All-cause medical service utilization				
Inpatient visits				
DAA (n = 298)	1.41	0.91	-0.49 (-0.93, -0.06)	0.74 (0.48, 1.13)
Non-DAA (n = 309)	2.80	2.46	-0.33 (-0.98, 0.31)	
ED visits				
DAA (n = 298)	1.33	1.13	-0.2 (-0.56, 0.16)	0.75 (0.52, 1.06)
Non-DAA (n = 309)	2.13	2.44	0.3 (-0.17, 0.78)	
Office visits				
DAA (n = 298)	16.10	12.96	-3.14 (-4.64, -1.65)	0.70 (0.60, 0.81)
Non-DAA (n = 309)	12.39	14.31	1.92 (0.39, 3.44)	
Other outpatient visits				
DAA (n = 298)	27.44	23.99	-3.45 (-6.58, -0.32)	0.75 (0.64, 0.90)
Non-DAA (n = 309)	22.24	25.76	3.52 (0.66, 6.39)	
SNF/long-term care visits				
DAA (n = 298)	0.45	0.87	0.42 (-0.26, 1.09)	3.96 (1.34, 11.73)
Non-DAA (n = 309)	2.41	1.17	-1.24 (-2.35, -0.13)	

^aResults were derived from the stabilized IPTW difference-in-differences approach after controlling for age (18-35, 36-50, 51-64, and > 64 years); sex at the index date; clinical conditions including the type of SUD, diabetes, hypertension, dyslipidemia, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, HIV infection, schizophrenia/bipolar disorder, depression, pregnancy, and other liver diseases (ie, alcoholic liver disease, nonalcoholic fatty liver disease, hepatitis B infection, hepatitis A infection), during the year before the index date, as well as current SUD status, medication for opioid use disorder or alcohol use, and pretreatment follow-up time.

^bBecause of the small sample size for liver-related SNF/long-term care visits, convergence was not achieved.

DAA = direct-acting antiviral; ED = emergency department; HCV = hepatitis C virus; IPTW = inverse probability of treatment weighting; PPPY = per person per year; RoRR = rate of rate ratio; SNF = skilled nursing facility; SUD = substance use disorder.

score to adjust for differences in baseline characteristics between patients with SUD and chronic HCV treated with DAAs (DAA group) and those not treated with DAAs (non-DAA group) stratified by baseline cirrhosis status. This propensity score represented the probability of the patient obtaining the DAA therapy, depending on the baseline covariates that were associated with HCV treatment and that may have had a high impact on the cost of

health care and the utilization of services.^{51,52} These covariates are listed in [Supplementary Table 4](#) (available in online article).⁵³

We then calculated each individual's stabilized inverse probability of treatment weighting (IPTW) using the propensity score.^{52,54} We considered the baseline characteristics to be balanced if the standardized difference of a given covariate between the 2 groups was less than 0.1.^{52,55}

We first estimated the relative changes in the rate of medical service utilization and costs from the pretreatment to the posttreatment periods within the DAA and non-DAA groups. We then compared the differences in the relative changes in rate of utilization and costs between the DAA and non-DAA groups using a difference-in-differences analysis.^{56,57} This approach controls for secular trends in outcomes of interest, as well as the unobserved fixed effects of patients with SUD and chronic HCV (eg, motivation to engage in health system such as for SUD treatment).⁵⁸

The stabilized IPTW difference-in-differences model can control for underlying trends in factors that could influence our selected outcomes and minimize selection bias.^{59,60} We tested the parallel pretreatment trends assumption in a regression model to meet the key assumption of difference-in-differences (for detailed information, see [Supplementary Appendix 1](#), available in online article).^{56,61}

To evaluate medical care utilization, we used zero-inflated negative binomial regression models for HCV and SUD-related medical service utilization and a generalized linear model (GLM) with a negative binomial distribution and a log link for all-cause medical service utilization (for additional detailed information about modeling choices, see [Supplementary Appendix 2A](#), available in online article).

