

Discontinuation of New Hepatitis C Drugs Among Medicare Patients

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Hepatitis C virus (HCV) infection is an important public health issue. It causes costly and serious liver diseases such as cirrhosis and liver cancer.¹ HCV also aggravates other conditions, such as renal insufficiency, vasculitis, and rheumatoid arthritis, through its extrahepatic effects, decreasing patients' quality of life and increasing economic burdens.²⁻⁵ In 2014, HCV caused more deaths in the United States than any other infectious disease, including HIV/AIDS.^{6,7}

The introduction of new HCV drugs—second-generation direct-acting antivirals (DAAs)—has provided an unprecedented opportunity to address the HCV epidemic.^{8,9} They are highly effective and easy to administer and have a short treatment period compared with earlier therapies. These features help patients complete the recommended course of DAAs, after which most patients are cured. Randomized trials found that only 1% to 2% of patients did not complete DAA therapy, which is a significant improvement over earlier HCV treatments.^{10,11} However, drug adherence in real-world practice may be poorer than in clinical trials because real-world patients are not as closely followed up as those in trials. High patient cost sharing for DAAs, a potential deterrent to therapy completion, is also likely in the real world.

Discontinuation of DAA therapy may limit the health benefits from the therapy and can place the patient at risk of developing resistance to future HCV treatments.¹¹ Furthermore, given the high costs of DAAs, discontinuation of DAA therapy adds to financial burdens on the healthcare system without corresponding health benefits.¹² It is thus important to monitor continuation of DAA prescriptions and identify patient characteristics related to prescription discontinuity. However, real-world evidence on DAA prescription continuity is limited. One study of commercial insurance enrollees reported that discontinuation of the first DAA (sofosbuvir, launched in December 2013) was 4 times higher than in clinical trials.¹² Another study of private plan enrollees also indicated higher DAA discontinuation in the real world than in clinical trials.¹³ No information exists on discontinuation of DAAs in Medicare, which has been the largest payer of DAAs.¹⁴

We examined factors associated with discontinuation of DAA therapy between 2014 and 2016 in a national cohort of Medicare

ABSTRACT

OBJECTIVES: To examine factors associated with discontinuation of new hepatitis C drugs—second-generation direct-acting antivirals (DAAs)—among Medicare beneficiaries with chronic hepatitis C.

STUDY DESIGN: A retrospective analysis using 2014-2016 Medicare claims.

METHODS: The study population was patients with chronic hepatitis C in fee-for-service Medicare with Part D who initiated a DAA therapy between January 1, 2014, and September 1, 2016. We defined discontinuation of DAA therapy as filling prescriptions for fewer weeks than the expected duration of the DAA identified. We estimated adjusted odds ratios (aORs) of DAA discontinuation by patient characteristics using multivariable logistic regression. We estimated the model separately for patients with a Part D low-income subsidy (LIS) and those without an LIS.

RESULTS: Of 82,056 patients who initiated a DAA therapy during the study period, 5171 (6.3%) did not complete the therapy. Discontinuation rates varied across DAAs, ranging from 4.7% (elbasvir/grazoprevir) to 11.8% (ombitasvir/paritaprevir/ritonavir/dasabuvir). Women with an LIS were more likely to discontinue DAA therapy than men with an LIS (aOR, 1.16; 95% CI, 1.08-1.25; $P < .01$). Non-LIS black and Hispanic patients had higher odds of discontinuation than non-LIS white patients (black: aOR, 1.49; 95% CI, 1.28-1.73; $P < .01$; Hispanic: aOR, 1.56; 95% CI, 1.01-2.44; $P < .05$). High comorbidity index score increased the odds of DAA discontinuation among patients with an LIS.

CONCLUSIONS: Real-world discontinuation of DAA therapy was low, but it was 3 times more likely than in clinical trials and varied by patient characteristics. Efforts to increase DAA adherence would help lower patients' risk of developing resistance to future treatments and reduce potential waste of resources.

