Direct-Acting Antiviral Treatment Use Remains Low Among Florida Medicaid Beneficiaries With Chronic Hepatitis C

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Medicaid prior authorization (PA) policies for treatment of hepatitis C virus (HCV) with direct-acting antiviral (DAA) therapy are changing. We aimed to evaluate effects of changes in PA requirements on treatment uptake and to determine the factors associated with DAA treatment among Florida Medicaid beneficiaries with HCV. This is a retrospective cohort analysis of Florida's Medicaid administrative claims and electronic medical records (2013-2018). A total of 14,063 newly diagnosed patients with HCV were grouped based on human immunodeficiency virus (HIV) co-infection and/or a substance use disorder (SUD) (7,735 HCV mono-infected with a SUD, 5,180 HCV mono-infected without a SUD, 564 HCV/HIV co-infected with a SUD, and 584 HCV/HIV co-infected without a SUD). Although the treatment rate increased three-fold after June 1, 2016, when a fibrosis-stage restriction was eliminated, only 8% received DAAs. Compared to HCV mono-infected without a SUD, HCV mono-infected with a SUD and HCV/HIV co-infected with a SUD were 47% (adjusted hazard ratio, 0.53; 95% confidence interval, 0.47-0.60) and 59% (adjusted hazard ratio, 0.41; 95% confidence interval, 0.28-0.61) less likely to initiate DAAs. Those with HCV/HIV/SUD did not experience a DAA initiation increase after a fibrosis-stage restriction was eliminated. Compared with Whites, Blacks were less likely to receive DAAs but were more likely to complete treatment. Use of medication-assisted therapy was low, despite those on medication-assisted therapy being 60% more likely to initiate DAA therapy and no more likely to discontinue therapy. *Conclusion:* Despite changes in Florida's Medicaid PA requirements for DAA treatment, only 8% received treatment. Disparities in treatment access were found among patients with HIV and a SUD, and who were Black. (*Hepatology Communications* 2021;5:203-216).

Hepatitis C virus (HCV) is the most frequently reported bloodborne infection in the United States and a leading cause of liver-related morbidity, liver transplantation, and mortality.[1] HCV treatment has greatly improved with the introduction of direct-acting antiviral (DAA) therapy, with therapeutic efficacy in more than 95% of patients across the four major HCV genotypes with limited adverse effects.[2,3] Curative DAA treatments for chronic HCV infection have allowed treatment in patients previously considered hard to treat in the interferon era (e.g., human immunodeficiency virus [HIV] co-infection).[2]

However, high drug costs have led private and public insurers, including Medicaid, to restrict access to these medications, requiring that patients meet

Abbreviations: AASLD, American Association for the Study of Liver Diseases; aHR, adjusted hazard ratio; CI, confidence interval; DAA, direct-acting antiviral; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; ICD-CM, International Classification of Diseases, Clinical Modification; IDSA, Infectious Diseases Society of America; MAT, Medication assisted therapy; PA, prior authorization; RBV, ribavirin; SUD, substance use disorder.

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specific prior authorization (PA) approval.[4-6] In recent years, although many states have eliminated or reduced their restrictions based on patients' liver disease stage and HIV co-infection, most of them restrict access to new HCV therapy from illicit drug or alcohol users. In Florida, the state with the third highest number of persons living with HCV infection (about 150,000 persons), Medicaid reduced its restrictions for patients with HCV/HIV co-infection and eliminated fibrosis-stage restrictions (Supporting Table S1) in 2016.[7] However, Florida Medicaid requires abstinence from illicit drugs and/or alcohol for 1 month and the prescribing of DAAs by or in consultation with a specialist.[7]

Medicaid's PA policy has generated concern about unintended consequences within the liver-health community and the public at large, as these restrictions are not grounded in clinical evidence.[6] Furthermore, this policy is inconsistent with HCV treatment guidelines and may create a disparity in access to HCV treatment. For example, the National Institutes of Health HCV guidelines and the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) advocate the inclusion of persons with a substance use disorder (SUD) in HCV treatment and recommend that persons with HIV/HCV co-infection and ongoing risk factors for transmission, including those who inject drugs, be given high priority for treatment because of their high risk for complications.[8] Patients denied access to HCV therapies may progress to hepatic fibrosis and be at risk for the development of end-stage liver disease and extra hepatic manifestations.[9-11] Indeed, a recent study suggests that deferring HCV therapy reduces treatment effectiveness and increases the risk of liver-related complications and death.[12]

Several studies have reported that nearly half of Medicaid beneficiaries have been denied access to DAA-based treatments for chronic HCV infection.[13-15] These studies were conducted before the restrictions against initiating DAA therapy for those on Medicaid were changed and updated in many states, and did not provide information about the reasons for these disparities in access to DAA therapy and or about therapy completion rates among Medicaid beneficiaries.

Therefore, we aimed to evaluate the effects of change in Florida Medicaid PA policies on DAA treatment uptake and to identify the population most at risk for not receiving DAA treatment as well as the factors (e.g., race/ethnicity) associated with access to HCV treatment among persons with HCV, to include those co-infected with HIV as well as those with and without a SUD among Florida Medicaid beneficiaries.

Materials and Methods

DATA SOURCE

We conducted a retrospective cohort study using Florida Medicaid administrative claims containing person-level information of enrollment, medical services, and prescriptions for over 4 million beneficiaries enrolled in the Florida Medicaid program. Of those, approximately 17% of Florida Medicaid beneficiaries' data were able to be extracted, as they had visited a One Florida health clinic, which uses an electronic medical record system under the OneFlorida Data Trust.[16] OneFlorida is a partnership of 11 health systems and affiliated practices in Florida, several statewide insurance programs, and Florida's Agency for Health Care Administration, which oversees Florida Medicaid. This study was approved by the institutional review board of the University of Florida.