To estimate medical costs, we used 2-part models for estimating HCV and SUD-related costs, which consisted of (1) logistic regression to predict the probability of having health care costs greater than zero and (2) a GLM with a gamma distribution and a log link.⁶² In addition, for all-cause costs estimation, a GLM with a gamma distribution and a log link were used.⁴⁹

TABLE 3 Adjusted Liver-Related, SUD-Related, and All-Cause Medical Service Utilization PPPY Before and After DAA Treatment in the Stabilized IPTW Patients With SUD and Chronic HCV Without Cirrhosis (N = 5,659)^a

	Mean adjusted pretreatment	Mean adjusted posttreatment	Mean adjusted difference from pre/post periods	RoRR for DAA vs non-DAA from pre/post periods
Liver-related medical service utilization				
Inpatient visits				
DAA (n = 1,219)	0.06	0.02	-0.04 (-0.07, -0.01)	0.51 (0.27, 0.96)
Non-DAA (n = 4,440)	0.09	0.06	-0.03 (-0.04, -0.01)	
ED visits				
DAA (n = 1,219)	0.005	0.01	0.005 (-0.003, 0.012)	1.32 (0.38, 4.62)
Non-DAA (n = 4,440)	0.005	0.008	0.002 (-0.002, 0.007)	
Office visits				
DAA (n = 1,219)	3.26	1.73	-1.53 (-1.74, -1.32)	1.11 (0.99, 1.26)
Non-DAA (n = 4,440)	0.93	0.44	-0.49 (-0.54, -0.43)	
Other outpatient visits				
DAA (n = 1,219)	3.52	2.40	-1.11 (-1.35, -0.88)	1.31 (1.17, 1.47)
Non-DAA (n = 4,440)	1.04	0.54	-0.50 (-0.56, -0.44)	
SNF/long-term care visits				
DAA (n = 1,219)	0.001	0.002	0.001 (-0.002, 0.004)	1.19 (0.07, 19.47)
Non-DAA (n = 4,440)	0.004	0.008	0.004 (-0.006, 0.013)	
SUD-related medical service utilization				
Inpatient visits				
DAA (n = 1,219)	0.62	0.51	-0.11 (-0.27, 0.05)	0.81 (0.59, 1.12)
Non-DAA (n = 4,440)	0.83	0.84	0.01 (-0.08, 0.10)	
ED visits				
DAA (n = 1,219)	0.18	0.14	-0.04 (-0.09, 0.02)	0.54 (0.38, 0.77)
Non-DAA (n = 4,440)	0.22	0.33	0.11 (0.06, 0.16)	
Office visits				
DAA (n = 1,219)	1.27	1.12	-0.16 (-0.42, 0.11)	0.83 (0.64, 1.06)
Non-DAA (n = 4,440)	1.37	1.46	0.09 (-0.08, 0.25)	
Other outpatient visits				
DAA (n = 1,219)	10.53	9.85	-0.68 (-2.60, 1.25)	0.84 (0.67, 1.04)
Non-DAA (n = 4,440)	9.80	11.25	1.45 (0.57, 2.33)	
SNF/long-term care visits				
DAA (n = 1,219)	0.15	0.05	-0.10 (-0.19, -0.01)	0.30 (0.13, 0.73)
Non-DAA (n = 4,440)	0.16	0.18	0.02 (-0.05, 0.08)	

continued on next page

All regression models included an interaction term between time (pretreatment vs posttreatment periods) and DAA status (DAA group vs non-DAA group), which we added to the model after the stabilized IPTWs and the control for covariates mentioned previously. The difference in the adjusted relative changes in the outcomes of interest from the pretreatment period to the posttreatment period between the DAA group and the non-DAA group were presented by the ratio of rate ratio (RoRR), which is the exponential of the interaction term (for additional detailed information, see [Supplementary Appendix 2B](#), available in online article).⁶³

Given that our outcomes of interest were not independent for each patient over time, we calculated clustered standard errors and the corresponding 95% CIs.^{61,64,65} We also conducted a sensitivity analysis based on any SUD-related services costs (eg, urine drug tests, behavioral health therapy, and respiratory therapy). We used 2-tailed tests with the significance level set at 0.05. All statistical analyses were performed using Stata software, version 13 (StataCorp) and SAS version 9.4 (SAS Institute).