Am J Manag Care. 2020;26(2):84-88

patients with HCV. Many baby boomers—the group with the highest prevalence of HCV—are enrolled in Medicare.¹⁵ Medicare also covers patients with high HCV infection rates—nonelderly individuals who are disabled and/or dually eligible for Medicare and Medicaid. Discovering patient characteristics related to DAA discontinuation among Medicare patients can help clinicians and payers devise targeted interventions to improve drug adherence.

TAKEAWAY POINTS

We examined factors associated with discontinuation of new hepatitis C virus drugs—second-generation direct-acting antivirals (DAAs)—among Medicare beneficiaries with chronic hepatitis C between 2014 and 2016. We found:

- ▶ Real-world discontinuation of DAA therapy among Medicare patients was low (6.3%), but it was about 3 times more likely than in clinical trials.
- ▶ No racial/ethnic gap in DAA adherence existed among Medicare patients with a low-income subsidy (LIS); however, non-LIS black and Hispanic patients were more likely to discontinue a therapy than non-LIS white patients.
- ▶ Discontinuation of DAA therapy was more likely among patients who had cirrhosis or more comorbidities.

METHODS

Study Population and Data

We identified all patients with HCV who were continuously enrolled in fee-for-service Medicare with Part D in a given year between 2014 and 2016 using Medicare data (eAppendix Table 1 [eAppendix available at ajmc.com] lists diagnosis codes of all conditions used in the study). From these, we selected patients who initiated a DAA therapy between January 1, 2014, and September 1, 2016, and who were alive at least 4 months after initiating the therapy because most DAA users are on regimens with a therapy duration of 12 weeks or less. We used Medicare Prescription Drug Event files to identify initiation of 1 of the following DAAs: elbasvir/grazoprevir, ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir plus dasabuvir, sofosbuvir, and sofosbuvir/velpatasvir. All DAAs except sofosbuvir are administered as monotherapy or in combination with ribavirin. Sofosbuvir is concomitantly used with peginterferon, ribavirin, simeprevir, or daclatasvir.

We obtained information on patient demographics and clinical characteristics from Medicare Beneficiary Summary Files.

Outcome

We defined discontinuation of a DAA as filling prescriptions for fewer weeks than the expected duration of the DAA identified from package inserts or randomized trials. Discontinuation for patients who switched to a different DAA was based on the last DAA used by the patient. Discontinuation for patients on a regimen of a DAA plus ribavirin was based on only the DAA because ribavirin is used as an adjunct therapy to DAAs.^{16,17}

DAA regimens vary by genotype and prior HCV treatment experience, which could not be identified from Medicare claims. However, the recommended duration of therapy indicated by package inserts is 12 weeks for most patients regardless of DAA regimen. For patients who have prior experience with other HCV treatments, the recommended treatment duration is 24 weeks (16 weeks for elbasvir/grazoprevir). Results of recent randomized trials for patients without cirrhosis showed that 8-week treatments are effective for elbasvir/grazoprevir, ledipasvir/sofosbuvir, and ombitasvir/paritaprevir/ritonavir/dasabuvir.¹⁸⁻²⁰ For these 3 DAAs, we required 8 weeks of treatment for patients without cirrhosis and 12 weeks for those with cirrhosis. For other DAAs, we applied

12 weeks to patients with and without cirrhosis. If patients filled prescriptions for more than 12 weeks (ie, patients were on regimens with expected duration >12 weeks), we applied 16 weeks for elbasvir/grazoprevir and 24 weeks for all other DAAs based on each drug's package insert. We considered an interval between fills of fewer than 60 days as continuation of the therapy.