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STUDY POPULATION

Identification of Newly Diagnosed Patients With Chronic HCV

We used Florida Medicaid administrative claims to establish the new chronic HCV cohort for the study period of January 1, 2013, to December 31, 2018. We included patients aged 18-64 years, who were not dually eligible for Medicare, whose first chronic HCV diagnosis occurred without any chronic HCV diagnosis in the previous 12 months using the International Classification of Diseases (ICD), Clinical Modification codes (ICD-9-CM codes 070.44, 070.54, 070.70, and 070.71, and ICD-10-CM codes B18.2, B19.20, B19.21, and Z22.52). A patient was determined to have chronic HCV if they had met a previously validated algorithm of one inpatient or two outpatient diagnoses of chronic HCV on separate days within 1 year.[17] Patients were also required to be continuously enrolled in Florida Medicaid 1 year before and 3 months after their first HCV diagnosis with a 30-day grace period. Patients were excluded if they had decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), or liver transplantation during the 1-year period before their first chronic HCV diagnosis. For this analysis, we also excluded patients with any HCV therapy before the index date.

Presence of a SUD and/or HIV Co-infection Among Patients With Chronic HCV

We further categorized patients with chronic HCV based on any SUD diagnosis and/or HIV co-infection recorded from 1 year before through 3 months after their first HCV diagnosis. Patients were grouped into four cohorts: (1) HCV mono-infected with a SUD; (2) HCV mono-infected without a SUD; (3) HCV/HIV co-infected with a SUD; and (4) HCV/HIV co-infected without a SUD (Fig. 1).

By using a previously validated algorithm, patients were considered to have a SUD if they had at least one inpatient or one outpatient claim of drug or alcohol use disorders using ICD-9/ICD-10 codes (Supporting Table S2) or had a record of methadone, buprenorphine, or naltrexone used for opioid use disorder or alcohol use disorder.[18-20] We used Current Procedural Terminology codes (H0020, J1230) in medical claims to capture methadone dispensed for opioid use disorder. We used National Drug Codes in pharmacy

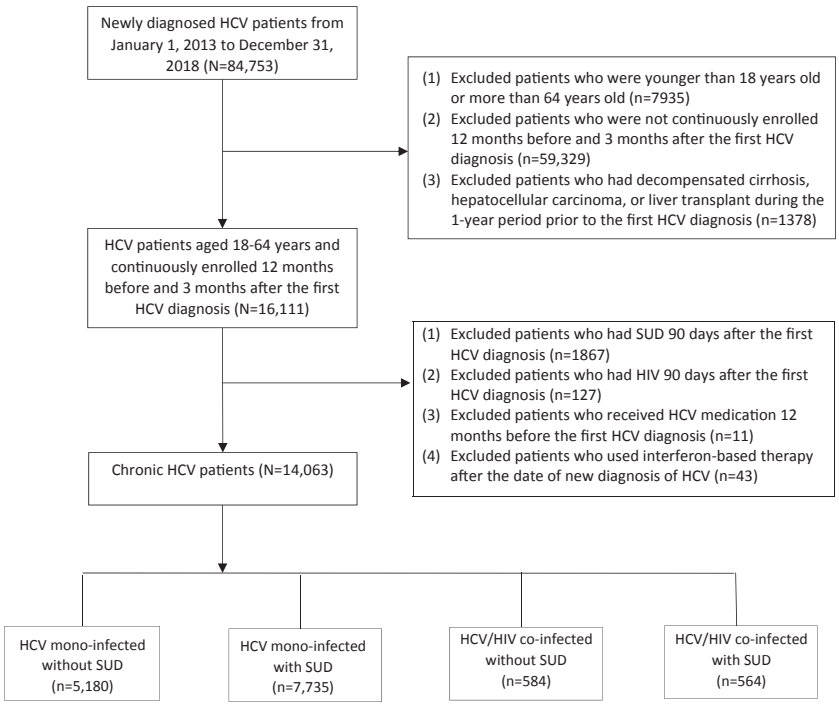


FIG. 1. Flow chart of the cohort creation.

claims to identify buprenorphine and naltrexone. The following SUD diagnoses were examined: opioid use disorder, other drug-related disorders (e.g., cocaine, heroin, sedatives), and alcohol use disorder. Patients were considered to have HIV co-infection if they had at least one inpatient or outpatient claim with an HIV diagnosis using ICD-9/ICD-10 codes.

DAA Treatment Initiation Rate

We included the following Food and Drug Administration–approved and available all-oral DAA therapies, or recommended by the AASLD/IDSA for treatment-naïve patients: [sofosbuvir/ledipasvir, sofosbuvir + simeprevir, sofosbuvir, sofosbuvir + daclatasvir, paritaprevir/ritonavir/ombitasvir ± dasabuvir, elbasvir/grazoprevir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, and glecaprevir/pibrentasvir] ± ribavirin (RBV). We grouped them into two types of DAA treatment: DAA only or DAA with RBV.

To estimate the initiation rate for DAA therapy, we used pharmacy claims data to determine when the first all-oral DAA prescription was filled and provided the overall rate as per 1,000 person-years over the study period. For each individual, the person-years of follow-up were calculated from the first chronic HCV diagnosis date to the date of first DAA prescription, end of enrollment, or December 31, 2018, whichever occurred first.