Results

PATIENT CHARACTERISTICS

We identified 6,266 newly diagnosed treatment-naïve chronic HCV patients with SUD who met our eligibility criteria ([Supplementary Figure 2](#)). Of the patients with SUD and chronic HCV who also had cirrhosis (n = 607), 49% (n = 298) initiated DAAs for their HCV, whereas of those without cirrhosis (n = 5,659), 22% (n = 1,219) initiated DAAs. The differences in baseline characteristics associated with DAA treatment for patients with SUD and chronic HCV stratified by cirrhosis status before stabilized IPTW are

TABLE 3 Adjusted Liver-Related, SUD-Related, and All-Cause Medical Service Utilization PPPY Before and After DAA Treatment in the Stabilized IPTW Patients With SUD and Chronic HCV Without Cirrhosis (N = 5,659)^a (continued)

	Mean adjusted pretreatment	Mean adjusted posttreatment	Mean adjusted difference from pre/post periods	RoRR for DAA vs non-DAA from pre/post periods
All-cause medical service utilization				
Inpatient visits				
DAA (n = 1,219)	1.26	0.89	-0.38 (-0.56, -0.19)	0.83 (0.69, 1.01)
Non-DAA (n = 4,440)	2.24	1.89	-0.35 (-0.49, -0.21)	
ED visits				
DAA (n = 1,219)	1.14	1.05	-0.1 (-0.25, 0.07)	0.75 (0.64, 0.88)
Non-DAA (n = 4,440)	1.78	2.17	0.39 (0.27, 0.51)	
Office visits				
DAA (n = 1,219)	12.73	10.86	-1.87 (-2.49, -1.26)	0.79 (0.74, 0.84)
Non-DAA (n = 4,440)	9.47	10.27	0.80 (0.49, 1.12)	
Other outpatient visits				
DAA (n = 1,219)	27.57	25.28	-2.29 (-4.32, -0.26)	0.78 (0.72, 0.85)
Non-DAA (n = 4,440)	23.10	27.15	4.05 (3.04, 5.07)	
SNF/long-term care visits				
DAA (n = 1,219)	0.76	0.38	-0.38 (-0.77, 0.01)	0.36 (0.18, 0.72)
Non-DAA (n = 4,440)	1.01	1.42	0.41 (0.05, 0.77)	

^aResults were derived from the stabilized IPTW difference-in-differences approach after controlling for age (18-35, 36-50, 51-64, and > 64 years); sex at the index date; clinical conditions including the type of SUD, diabetes, hypertension, dyslipidemia, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, HIV infection, schizophrenia/bipolar disorder, depression, pregnancy, and other liver diseases (ie, alcoholic liver disease, nonalcoholic fatty liver disease, hepatitis B infection, hepatitis A infection), during the year before the index date, as well as current SUD status, medication for opioid use disorder or alcohol use, and pretreatment follow-up time.

DAA = direct-acting antiviral; ED = emergency department; HCV = hepatitis C virus; IPTW = inverse probability of treatment weighting; PPPY = per person per year; RoRR = rate of rate ratio; SNF = skilled nursing facility; SUD = substance use disorder.

summarized in [Supplementary Table 5](#) (available in online article).

After we applied the stabilized IPTW, the DAA and non-DAA groups achieved an acceptable balance (with a standardized difference of each covariate < 0.1), regardless of cirrhosis status (Table 1). The majority in the DAA and non-DAA groups with cirrhosis were male (73% in both groups); were aged 51-64 years (DAA: 69% vs non-DAA: 61%); had hypertension

(DAA: 56% vs non-DAA: 57%); and had alcohol use disorder (64% vs. 66%). Less than one-fifth of each group had a history of SUD-related hospitalizations or ED visits (13% vs 14%) or received medication treatment for SUD (16% in both groups).