Analysis

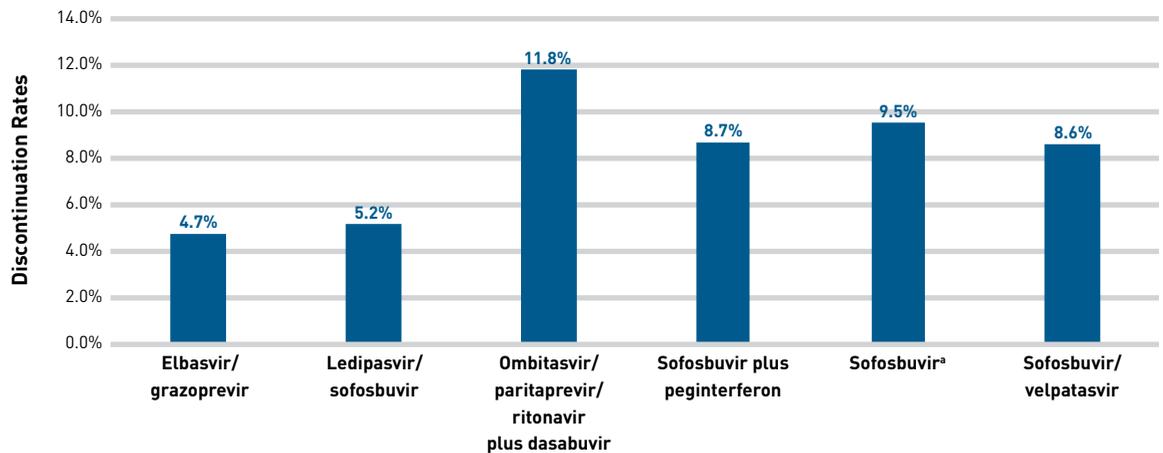
We used multivariable logistic regression to estimate adjusted odds ratios (aORs) of discontinuation by patient factors. We estimated the model separately for patients with and without a Part D low-income subsidy (LIS), which is offered to those with income below 150% of the federal poverty level.²¹ Cost sharing for non-LIS patients exceeded \$6000 over the course of DAA treatment in all Part D plans in 2014.²¹ However, cost sharing was as low as \$10.80 among patients with an LIS. We also estimated the model for the whole study population to determine the overall effects.

Patient characteristics were measured in the year of the DAA initiation. They included gender, age, race, urban/rural residence (*urban* refers to metropolitan areas identified by the Rural-Urban Continuum Codes²²), cirrhosis status, and comorbidities. eAppendix Table 1 reports diagnosis codes or references of the established algorithms used to identify all the conditions used in the study. We also controlled for drug and Census region fixed effects.

We performed several sensitivity analyses. First, we estimated the logistic regression excluding patients with sofosbuvir plus peginterferon. This was the first new DAA regimen, but it is no longer recommended. Noncontinuation may be high with this regimen because of adverse effects of peginterferon. Second, we estimated the model separately for patients on regimens with and without ribavirin. Noncontinuation may be high for ribavirin-containing regimens because of adverse effects of ribavirin. Finally, we conducted analyses requiring patients to be alive at least 6 months after the initiation of the therapy because the expected duration of certain regimens was longer than 4 months.

We clustered the standard errors within Part D plans to account for potential correlations among beneficiaries subject to the same plan policies. We used SAS 9.4 (SAS Institute; Cary, North Carolina) for all analyses.

FIGURE. Discontinuation of DAAs Among Fee-for-Service Medicare Patients



DAA	Patients initiated, n	Patients discontinued, n	Patients discontinued, %
Elbasvir/grazoprevir	1295	61	4.7
Ledipasvir/sofosbuvir	59,219	3055	5.2
Ombitasvir/paritaprevir/ritonavir plus dasabuvir	1672	197	11.8
Sofosbuvir plus peginterferon	3415	296	8.7
Sofosbuvir*	16,002	1523	9.5
Sofosbuvir/velpatasvir	453	39	8.6

DAA indicates direct-acting antiviral.

*Concomitantly used with ribavirin, daclatasvir, or simeprevir.

RESULTS

Of 82,056 patients who initiated a DAA therapy during the study period, 5171 (6.3%) did not complete the therapy (eAppendix Table 2). Compared with patients who completed DAA therapy, those who discontinued were more likely to have compensated cirrhosis (26.8% vs 18.9%; $P < .001$), decompensated cirrhosis (16.1% vs 9.5%; $P < .001$), or anemia (38.7% vs 31.2%; $P < .001$).

Discontinuation rates varied across DAAs, from 4.7% with elbasvir/grazoprevir to 11.8% with ombitasvir/paritaprevir/ritonavir plus dasabuvir (Figure). Sofosbuvir combined with peginterferon had a relatively high discontinuation rate (9.5%). The discontinuation rate was 5.2% among patients who used ledipasvir/sofosbuvir, the most commonly used DAA.