DAA Treatment Discontinuation Rate

For patients with chronic HCV who initiated all-oral DAA therapy, we compared early discontinuation rates among the four groups. Discontinuation was defined as a gap in therapy of ≥30 days.[21] 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 date of the last prescription claim's fill date plus the last prescription claim's days' supply) plus 30 days was shorter than the expected treatment. The expected treatment duration was based on 2017 AASLD/IDSA treatment guidelines, accounting for baseline cirrhosis diagnosis before the index date.[22] For example, we used 8 weeks for sofosbuvir/ledipasvir among patients without cirrhosis and 12 weeks for the other all-oral therapies with and without cirrhosis. Because the 8-week regimen for sofosbuvir/ledipasvir was not recommended by guidelines until 2016, we performed a sensitivity analysis for discontinuation using 12 weeks of sofosbuvir/ledipasvir for 2014-2015 and 8 weeks for 2016.

STATISTICAL ANALYSIS

Baseline characteristics were compared among the four groups using chi-square tests for categorical variables. To test trends across years, the Cochrane-Armitage test was used. To compare treatment initiation rates before and after June 1, 2016, chi-square tests were used. We used a multivariable Cox proportional hazards regression model to estimate hazard ratios of DAA treatment initiation rates among the four groups, controlling for covariates. Covariates included demographics (i.e., age, sex, race, and ethnicity), comorbidities (i.e., diabetes, mental health disorder, and pregnancy), and other liver diseases (i.e., hepatitis B virus, nonalcoholic fatty liver disease [NAFLD], compensated cirrhosis, DCC, and HCC). It is important to note that although we excluded patients with DCC and HCC before the study initiation date, some patients may have developed it before the initiation of DAAs.

Due to missing values in laboratory data, we were not able to control for laboratory data. We also used a multivariable Cox proportional hazards regression model to estimate hazard ratios of early DAA discontinuation rates among the four groups, controlling for the aforementioned covariates as well as treatment with a DAA alone or DAA + RBV. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

PATIENT CHARACTERISTICS

Between January 2013 and December 2018, we identified 14,063 Florida Medicaid patients newly diagnosed with HCV, of which 59% had a SUD diagnosis and 8% had an HIV diagnosis (Table 1). The distribution among the groups was as follows: (1) 7,735 HCV mono-infected patients with a SUD (55.0%), (2) 5,180 HCV mono-infected without a SUD (36.8%), (3) 564 HCV/HIV co-infected patients with a SUD (4.0%), and (4) 584 HCV/HIV co-infected patients without a SUD (4.2%).

HCV mono-infected patients without a SUD were more likely to be female (57.0%) and white (57.3%),

TABLE 1. BASELINE CHARACTERISTICS OF FLORIDA MEDICAID PATIENTS WITH CHRONIC HCV

	Total (n = 14,063)	HCV Mono-infected With SUD (n = 7,735)	HCV Mono-infected Without SUD (n = 5,180)	HCV/HIV Co-infected With SUD (n = 564)	HCV/HIV Co-infected Without SUD (n = 584)	*P* Value
Age (years)						<0.001
Mean (SD)	47.0 (12.7)	44.5 (12.9)	50.0 (12.4)	48.4 (10.5)	51.8 (9.7)	
18-34	3,265 (23.2%)	2,290 (29.6%)	860 (16.6%)	77 (13.7%)	38 (6.5%)	
35-44	2,175 (15.5%)	1,396 (18.0%)	603 (11.6%)	96 (17.0%)	80 (13.7%)	
45-54	3,165 (22.5%)	1,606 (20.8%)	1,171 (22.6%)	202 (35.8%)	186 (31.8%)	
55-64	5,458 (38.8%)	2,443 (31.6%)	2,546 (49.2%)	189 (33.5%)	280 (47.9%)	
Gender						<0.001
Male	6,334 (45.0%)	3,425 (44.3%)	2,228 (43.0%)	321 (56.9%)	360 (61.6%)	
Female	7,729 (55.0%)	4,310 (55.7%)	2,952 (57.0%)	243 (43.1%)	224 (38.4%)	
Race						<0.001
White	9,006 (64.0%)	5,647 (73.0%)	2,968 (57.3%)	216 (38.3%)	175 (30.0%)	
Black	2,535 (18.0%)	871 (11.3%)	1,133 (21.9%)	247 (43.8%)	284 (48.6%)	
American Indian/Alaska Native/Asian/native Hawaiian/other Pacific Islander	112 (0.8%)	40 (0.5%)	71 (1.4%)	—	—	
Other*	904 (6.4%)	383 (5.0%)	423 (8.2%)	37 (6.6%)	61 (10.4%)	
Unknown	1,506 (10.7%)	794 (10.3%)	585 (11.3%)	64 (11.3%)	63 (10.8%)	
Ethnicity						<0.001
Hispanic	1,191 (8.5%)	486 (6.3%)	561 (10.8%)	61 (10.8%)	83 (14.2%)	
Non-Hispanic	11,158 (79.3%)	6,348 (82.1%)	3,941 (76.1%)	436 (77.3%)	433 (74.1%)	
Other†	1,714 (12.2%)	901 (11.6%)	678 (13.1%)	67 (11.9%)	68 (11.6%)	
Comorbidity						
Diabetes	2,783 (19.8%)	1,264 (16.3%)	1,263 (24.4%)	125 (22.2%)	131 (22.4%)	<0.001
Schizophrenia/bipolar	2,450 (17.4%)	1,612 (20.8%)	617 (11.9%)	163 (28.9%)	58 (9.9%)	<0.001
Depression	5,560 (39.5%)	3,708 (47.9%)	1,411 (27.2%)	302 (53.5%)	139 (23.8%)	<0.001
Epilepsy	1,115 (7.9%)	757 (9.8%)	265 (5.1%)	60 (10.6%)	33 (5.7%)	<0.001
Pregnancy	1,471 (10.5%)	1,013 (13.1%)	422 (8.1%)	19 (3.4%)	17 (2.9%)	<0.001
Other liver disease						
Nonalcoholic liver disease	662 (4.7%)	393 (5.1%)	221 (4.3%)	36 (6.4%)	12 (2.1%)	<0.001
Hepatitis B virus	591 (4.2%)	302 (3.9%)	157 (3.0%)	68 (12.1%)	64 (11.0%)	<0.001
Liver severity						
Cirrhosis	682 (4.8%)	412 (5.3%)	240 (4.6%)	11 (2.0%)	19 (3.3%)	<0.001
SUD						
Opioid	4,016 (28.6%)	3,842 (49.7%)	NA	174 (30.9%)	NA	<0.001
Other drug-related	5,920 (42.1%)	5,463 (70.6%)	NA	457 (81.0%)	NA	<0.001
Cocaine, heroin	2,647 (18.8%)	2,379 (30.8%)	NA	268 (47.5%)	NA	<0.001