The majority of the patients in the DAA and non-DAA groups without cirrhosis were female (62% in both groups); aged 18-35 years (DAA: 44% vs non-DAA: 43%); had depression (DAA:

43% vs non-DAA: 44%); and had opioid use disorder (DAA: 58% vs non-DAA: 59%). Approximately 27% of each group had a history of SUD-related hospitalizations or ED visits, and one-third received medications for SUD.

ANNUAL MEDICAL SERVICE UTILIZATION

The changes in the mean annual adjusted liver-related, SUD-related, and all-cause visits per person from the pre- to posttreatment periods of the DAA and non-DAA groups among patients with cirrhosis are shown in Table 2. For patients with SUD and chronic HCV who had cirrhosis (n = 607), there were no significant differences in the relative changes of rate of utilization of liver-related or SUD-related medical services between the 2 groups (Table 2). As for all-cause visits, all-cause office visits decreased by 3.1 visits (95% CI = -4.6, -1.7) for the DAA group and increased by 1.9 visits (95% CI = 0.39, 3.44) for the non-DAA group. The all-cause other outpatient visits decreased by 3.5 visits (95% CI = -6.6, -0.3) for the DAA group and increased by 3.5 visits (95% CI = 0.66, 6.39) for the non-DAA group.

The statistically significant differences in relative changes (in rate ratio scale) between groups from the pre- to posttreatment periods in the rate of all-cause office visits (rate ratio: 0.80 vs 1.15, RoRR: 0.70, 95% CI = 0.60, 0.81) and rate of all-cause other outpatient visits (rate ratio: 0.87 vs 1.16, RoRR: 0.75, 95% CI = 0.64, 0.90) showed decreases for the DAA group and increases for the non-DAA group (Table 2).

For patients with SUD and chronic HCV without cirrhosis (n = 5,659), the liver-related hospitalizations decreased by 0.04 visits (95% CI = -0.07, -0.01) for the DAA group and 0.03 visits (95% CI = -0.04, -0.01) for the non-DAA group (Table 3). The statistically significant differences in

FIGURE 1 Adjusted Medical Service Costs Among the Stabilized IPTW Patients With SUD and Chronic HCV and Cirrhosis: Liver-Related Costs^{a,b}

^aResults were derived from the stabilized IPTW difference-in-differences approach after controlling for age (18-35, 36-50, 51-64, and >64 years); sex at the index date; clinical conditions including the type of SUD, diabetes, hypertension, dyslipidemia, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, HIV infection, schizophrenia/bipolar disorder, depression, pregnancy, and other liver diseases (ie, alcoholic liver disease, nonalcoholic fatty liver disease, hepatitis B infection, hepatitis A infection), during the year before the index date, as well as current SUD status, medication for opioid use disorder or alcohol use, and pretreatment follow-up time.

^bCosts were adjusted to 2018 U.S. dollars using an annual 3% inflation rate.

DAA=direct-acting antiviral; HCV=hepatitis C virus; IPTW=inverse probability of treatment weighting; RoRR=rate of rate ratio; SUD=substance use disorder.

relative changes between groups from the pre- to posttreatment periods in rate of liver-related hospitalizations (rate ratio: 0.33 vs 0.67, RoRR: 0.51, 95% CI=0.27, 0.96) showed that the rate of liver-related hospitalizations decreased more in the DAA group than in the non-DAA group. On the other hand, the rate of liver-related other outpatient visits in the DAA group decreased statistical significantly less compared with the non-DAA group (rate ratio: 0.68 vs 0.52, RoRR: 1.31, 95% CI=1.17, 1.47).

In addition, the DAA group without cirrhosis was found to be associated with greater relative decreases in the rate of SUD-related ED visits (rate ratio: 0.78 vs 1.50, RoRR: 0.54, 95%

CI=0.38, 0.77); SUD-related SNF/long-term care visits (rate ratio: 0.33 vs 1.13, RoRR: 0.30, 95% CI=0.13, 0.73); all-cause ED visits (rate ratio: 0.92 vs 1.22, RoRR: 0.75, 95% CI=0.64, 0.88); and all-cause SNF/long-term care visits (rate ratio: 0.50 vs 1.41, RoRR: 0.36, 95% CI=0.18, 0.72) from the pre- to posttreatment periods that were statistically significant compared with the relative changes in the non-DAA group without cirrhosis (Table 3).