The Table presents the results from multivariable logistic regressions. The associations of gender and race with DAA discontinuation depended on LIS status. Female patients with an LIS were more likely to discontinue DAA therapy than male patients (aOR, 1.16; 95% CI, 1.08-1.25; $P < .001$). No differences in DAA discontinuation existed across racial/ethnic groups with an LIS. No gender gap in DAA continuation was present among non-LIS patients, but non-LIS black and Hispanic patients had higher odds of discontinuation than white patients (black: aOR, 1.49; 95% CI, 1.28-1.73; $P < .001$; Hispanic: aOR, 1.56; 95% CI, 1.01-2.44; $P < .05$).

The association between cirrhosis status and DAA continuation did not differ by LIS status, and in the entire sample, patients with compensated or decompensated cirrhosis had higher odds of discontinuation than those without cirrhosis (compensated: aOR, 1.79; 95% CI, 1.66-1.94; $P < .001$; decompensated: aOR, 1.92; 95% CI,

1.69-2.18; $P < .001$). High Charlson Comorbidity Index scores increased the odds of DAA discontinuation only among patients with an LIS (aOR, 1.02; 95% CI, 1.01-1.05; $P < .01$).

We found similar results from analyses excluding patients on sofosbuvir with peginterferon or requiring patients to be alive for at least 6 months after initiating a therapy (eAppendix Tables 3 and 4). The analysis by ribavirin use showed that patients with anemia were more likely to discontinue regimens without ribavirin than those without anemia, but they were less likely to discontinue regimens with ribavirin (eAppendix Table 5).

DISCUSSION

Real-world discontinuation of DAA therapy among Medicare patients between 2014 and 2016 was 6.3%. The discontinuation rate varied across DAAs, but it was high for a DAA that required patients to take multiple pills (at different times) daily (eg, ombitasvir/paritaprevir/ritonavir plus dasabuvir). More DAAs with simpler regimens have become available in recent years. Discontinuation of DAA therapy may have decreased after the study period. However, continued assessment of population-level risk factors related to DAA discontinuation is needed to help clinicians make focused efforts on patients with risk factors, such as advising those patients to use specialty pharmacies, which has been shown to improve DAA completion.¹²

We found differences in DAA continuation by patient demographics and health risk factors. Female patients with an LIS had a higher rate of DAA discontinuation than male patients. Prior studies of HCV treatments also found a gender gap: Women were less likely to initiate a DAA therapy than men,²³ and among DAA users, women

were less likely to complete a DAA therapy.¹⁴ Our study refines this existing knowledge by showing that the gender gap in Medicare is prominent among low-income beneficiaries. LIS patients have nominal cost sharing for DAAs.²¹ Thus, the gender gap in DAA adherence is likely due to certain characteristics of the LIS group (other than cost sharing) that are not observed in our data. Discovering reasons for that gap was beyond the scope of our study. However, it is an important inquiry for future research to pursue, and efforts are needed to explore ways to close the gender gap in DAA continuation.

We found no racial/ethnic differences in DAA adherence among patients with an LIS. However, racial/ethnic minority patients without an LIS were more likely to discontinue DAA therapy than white non-LIS patients. The non-LIS group includes patients with relatively low incomes who may have had high financial burdens from DAA therapy. Prior literature showed that generous insurance benefits (eg, cost-sharing reductions or coverage expansions) for relatively low-income people improved service use or prescription drug adherence more in racial/ethnic minorities than in whites.^{24,25} Expanding cost-sharing subsidies for DAAs, which are highly effective, to patients who do not currently qualify for an LIS may help increase adherence to those treatments and mitigate racial/ethnic disparities.

Finally, discontinuation was more likely among patients with cirrhosis or other comorbidities. Patients with cirrhosis have longer treatment periods with more refills, which may increase the likelihood of discontinuation. Sicker patients with more comorbidities may have difficulties in completing DAA therapy because of competing demands for treating other conditions, or they may have experienced worsening prognosis while on DAA therapy, leading them to stop the therapy.