TABLE 1. *Continued*

	Total (n = 14,063)	HCV Mono-infected With SUD (n = 7,735)	HCV Mono-infected Without SUD (n = 5,180)	HCV/HIV Co-infected With SUD (n = 564)	HCV/HIV Co-infected Without SUD (n = 584)	PValue
Sedatives, hypnotics, anxiolytics, tranquilizers, and barbiturates	761 (5.4%)	721 (9.3%)	NA	40 (7.1%)	NA	<0.001
Stimulants	748 (5.3%)	707 (9.1%)	NA	41 (7.3%)	NA	<0.001
Other (unspecified or specified) drug dependence and drug-induced mental disorders	4,039 (28.7%)	3,757 (48.6%)	NA	282 (50.0%)	NA	<0.001
Cannabis	1,851 (13.2%)	1,684 (21.8%)	NA	167 (29.6%)	NA	<0.001
Hallucinogens	85 (0.6%)	80 (1.0%)	NA	—	NA	<0.001
Alcohol	3,081 (21.9%)	2,852 (36.9%)	NA	229 (40.6%)	NA	<0.001
Medication-assisted therapy for opioid use disorder	532 (3.8%)	516 (6.7%)	NA	16 (2.8%)	NA	
Methadone	250 (1.8%)	240 (3.1%)	NA	—	NA	<0.001
Buprenorphine	220 (1.6%)	217 (2.8%)	NA	—	NA	<0.001
Naltrexone	66 (0.5%)	63 (0.8%)	NA	—	NA	<0.001

Note: Data are reported as numbers (percentages) unless otherwise indicated. "—" indicates the numbers of patients with 10 or less observations were not presented.
*Multiple races, refused to answer, and other.
†No information, other, refused to answer, and unknown.

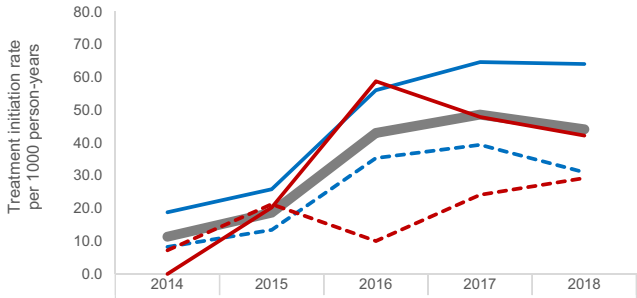
whereas HCV/HIV co-infected patients without a SUD were more likely to be male (61.6%) and Black (48.6%). HCV mono-infected with a SUD were more likely to be White (73.0%), whereas HCV/HIV co-infected patients with a SUD were more likely to be Black (43.8%). Among patients with a SUD, almost 50% of HCV mono-infected patients had a diagnosis of opioid use disorder, whereas HCV/HIV co-infected patients tended to have a diagnosis of cocaine or heroin use disorder. Only 3.8% of patients with a SUD received medication assisted therapy (MAT) for opioid use disorder. Among the pregnant women, almost 70% also had a SUD.

TRENDS IN INITIATION RATE OF ALL-ORAL DAAs AMONG FLORIDA MEDICAID PATIENTS WITH CHRONIC HCV DURING 2013-2018

Figure 2 displays the trends in the treatment initiation rates between 2014 (November 2013 to December 2014) and 2018, going from 11.4 to 44.1 per 1,000 person-years, which equates to 26 patients treated in 2014 to 350 patients in 2018. During 2014-2018, for the HCV mono-infected patients, DAA initiation rates (per 1,000 person-years) increased from 8.3 to 31.0 (3.7 times) and from 18.8 to 64.1 (3.4 times) for those with and without a SUD, respectively. A similar trend was observed in HCV/HIV co-infected patients. For HCV/HIV co-infected patients with a SUD, DAA initiation rates (per 1,000 person-years) increased from 7.2 to 29.2 (4.1 times), and for HCV-HIV co-infected patients without a SUD, it increased from 0 to 58.8 in 2016 and then decreased to 42.2 in 2018.

DAA TREATMENT INITIATION RATES BEFORE AND AFTER JUNE 1, 2016

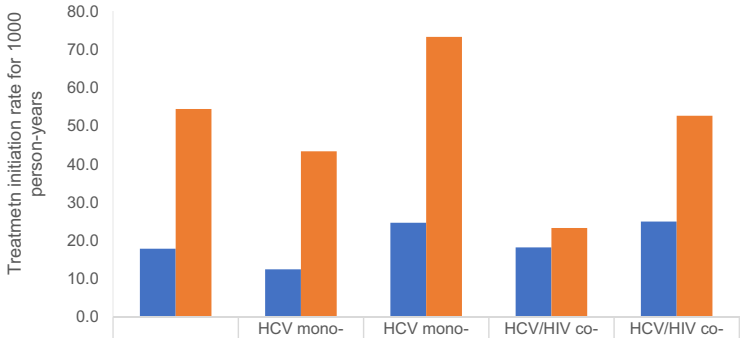
Since Florida Medicaid changed its policy on who was able to receive DAA therapy based on staging of liver fibrosis on June 1, 2016, we compared DAA-initiation person time rates before and after June 1, 2016. Figure 3 displays these changes. There was a significant increase in DAA initiation for all patients from before and after June 1, 2016 (17.9 to 54.5 per 1,000 person-years, $P < 0.01$). There also was a significant difference in the rate of initiation between groups in which the HCV mono-infected group with a SUD had a 3.5-times increase in their initiation rate,