ANNUAL MEDICAL SERVICE COSTS

Among patients with SUD and chronic HCV who had cirrhosis, the changes in the mean adjusted liver-related, SUD-related, and all-cause medical services per person per year (PPPY)

costs from the pre- to posttreatment periods for the DAA and non-DAA groups are summarized in Figure 1 and [Supplementary Figure 3](#) (available in online article). Overall, for patients with SUD and chronic HCV and cirrhosis, the liver-related PPPY cost decreased by \$6,213 (95% CI=−\$8,571, −\$3,856) for the DAA group and \$1,585 (95% CI=−\$4,659, \$1,490) for the non-DAA group; the relative decreases in the rate of liver-related PPPY cost were larger for the DAA group than for the non-DAA group, and the relative changes between groups were significantly different (rate ratio: 0.34 vs 0.77, RoRR: 0.37, 95% CI=0.19, 0.73; Figure 1). The principal driver of this cost reduction was liver-related other outpatient PPPY costs (rate ratio: 0.24 vs 0.58, RoRR: 0.34, 95% CI=[0.19, 0.62; [Supplementary Table 6](#), available in online article).

There were no significant differences in relative changes from the pre- to posttreatment periods in rate of SUD-related PPPY costs (rate ratio: 1.31 vs 1.07, RoRR: 1.40, 95% CI=0.67, 2.92; [Supplementary Figure 3A](#)) or in rate of all-cause PPPY costs (rate ratio: 0.68 vs 0.54, RoRR: 1.26, 95% CI=0.89, 1.78) between the DAA group and non-DAA group ([Supplementary Figure 3B](#)).

Similarly, the patients with SUD and chronic HCV who did not have cirrhosis showed a larger relative decrease from the pre- to posttreatment periods in rate of liver-related PPPY costs in the DAA group than in the non-DAA group, and the relative changes were significantly different between the groups (rate ratio: 0.19 vs. 0.25, RoRR: 0.54, 95% CI=0.42, 0.70; Figure 2). The principal driver of this cost reduction was also liver-related other outpatient PPPY costs (rate ratio: 0.17 vs 0.27, RoRR: 0.44, 95% CI=0.33, 0.58; [Supplementary Table 7](#), available in online article). The differences in the relative changes from the pre- to posttreatment periods in

FIGURE 2 Adjusted Medical Service Costs Among the Stabilized IPTW Patients With SUD and Chronic HCV but Without Cirrhosis: Liver-Related Costs^{a,b}

^aResults were derived from the stabilized IPTW difference-in-differences approach after controlling for age (18-35, 36-50, 51-64, and >64 years); sex at the index date; clinical conditions including the type of SUD, diabetes, hypertension, dyslipidemia, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, HIV infection, schizophrenia/bipolar disorder, depression, pregnancy, and other liver diseases (ie, alcoholic liver disease, nonalcoholic fatty liver disease, hepatitis B infection, hepatitis A infection), during the year before the index date, as well as current SUD status, medication for opioid use disorder or alcohol use, and pretreatment follow-up time.

^bCosts were adjusted to 2018 U.S. dollars using an annual 3% inflation rate.

DAA=direct-acting antiviral; HCV=hepatitis C virus; IPTW=inverse probability of treatment weighting; RoRR=rate of rate ratio; SUD=substance use disorder.

rate of the SUD-related PPPY costs in the DAA group and the non-DAA group were not significantly different (rate ratio: 0.82 vs 0.74, RoRR: 1.17, 95% CI=0.89, 1.54; [Supplementary Figure 4A](#), available in online article).