Limitations

We note several limitations of the study. First, Medicare claims lack detailed clinical data, such as fibrosis stage and genotype. We could not incorporate those clinical factors, which may be related to DAA discontinuation. Second, we could not distinguish physician-initiated DAA discontinuation due to worsening prognosis from patient nonadherence. However, our

TABLE. Results From Multivariable Logistic Regression

Characteristics	Adjusted Odds Ratio (95% CI) ^a		
	Subgroup Analysis		
	With LIS (n = 58,735)	Without LIS (n = 23,321)	All Patients (N = 82,056)
LIS	–	–	0.92 (0.76-1.10)
Female	1.16 (1.08-1.25)***	0.99 (0.90-1.09)	1.11 (1.05-1.18)***
Age group in years		Reference	
<65		Reference	
65-69	1.14 (1.04-1.24)***	1.02 (0.86-1.21)	1.09 (1.01-1.19)**
70-74	1.08 (0.94-1.23)	0.90 (0.73-1.10)	1.00 (0.90-1.12)
≥75	0.99 (0.81-1.22)	0.99 (0.80-1.21)	1.01 (0.89-1.16)
Race/ethnicity		Reference	
White		Reference	
Black	1.05 (0.96-1.14)	1.49 (1.28-1.73)***	1.14 (1.06-1.23)***
Hispanic	1.05 (0.91-1.22)	1.56 (1.01-2.44)**	1.11 (0.96-1.27)
Other	1.10 (0.94-1.29)	1.00 (0.78-1.28)	1.09 (0.95-1.25)
Income (zip code median)		Reference	
Lowest tertile		Reference	
Middle tertile	0.91 (0.81-1.02)	1.04 (0.80-1.35)	0.94 (0.84-1.05)
Highest tertile	0.94 (0.86-1.02)	1.04 (0.85-1.28)	0.96 (0.89-1.04)
Education (zip code % college educated)		Reference	
Below mean		Reference	
Above mean	1.03 (0.93-1.13)	1.05 (0.88-1.24)	1.03 (0.95-1.12)
Residing in urban area ^b	1.05 (0.95-1.16)	1.03 (0.86-1.24)	1.04 (0.96-1.14)
Cirrhosis status		Reference	
No cirrhosis		Reference	
Compensated cirrhosis	1.77 (1.63-1.92)***	1.84 (1.57-2.15)***	1.79 (1.66-1.94)***
Decompensated cirrhosis	1.90 (1.67-2.15)***	1.98 (1.56-2.51)***	1.92 (1.69-2.18)***
Comorbidities			
CCI score ^c	1.02 (1.01-1.05)**	1.02 (0.99-1.04)	1.02 (1.01-1.04)***
HIV infection	1.00 (0.86-1.16)	0.85 (0.61-1.18)	0.96 (0.84-1.09)
Drug/substance use	1.23 (1.15-1.32)***	1.04 (0.90-1.20)	1.18 (1.11-1.26)***
Kidney disease	1.24 (1.14-1.35)***	1.24 (1.08-1.42)***	1.24 (1.16-1.33)***
Anemia	1.00 (0.92-1.09)	1.03 (0.91-1.17)	1.01 (0.95-1.08)
Lung disease	1.14 (1.06-1.23)***	1.24 (1.09-1.41)***	1.17 (1.09-1.25)***
Cancer	0.97 (0.87-1.09)	1.01 (0.86-1.18)	0.99 (0.90-1.10)
Cardiovascular disease	0.92 (0.84-1.01)*	0.98 (0.86-1.13)	0.94 (0.87-1.02)
Dementia	1.23 (1.06-1.44)***	1.22 (0.96-1.56)	1.22 (1.08-1.39)***
Psychiatric disease	1.05 (0.98-1.14)	1.16 (1.01-1.33)	1.08 (1.01-1.16)**
Diabetes	0.93 (0.86-1.01)*	0.91 (0.79-1.04)	0.93 (0.87-0.99)**
Cataract or glaucoma	0.93 (0.84-1.02)	0.92 (0.81-1.04)	0.92 (0.85-0.99)**
Arthritis	0.95 (0.89-1.03)	1.02 (0.91-1.15)	0.97 (0.91-1.04)
End-stage renal disease	1.21 (1.01-1.45)**	1.16 (0.85-1.59)	1.20 (1.03-1.41)**
Region		Reference	
Northeast		Reference	
Midwest	1.01 (0.89-1.16)	0.74 (0.52-1.03)*	0.92 (0.79-1.06)
South	1.02 (0.91-1.14)	0.78 (0.60-1.02)*	0.94 (0.83-1.06)
West	1.00 (0.86-1.17)	0.69 (0.49-0.98)**	0.89 (0.76-1.05)

CCI indicates Charlson Comorbidity Index; LIS, low-income subsidy.