	2014	2015	2016	2017	2018
All patients	11.4	18.7	43.0	48.6	44.1
HCV mono-infected with SUD	8.3	13.4	35.4	39.4	31.0
HCV mono-infected without SUD	18.8	25.9	56.1	64.7	64.1
HCV/HIV co-infected with SUD	7.2	21.3	10.0	24.2	29.2
HCV/HIV co-infected without SUD	0.0	20.3	58.8	47.9	42.2

HCV: hepatitis C virus, SUD: substance use disorders, HIV: human immunodeficiency virus
* Cochran-Armitage test was used to test trends (P<0.001).

FIG. 2. Trends in initiation rates of all-oral DAAs per 1,000 person years among Florida Medicaid patients with chronic HCV, stratified by HIV co-infection and/or SUD, 2014-2018.



	All patients	HCV mono-infected with SUD	HCV mono-infected without SUD	HCV/HIV co-infected with SUD	HCV/HIV co-infected without SUD
Before June 1, 2016	17.9	12.5	24.7	18.3	25.0
After June 1, 2016	54.5	43.4	73.4	23.3	52.7

DAA: direct-acting antiviral, HCV: hepatitis C virus, SUD: substance use disorders, HIV: human immunodeficiency virus
Chi-square tests were used to compare treatment initiation rates before and after June 1, 2016. (all groups had significant increases within each group (P<0.01) except those with HCV/HIV with SUD (P=0.08).

FIG. 3. Initiation rates of all-oral DAA therapy per 1,000 person-years among Florida Medicaid patients with chronic HCV before and after June 1, 2016, stratified by HIV co-infection and/or SUD.

whereas the HCV/HIV with a SUD group had the lowest increase of only 1.3 times. In addition, all groups had significant increases within each group ($P < 0.01$), except those with HCV/HIV with a SUD ($P = 0.08$).

OVERALL DAA TREATMENT INITIATION RATES AMONG FLORIDA MEDICAID PATIENTS

From 2013 to 2018, of the 14,063 Florida Medicaid enrollees with a diagnosis of HCV, only 8% of these patients (n = 1,118) received all-oral DAA treatment (Table 2), of which 76% received DAA only (n = 852) and 24% received DAA plus RBV (n = 266). The remaining 92% (n = 12,945) did not receive any HCV treatment. Only 5.9% of HCV mono-infected patients with a SUD and 4.8% of HCV/HIV co-infected patients with a SUD initiated DAA therapy, which was significantly lower compared with the initiation rate of 11.1% and 9.6% among HCV mono-infected and HCV/HIV co-infected patients without a SUD ($P < 0.01$), respectively. After adjusting for covariates, compared to HCV mono-infected patients without a SUD, HCV mono-infected patients with a SUD and

TABLE 2. UNADJUSTED AND ADJUSTED INITIATION RATES OF ALL-ORAL DAA THERAPY FOR FLORIDA MEDICAID PATIENTS WITH CHRONIC HCV, STRATIFIED BY THE PRESENCE OF HIV CO-INFECTION AND/OR SUD (n = 14,063)

	No. of DAA Initiation	% of DAA Initiation	Person-Years	Crude Incidence / 1,000 Person-Years	Adjusted HR* (95% CI)
Total (n = 14,063)	1,118	7.9%	29,068	38.5	N/A
DAA only†	852				
DAA + RBV‡	266				
HCV mono-infected with SUD (n = 7,735)	459	5.9%	15,479	29.7	0.53 (0.47-0.60)
DAA only†	341				
DAA + RBV‡	118				
HCV mono-infected without SUD (n = 5,180)	576	11.1%	10,822	53.2	Reference
DAA only†	435				
DAA + RBV‡	141				
HCV/HIV co-infected with SUD (n = 564)	27	4.8%	1,346	20.1	0.41 (0.28-0.61)
DAA only†	25				
DAA + RBV‡	2				
HCV/HIV co-infected without SUD (n = 584)	56	9.6%	1,422	39.4	0.85 (0.64-1.13)
DAA only†	51				
DAA + RBV‡	5				

*Cox proportional hazards model was used to adjust for age, sex, race, ethnic, diabetes, mental disorder, pregnancy, nonalcoholic liver disease, hepatitis B virus, cirrhosis, DCC, and HCC.
†Included sofosbuvir, sofosbuvir + simeprevir, sofosbuvir/ledipasvir, paritaprevir/ritonavir/ombitasvir ± dasabuvir, elbasvir/grazoprevir, sofosbuvir/velpatasvir ± voxilaprevir, daclatasvir, and glecaprevir/pibrentasvir.
‡Included [sofosbuvir, sofosbuvir + simeprevir, sofosbuvir/ledipasvir, paritaprevir/ritonavir/ombitasvir ± dasabuvir, elbasvir/grazoprevir, sofosbuvir/velpatasvir ± voxilaprevir, daclatasvir, and glecaprevir/pibrentasvir] + RBV.

HCV/HIV co-infected patients with a SUD were 47% (adjusted hazard ratio [aHR], 0.53; 95% confidence interval [CI], 0.47-0.60) and 59% (aHR, 0.41; 95% CI, 0.28-0.61) less likely to initiate DAAs; however, no significant difference was observed in HCV/HIV co-infected patients without a SUD (aHR, 0.85; 95% CI, 0.64-1.13).