Although there were statistically significant differences in the absolute decreases in all-cause PPPY costs in the DAA group and the non-DAA group separately from the pre- to posttreatment periods (decreased by \$16,226, 95% CI=−\$20,770, −\$11,681, for the DAA group and \$29,625, 95% CI=−\$33,025, −\$26,226, for the non-DAA group), the relative decrease in the rate of all-cause PPPY costs was smaller for the DAA group compared with that of the non-DAA group (rate

ratio: 0.63 vs 0.54, RoRR: 1.18, 95% CI=1.02, 1.37; [Supplementary Figure 4B](#), available in online article), largely due to a greater reduction in the all-cause hospitalization PPPY cost from the pre- to posttreatment periods for the non-DAA group (\$17,195) than for the DAA group (\$6,250; RoRR: 1.20, 95% CI=0.91, 1.58; [Supplementary Table 7](#)). This reduction compensated for that in the all-cause other outpatient PPPY costs for the DAA group (\$10,609 for the DAA group vs \$9,402 for the non-DAA group; RoRR: 0.98, 95% CI=0.83, 1.15; [Supplementary Table 7](#)).

There were no significant coefficients for the interaction terms of time and DAA treatment in the pre-treatment period for the liver-related

medical services visits ($P=0.28$) and other outcomes, suggesting that the parallel assumption holds ([Supplementary Table 8](#), available in online article).

SENSITIVITY ANALYSIS

In a separate sensitivity analysis examining any SUD-related services (eg, urine drug tests), there was no significant difference in the relative changes from the pre- to posttreatment periods in the rate of costs of any SUD-related services between the DAA and non-DAA groups ([Supplementary Table 9](#), available in online article).

Discussion

This retrospective cohort study provides real-world evidence on the changes from the pre- to posttreatment periods in liver-related, SUD-related, and all-cause medical service utilization and costs among commercially insured treatment-naïve chronic HCV patients with SUD treated with and without DAAs. For patients without cirrhosis, DAA treatment significantly reduced the rate of liver-related hospitalizations, SUD-related ED visits, SUD-related SNF/long-term care visits, and all-cause visits (except for all-cause inpatient visits).

For patients with cirrhosis, DAA treatment led to more significant relative reductions in the rate of all-cause office visits and other outpatient visits, whereas there was no statistically difference in relative changes in the rate of liver-related or SUD-related visits or other all-cause visits after DAAs between the 2 groups. We found that, regardless of cirrhosis status, patients who received DAAs were associated with significantly greater relative reductions in the rate of liver-related costs than their non-DAA peers; however, no significant

differences in relative changes of the rate of SUD-related costs or all-cause costs were found.

Although less than a quarter of the all patients with SUD and chronic HCV initiated DAA therapy, our finding of greater relative reductions in the rate of liver-related costs in this group are encouraging. Previous researchers have reported a decreased risk of developing end-stage liver disease and reduced liver-related expenditures for a privately insured or Medicare-insured chronically HCV-infected population (with cirrhosis) who underwent DAA treatment.^{10,66} Nevertheless, little was known about whether this conclusion held among patients with SUD and chronic HCV.

Our results further suggest that, even for patients with SUD and chronic HCV with access, barriers exist that are potentially related to providers' concerns regarding patients' risky behaviors and reinfections.³⁵ DAA treatment was associated with a decrease in liver-related health care utilization and liver-related medical services costs. Thus, our results provide evidence for physicians and payers that expanding access to DAA treatment for patients with SUD and chronic HCV may be effective in reducing liver-related costs.

According to the Centers for Disease Control and Prevention, SUD-related ED visits continued to rise from 2016 to 2017 because of nonfatal overdoses from prescription and illicit drugs.^{67,68} In light of this information, our finding that SUD-related ED visits and long-term care visits had a significantly greater reduction in the rate for the DAA group than for the non-DAA group among patients with SUD and chronic HCV without cirrhosis may suggest that the benefits of DAAs extend beyond liver-related outcomes, with treatment having a positive effect on patients' high-risk behaviors, especially among those without cirrhosis.⁶⁹

On the one hand, our finding of notable decreasing trends in SUD-related visits counters the argument that treating patients with SUD and chronic HCV with DAAs could lead to increased injection drug use or risky behaviors.^{31,69,70} On the other hand, it is also likely that the reduction in SUD-related visits reflects that patients in the DAA group are ready to make health changes and are more willing to accept harm reduction education (eg, sterile syringe access).^{35,71} We controlled for history of SUD pharmacotherapy to mitigate the imbalance between the two groups during the pretreatment period. However, future research is needed that includes patient attitudes and readiness for HCV treatment in the model.