*P < .10; **P < .05; ***P < .01.

^aEstimates from logistic model with patient characteristics and drug fixed effects.

^bUrban residence is defined as living in a metropolitan area based on Rural-Urban Continuum Codes.

^cThe CCI score is an index that predicts mortality based on 19 conditions in claims over the past 12 months.

TRENDS FROM THE FIELD

findings can help clinicians gain insights into where to focus efforts to improve DAA completion. Finally, our study has limited generalizability to Medicare Advantage plans, commercial insurance settings, and newer DAAs that became available after our study period.

CONCLUSIONS

Despite these limitations, we offer the first national estimate of DAA discontinuation among Medicare patients in real-world practice. We also provide information on patient demographic and risk factors that clinicians and payers could target to increase DAA adherence. Continued efforts to monitor and improve DAA adherence would help lower patients' risk of developing resistance to future treatments and reduce potential waste of resources while increasing patients' health benefits. ■

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Source of Funding: National Institutes of Health/National Institute of Aging grant number R01 AG055636-01A1 and National Institutes of Health grant number R24 HD041025.

Author Disclosures: Dr Feldman owns a small amount of stock in Gilead Sciences. The remaining authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (JJ, PD, RF, TR); acquisition of data (JJ); analysis and interpretation of data (JJ, PD, RF, TR); drafting of the manuscript (JJ, PD, TR); critical revision of the manuscript for important intellectual content (PD, RF, TR); obtaining funding (JJ, PD, RF); and supervision (TR).

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eAppendix Table 1. Diagnosis codes and sources of established algorithms to identify the conditions used in the analysis

Condition^a	ICD-9-CM[*]	ICD-10-CM[*]
Chronic hepatitis C infection	07044, 07054, 07070, 07071	B182, B1920, B1921
Cirrhosis	5715	K740, K7460, K7469
Decompensated Cirrhosis ^c	5722, 5723, 5724, 56723, 7824, 78951, 78959	K652, K767, K7290, K7291, K766, R17, R180, R188
Condition^b	Source	
HIV infection	ccwdata.org/documents/10280/19139421/other-condition-algorithms.pdf	
Drug/substance use disorder	ccwdata.org/documents/10280/19139421/other-condition-algorithms.pdf	
Kidney disease	ccwdata.org/documents/10280/19139421/ccw-chronic-condition-algorithms.pdf	
Anemia	ccwdata.org/documents/10280/19139421/ccw-chronic-condition-algorithms.pdf	
Lung disease	ccwdata.org/documents/10280/19139421/ccw-chronic-condition-algorithms.pdf	
Cancer	ccwdata.org/documents/10280/19139421/ccw-chronic-condition-algorithms.pdf	
Cardiovascular disease	ccwdata.org/documents/10280/19139421/ccw-chronic-condition-algorithms.pdf	
Dementia	ccwdata.org/documents/10280/19139421/ccw-chronic-condition-algorithms.pdf	
Psychiatric disease	ccwdata.org/documents/10280/19139421/ccw-chronic-condition-algorithms.pdf and ccwdata.org/documents/10280/19139421/other-condition-algorithms.pdf	
Diabetes mellitus	ccwdata.org/documents/10280/19139421/ccw-chronic-condition-algorithms.pdf	
Cataract or glaucoma	ccwdata.org/documents/10280/19139421/ccw-chronic-condition-algorithms.pdf	
Arthritis	ccwdata.org/documents/10280/19139421/ccw-chronic-condition-algorithms.pdf	
End-stage renal disease	ccwdata.org/documents/10280/19139421/ccw-chronic-condition-algorithms.pdf	