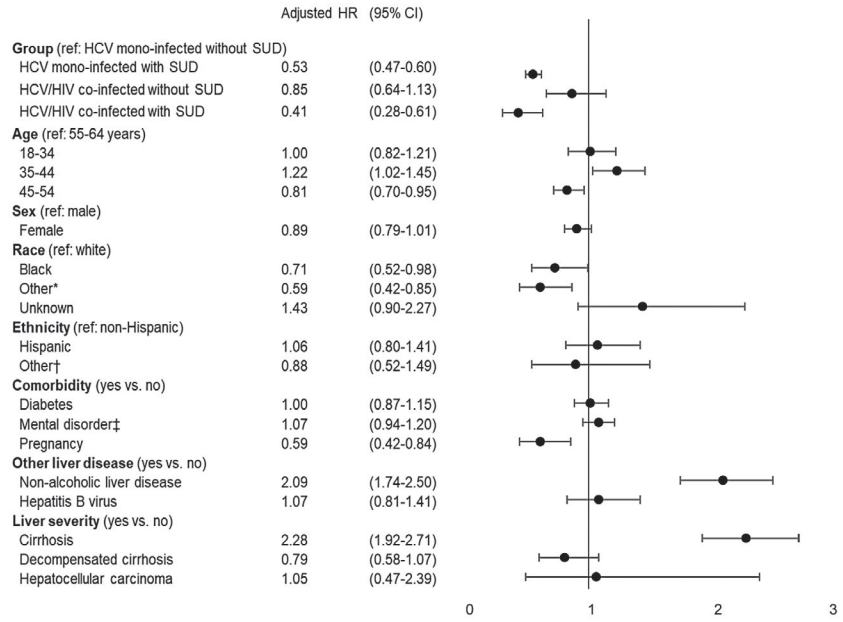
FACTORS RELATED TO THE RECEIPT OF DAA THERAPY

Figure 4 summarizes the other factors associated with DAA initiation among Florida Medicaid patients with chronic HCV. Factors associated with a significantly lower probability of initiating DAAs included being 45-55 years old (compared with being 55-64 years old; aHR, 0.81; 95% CI, 0.70-0.95), being Black (aHR, 0.71; 95% CI, 0.52-0.98), and being of other race (aHR, 0.59; 95% CI, 0.42-0.85), compared with being White and pregnant (aHR, 0.59; 95% CI, 0.42-0.84). In contrast, patients with cirrhosis (aHR, 2.28; 95% CI, 1.92-2.71) and NAFLD (aHR, 2.09; 95% CI, 1.74-2.50) were more likely to receive DAAs. Furthermore, as indicated in Supporting Table S3, for those patients with chronic HCV with available laboratory data, the treated patients had more advanced liver disease compared with the untreated patients.

Among patients with chronic HCV with a SUD, patients with alcohol as well as opioid or other drugs (aHR, 0.53; 95% CI, 0.40-0.70) or opioid with other drugs (aHR, 0.61; 95% CI, 0.45-0.82) polysubstance use disorders, compared to those with other drugs alone were less likely to receive DAAs. However, patients receiving MAT for a SUD were more likely to receive DAAs (aHR, 1.60; 95% CI, 1.10-2.33) (Supporting Fig. S1).

DAA TREATMENT DISCONTINUATION RATE

Because of the small sample size for HCV/HIV co-infected patients who discontinued DAAs (<5), we regrouped patients into two groups (patients with HCV with a SUD versus patients with HCV without a SUD) to evaluate whether there were differences in DAA discontinuation among patients with HCV with (n = 486) and without (n = 632) a SUD. Overall, approximately 6.8% of patients with HCV



DAA: direct-acting antiviral, HCV: hepatitis C virus, HR: hazard ratio, CI: confidence interval, HIV: human immunodeficiency virus
*American Indian/Alaska Native/Asian/Native Hawaiian/other Pacific Islander, multiple race, refuse to answer, and other
†No information, other, refuse d to answer, and unknown
‡Schizophrenia/bipolar, depression, and epilepsy

FIG. 4. Forest plot of the receipt of all-oral DAAs among Florida Medicaid patients with chronic HCV.

TABLE 3. UNADJUSTED AND ADJUSTED DISCONTINUATION RATES OF ALL-ORAL DAA THERAPY FOR FLORIDA MEDICAID PATIENTS WITH CHRONIC HCV, STRATIFIED BY PRESENCE OF SUD (n = 1,118)

	No. of DAA Discontinuations	% of DAA Discontinuations	Person-Weeks	Crude Incidence/1,000 Person-Weeks	Adjusted HR* (95% CI)
HCV with SUD (n = 486)	36	7.4%	5,355	6.7	1.41 (0.87-2.17)
DAA only†	24				
DAA + RBV‡	13				
HCV without SUD (n = 632)	40	6.3%	6,830	5.9	Reference
DAA only†	33				
DAA + RBV‡	7				

*Cox proportional hazards model was used to adjust for age, sex, race, ethnic, diabetes, mental disorder, pregnancy, HIV, nonalcoholic liver disease, hepatitis B virus, cirrhosis, and DCC.
†Included sofosbuvir, sofosbuvir + simeprevir, sofosbuvir/ledipasvir, paritaprevir/ritonavir/ombitasvir ± dasabuvir, elbasvir/grazoprevir, sofosbuvir/velpatasvir ± voxilaprevir, daclatasvir, and glecaprevir/pibrentasvir.
‡Included [sofosbuvir, sofosbuvir + simeprevir, sofosbuvir/ledipasvir, paritaprevir/ritonavir/ombitasvir ± dasabuvir, elbasvir/grazoprevir, sofosbuvir/velpatasvir ± voxilaprevir, daclatasvir, and glecaprevir/pibrentasvir] + RBV.

who initiated DAA therapy discontinued treatment early (Table 3). The DAA treatment discontinuation rate was slightly higher for patients with a SUD compared to patients without a SUD (6.7 vs. 5.9 per 1,000 person-weeks). However, after adjusting for covariates, there was no significant difference in the early treatment discontinuation rates between the SUD and non-SUD groups (aHR, 1.41; 95% CI, 0.87-2.17).