STRENGTHS AND LIMITATIONS

Our study has several strengths. First, this study has methodological strength as a result of using prescription

time-distribution matching to adjust time to initiate DAA treatment after diagnosis and the stabilized IPTW difference-in-differences model controlling for underlying trends in factors that could influence our selected outcomes. The difference-in-differences model reduced bias in the post-treatment period comparison that could be the result from inherent differences between adults with SUD and chronic HCV treated with DAAs and those without DAAs, as well as biases from comparisons over time in the treatment group that could be the result of trends from other causes of the outcome. This approach has not been applied in previous economic analyses of the effects of DAA therapy in patients with HCV and should be used in future economic analyses, given its robust methodological strengths.^{58,72}

Second, to our knowledge, our work provides the first real-world evidence about the favorable current health care resource utilization and cost patterns among patients with SUD and chronic HCV, which can be used for future economic models that focus on this population with barriers to care.⁷²

Our study results also have several limitations. First, we used ICD-9/10-CM codes and pharmacy claims to identify patients with SUD, chronic HCV, and cirrhosis, which may have led to an underestimation of the number of targeted individuals and a lack of granularity on the severity and current status of the disease (eg, fibrosis staging and SUD with illicit injectable opioids vs prescription opioids), although validated algorithms were used.^{40,73} Also, our results may have suffered from potential selection bias despite our use of stabilized IPTW to balance the 2 groups.⁵¹

Second, given the current reimbursement requirements, it is possible that our population might have had to abstain from alcohol or injectable drug use for a certain period of time to be able to obtain the insurance approvals necessary to cover the costs of DAA treatment.^{29,65} Thus, our DAA group may have been more likely to be former substance users, but our non-DAA group may have been more likely to be current substance users. We attempted to mitigate this limitation by controlling for SUD-related ED or inpatient visits at baseline. In addition, several patients were excluded because of unconfirmed continuous eligibility, which is required for ascertainment of baseline covariates and previous medication use.

Third, selection bias could have been introduced by the inclusion of individuals with continuous eligibility of at least 1 year, considering that several patients with SUD might have encountered a coverage loss. Therefore, our results from the privately insured population may not be generalizable to those who are uninsured and other populations (eg, Medicare and Medicaid).⁷⁴

Finally, we could not ascertain several important variables, such as patient race/ethnicity and current injection drug use behavior, in the propensity score, which may have had an effect on the outcomes.

Conclusions

Among treatment-naïve chronic HCV patients with SUD, the use of DAA therapy resulted in significant reductions in the rate of liver-related costs without increasing the rate of SUD-related and all-cause costs in this population with barriers to care, regardless of cirrhosis status. We found a significant decline in the rate of SUD-related ED and long-term care visits for the DAA group compared with the non-DAA group among those without cirrhosis, suggesting the value of early treatment of patients with SUD and chronic HCV. Future work is needed on the strategies necessary to improve access to DAA treatment, especially for SUD subpopulations, to meet World Health Organization and US goals for eliminating hepatitis C by 2030.

DISCLOSURES

Research reported in this publication was supported in part by the National Institute on Drug Abuse of the National Institutes of Health (K01DA045618). The funder did not have a role in the design, the execution, the analyses, the interpretation of the data, or the decision to submit the results of this study. The authors have no potential conflicts of interest.

ACKNOWLEDGMENTS

The authors thank Debbie L. Wilson, PhD (University of Florida), for providing editorial assistance in the preparation of this manuscript.

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