*International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification

a: Identified based on diagnosis codes listed in the table;

b: “Decompensated cirrhosis” is defined as having symptomatic complications related to cirrhosis, including jaundice, ascites, variceal hemorrhage, hepatic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome. It was thus identified as having cirrhosis and at least of one of those symptomatic complications based on the diagnosis codes listed in the table. “Compensated cirrhosis” refers to asymptomatic cirrhosis and was thus identified as having cirrhosis but no symptomatic complication listed above.

c: Identified based on the established algorithms specified in the references in the table

eAppendix Table 2. Characteristics of Fee-for-Service Medicare Patients with Chronic Hepatitis C

Characteristics	No.(%)		P-value
	Completed DAA therapy (n=76,885)	Discontinued DAA therapy (n=5,171)	
<i>Low Income Subsidy</i>	55,025(71.6%)	3,710(71.7%)	0.783
<i>Female</i>	31,715(41.2%)	2,228(43.1%)	0.009
<i>Age group (years)</i>			0.728
<65	45,467(59.1%)	3,035(58.7%)	
65-70	19,910(25.9%)	1,370(26.5%)	
70-75	6,879(8.9%)	449(8.7%)	
>75	4,629(6.0%)	317(6.1%)	
<i>Race/Ethnicity</i>			0.473
White	49,988(65.0%)	3,353(64.8%)	
Black	20,706(26.9%)	1,375(26.6%)	
Hispanic	2,520(3.3%)	189(3.7%)	
Other	3,671(4.8%)	254(4.9%)	
<i>Income (ZIP median income)</i>			0.276
Lowest tertile	25,691(33.4%)	1,781(34.4%)	
Middle tertile	27,288(35.5%)	1,791(34.6%)	
Highest tertile	23,906(31.1%)	1,599(30.9%)	
<i>Education (ZIP % college educated)</i>			0.487
Below mean	38,661(50.3%)	2,626(50.8%)	
Above mean	38,224(49.7%)	2,545(49.2%)	
<i>Residing in urban area^a</i>	65,120(84.7%)	4,408(85.2%)	0.290
<i>Cirrhosis Status</i>			<0.001
No Cirrhosis	55,113(71.7%)	2,955(57.1%)	
Compensated Cirrhosis	14,504(18.9%)	1,385(26.8%)	
Decompensated Cirrhosis	7,268(9.5%)	831(16.1%)	
<i>Co-morbidities</i>			
Charlson score (SD) ^b	3.8(3.2)	4.5(3.7)	<0.001
HIV infection	6,011(7.8%)	403(7.8%)	0.949
Drug/Substance use disorder	33,437(43.5%)	2,553(49.4%)	<0.001
Kidney disease	17,963(23.4%)	1,576(30.5%)	<0.001
Anemia	24,020(31.2%)	2,002(38.7%)	<0.001
Lung disease	18,027(23.4%)	1,496(28.9%)	<0.001
Cancer	8,796(11.4%)	631(12.2%)	0.096
Cardiovascular disease	53,912(70.1%)	3,741(72.3%)	<0.001
Dementia	3,519(4.6%)	335(6.5%)	<0.001
Psychiatric disease	36,297(47.2%)	2,633(50.9%)	<0.001
Diabetes mellitus	24,558(31.9%)	1,790(34.6%)	<0.001
Cataract or glaucoma	14,261(18.5%)	921(17.8%)	0.186
Arthritis	30,320(39.4%)	2,093(40.5%)	0.139
End-stage renal disease	2,398(3.1%)	226(4.4%)	<0.001
<i>Region</i>			0.222
Northeast	18,139(23.6%)	1,268(24.5%)	
Midwest	14,117(18.4%)	925(17.9%)	
South	28,065(36.5%)	1,910(36.9%)	
West	16,564(21.5%)	1,068(20.7%)	

Abbreviations: DAA, Direct acting antiviral agents; HIV, human immunodeficiency virus; SD, standard deviation; P values are based on χ^2 tests for categorical variables and *t* tests for continuous variables.

^a Urban residence is defined as living in a metropolitan area based on Rural-Urban Continuum Codes.

^b The Charlson score is an index that predicts mortality based on 19 conditions in claims over the past 12 months.