Compared with Whites, Blacks (aHR, 0.14; 95% CI, 0.04-0.49) and other races (aHR, 0.17; 95% CI, 0.04-0.66) were less likely to discontinue their DAA treatment early, as were those aged 35-44 (compared

to those aged 55-64 [aHR, 0.35; 95% CI, 0.16-0.79]) and those with cirrhosis (aHR, 0.46; 95% CI, 0.23-0.94) (Supporting Fig. S2). All other factors were not significantly associated with early discontinuation.

Among those with a SUD, only Blacks (aHR, 0.04; 95% CI, 0.00-0.55) or other races (aHR, 0.03; 95% CI, 0.00-0.53) when compared with Whites were less likely to discontinue DAA treatment early (Supporting Fig. S3). In a sensitivity analysis using a 12-week sofosbuvir/ledipasvir treatment during 2014-2015 and an 8-week treatment during 2016 for treatment discontinuation, the study results remained consistent (Supporting Table S4).

Discussion

In this study of Florida Medicaid beneficiaries with chronic HCV, we found that from 2013 to 2018, the DAA treatment rate increased 4-fold with a very low early discontinuation rate (<7%), but DAA treatment overall was extremely low, as only 8% of Florida Medicaid patients with chronic HCV received DAA treatment. The increase in treatment rate can be attributed to the changes of DAA treatment eligibility over the course of the study. Specifically, on June 1, 2016, Florida Medicaid relaxed the criteria necessary for reimbursement of DAA treatment especially for patients with a fibrosis level < F3, recommending treating those co-infected with HIV as well as reducing the prescribers' requirement burden. These findings are encouraging in that as barriers are removed for treatment, treatment uptake may continue to increase with very few patients discontinuing treatment.

On the other hand, despite changes in policy, 92% of patients with chronic HCV on Medicaid remained untreated. Although reimbursement restrictions based on fibrosis stage were lifted in 2016, it is important to note that barriers to accessing DAA therapies based on 1 month of sobriety and DAA prescriptions provided by or in consultation with a specialist still remain in Florida, preventing those at the highest risk of complications from receiving HCV treatment. In addition to the barriers due to Medicaid policy, we think there are other multilevel issues related to the provider, patient, and health system structure that have led to low HCV treatment rates.[23,24] Many physicians are unwilling or hesitant to treat people actively using drugs with DAA therapies due to concerns about reinfection, adherence, and medication cost.[25] Patient-level barriers include poor knowledge of HCV, leading to misperceptions about HCV infection and its treatment, ongoing stigma associated with having HCV, mental health issues, and general challenges with accessing the health care system.[26] At the system level, limited infrastructure for providing HCV assessment and treatment, particularly in primary care services and substance treatment centers as well as limited accessibility of testing locations, are also large barriers to care.[26,27]

In addition, those with a SUD and chronic HCV received treatment at an even lower rate (5.9%), which is substantially lower than those covered by other insurance or indigent care (14%).[13] However, those on MAT were almost 60% more likely to initiate DAA treatment and were no more likely to discontinue treatment than those without MAT. Similar to our findings, a previous study reported that individuals retained in buprenorphine treatment were more likely to initiate HCV treatment, most likely as a result of better engagement with the health care system.[28] However, despite this finding, we found that less than 4% (the national average is 28%) were receiving MAT.[29] The role of MAT in the prescriber's and patient's behavior is an area that needs further exploration if the uptake of DAA treatment is to happen; however, enhancing access to MAT treatment should be taken into consideration.[30-32]

In addition, the group least likely to be treated with DAAs over this study period and one that saw no change in their uptake of treatment was that with HCV/HIV and a SUD. This finding should come as no surprise, as all three diseases carry a substantial burden of stigmatization resulting in difficulty treating this cohort due to their transience, social isolation, and inadequate medical and substance use disorder treatment services.[33] Therefore, proven harm-reduction strategies such as the pairing of needle exchange sites with MAT therapy, HCV and HIV testing, as well as investigating ways to decrease the stigma associated with these diseases will be needed to reach the goal of eliminating hepatitis by 2030.[34,35]

We also found that racial disparities exist in those receiving DAA treatment, as Blacks, who represented about 20% of Florida Medicaid patients with HCV and approximately 50% of the HCV/HIV population, were almost 30% less likely to receive HCV treatment compared with Whites. Such a finding is disquieting

for several reasons. First, recent studies have confirmed that DAAs have similar effectiveness in Blacks compared with Whites, so they should be prescribed as indicated. We also found that once Blacks initiated treatment, they were 86% less likely to discontinue treatment after controlling for all other covariates. In addition, because Blacks made up 50% of the HCV/HIV population, this group was at higher risk for disease progression, which would suggest that treatment was necessary, especially as the presence of HIV is known to hasten liver disease progression and Blacks are more likely to experience complications of HCV including HCC, end-stage liver disease, and death from cirrhosis.[22,29] Future studies are needed to advance our understanding about the reasons for this racial disparity.

Not surprisingly, patients with cirrhosis were more likely to receive and continue treatment once initiated. Such a finding is probably a result of more health care encounters due to their advanced liver disease and the fact that Florida Medicaid's original requirements necessary to receive DAA treatment was the presence of advanced liver disease. However, a somewhat surprising finding was that among the pregnant women with chronic HCV, almost 70% also had a SUD. Because DAA treatment is not yet approved or recommended by AASLD for use during pregnancy, this group will need to be followed very closely so that treatment can be initiated when eligible. Currently, there are ongoing clinical trials investigating treatment in pregnant women with ledipasvir/sofosbuvir.[36-38] Another study on the use of sofosbuvir/velpatasvir during the postpartum period is ongoing, with results due in September 2020.[39] As such, this group should be targeted to better understand their unique treatment needs and evaluate the risks and benefits to mother and fetus, and efforts should be made to treat women of childbearing age before pregnancy.[40]

These findings also point to opportunities to examine Medicaid program policies nationally, as Medicaid is the single largest source of coverage for individuals with a SUD and/or HIV in the United States. With a provision of the Patient Protection and Affordable Care Act of 2020, previously uninsured adults become eligible in Medicaid expansion plans. This provision can positively affect those with HCV, as their prevalence is twice as high among the uninsured compared with the rest of the U.S. population. Therefore, we suggest that our findings can help state and national Medicaid policymakers determine how to best expand their plans to capture the most underserved HCV populations to increase the uptake of treatment, especially among those with a SUD and/or HIV and those who are Black. To overcome these barriers, we suggest several strategies that include regular HCV screening to enhance HCV case finding, providing continual updated education to health care professionals and allowing all nonspecialist care providers the ability to prescribe treatment for qualified candidates, and colocating screening, diagnosis, and treatment services for HCV at current SUD treatment centers, both inpatient or outpatient.[24] Interventions to enhance HCV treatment uptake include integrated HCV care, MAT use, and psychiatric services delivered by a multidisciplinary team with case management services.[41,42] The potential integrated care model in which infectious disease specialists and addiction specialists coordinate SUD and HCV treatment in clinical care has been highlighted in other studies.[28,43,44] Our findings inform state Medicaid policymakers about the low HCV treatment uptake and low MAT use in Florida, even though some restrictions to HCV treatment have been removed. As such, other states should note that when barriers are in place, HCV treatment uptake may not be optimal. To the best of our knowledge, there has been no formal study among the states that have loosened their criteria for HCV treatment to which we could compare our findings. This is an important point, as it demonstrates a gap in our knowledge about how changes in policies are being reflected in actual real-world practice. We encourage other states to conduct similar studies to enhance our knowledge about how policy changes are translated into clinical practice and their associated outcomes, so that appropriate plans can be initiated to ensure a successful expansion of Medicaid.

This study has several strengths. Unlike previous studies that used a sample of patients with HCV from one specialty pharmacy or outpatient-based urban health care settings, our study included all Florida Medicaid patients with HCV and compared their treatment uptake and completion of therapy by the presence of HIV co-infection and/or SUD. We included prescriptions for HCV treatment, which allowed us to estimate the completion of therapy and early discontinuation. Another strength of this study is the relatively large number of Medicaid patients with HCV, which allowed us the opportunity to conduct several

subgroup analyses (e.g., race/ethnicity). This study provides the first real-world evidence of HCV treatment access and completion of DAA treatment among the vulnerable Medicaid population in the United States, which may help other states with similar PA policies understand the disparities in access among patients with chronic HCV with and without SUDs.

There are also limitations to this study, as this was an analysis of administrative claims data using ICD-9/ICD-10 codes. Although a prior study validated the use of billing ICD codes for the diagnosis of a SUD, and this approach is commonly used in retrospective claims data analyses, some individuals with a SUD remain unrecognized and underdiagnosed in routine practice. It is also possible that individuals with chronic HCV were not screened, and if screened, did not follow up with primary care providers or specialists for further diagnostic evaluation and treatment. Thus, we may have underestimated the number of patients with chronic HCV.[17,19,45] In addition, we used prescription claims, so we do not know the reasons related to patients not receiving treatment. Many patients lacked follow-up lab work after treatment, so we were unable to determine the overall sustained virologic response (SVR) rate or whether there is a lower SVR in certain populations. Although our results suggest that restrictive PA policies for DAA therapies have resulted in access disparities to HCV therapy among Florida Medicaid patients, other factors including patients' refusal and physician's concern about reinfection might contribute to the low treatment rates. In addition, Medicaid restrictions apply to recent substance use; however, we were not able to differentiate between patients with a former and current SUD, which may alter our results, but given the low uptake, our results would unlikely change much, if at all. Although we excluded patients who received prior HCV treatment (e.g., interferon-based treatment), we recognize that we may have inadvertently included patients who received treatment outside of Florida. Finally, our results might not be generalizable to patients in other states where reimbursement policies differ.

Despite current availability of effective DAA therapies, this study demonstrates that only 8% of Florida Medicaid patients with HCV received DAA treatment during 2013-2018. Access to HCV treatment improved since Florida Medicaid relaxed the restriction on fibrosis staging in 2016, but Medicaid patients with chronic HCV still lack access to treatment. Disparities in access to care are also seen among those who are Black, who have a SUD, and who have HIV. However, once patients with a SUD and/or HIV co-infection initiated DAA therapy, they completed therapy at the same rate as those without a SUD or HIV co-infection. Therefore, to improve access to care, Medicaid programs nationally and Florida's Medicaid policy makers need to consider offering less-restrictive requirements for HCV treatment and further investigate the barriers to treatment that still exist for those patients with a SUD and/or HIV, so that access to DAA treatment can increase. The lack of treatment uptake in these populations may hinder the United States in reaching the global health goal of eliminating hepatitis by 2030.

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Supporting Information

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