* <.10, ** <0.05; * <0.01

Appendix Table 3. Results from regression excluding sofosbuvir/peginterferon regimen

Characteristics	Adjusted Odds Ratio (95% Confidence Interval)		
	Subgroup analysis		All patients (N=78,641)
	with LIS (N=56,069)	without LIS (N=22,572)	
<i>Low Income Subsidy</i>	-	-	0.91(0.85-0.98)**
<i>Female</i>	1.16(1.08-1.25)***	0.98(0.86-1.10)	1.10(1.04-1.18)***
<i>Age group (years)</i>			
<65		Reference	
65-70	1.14(1.04-1.25)***	0.99(0.86-1.14)	1.09(1.01-1.17)**
70-75	1.05(0.90-1.22)	0.87(0.73-1.05)	0.98(0.87-1.10)
>75	0.99(0.81-1.21)	0.98(0.80-1.20)	1.01(0.89-1.16)
<i>Race/Ethnicity</i>			
White		Reference	
Black	1.05(0.96-1.15)	1.51(1.30-1.76)***	1.15(1.07-1.24)***
Hispanic	1.08(0.91-1.28)	1.68(1.05-2.67)**	1.14(0.98-1.34)*
Other	1.12(0.95-1.32)	1.07(0.81-1.40)	1.12(0.97-1.29)
<i>Income (ZIP median)</i>			
Lowest tertile		Reference	
Middle tertile	0.89(0.79-0.99)	1.05(0.85-1.30)	0.92(0.83-1.02)
Highest tertile	0.93(0.85-1.02)	1.06(0.89-1.25)	0.96(0.88-1.04)
<i>Education (ZIP % college educated)</i>			
Below mean		Reference	
Above mean	1.04(0.94-1.15)	1.04(0.88-1.23)	1.04(0.96-1.13)
<i>Residing in urban area^a</i>	1.04(0.94-1.15)	1.03(0.86-1.23)	1.04(0.95-1.13)
<i>Cirrhosis Status</i>			
No Cirrhosis		Reference	
Compensated Cirrhosis	1.84(1.69-2.01)***	1.93(1.69-2.20)***	1.87(1.74-2.01)***
Decompensated Cirrhosis	1.94(1.72-2.18)***	2.08(1.73-2.49)***	1.98(1.79-2.18)***
<i>Co-morbidities</i>			
Charlson score ^b	1.02(1.01-1.04)***	1.01(0.99-1.04)	1.02(1.01-1.04)***
HIV infection	1.00(0.86-1.17)	0.91(0.64-1.30)	0.98(0.85-1.12)
Drug/Substance use	1.21(1.12-1.31)***	1.06(0.92-1.21)	1.17(1.10-1.25)***
Kidney disease	1.21(1.11-1.33)***	1.22(1.05-1.42)***	1.22(1.12-1.32)***
Anemia	1.03(0.95-1.12)	1.04(0.92-1.18)	1.04(0.97-1.11)
Lung disease	1.13(1.04-1.23)**	1.24(1.07-1.44)***	1.16(1.08-1.25)***
Cancer	0.97(0.86-1.09)	1.02(0.87-1.20)	1.00(0.91-1.10)
Cardiovascular disease	0.91(0.83-0.99)**	0.99(0.86-1.13)	0.93(0.87-0.99)*
Dementia	1.22(1.06-1.40)***	1.23(0.95-1.59)	1.22(1.08-1.38)***
Psychiatric disease	1.07(0.99-1.16)*	1.16(1.03-1.32)**	1.10(1.03-1.17)***
Diabetes mellitus	0.95(0.87-1.03)	0.90(0.78-1.03)	0.94(0.87-1.01)*
Cataract or glaucoma	0.92(0.83-1.01)*	0.92(0.81-1.06)	0.92(0.85-0.99)**
Arthritis	0.96(0.89-1.03)	1.03(0.91-1.15)	0.98(0.92-1.04)
End-stage renal disease	1.18(0.97-1.44)*	1.14(0.80-1.64)	1.18(0.99-1.39)*
<i>Region</i>			
Northeast		Reference	
Midwest	0.99(0.88-1.10)	0.75(0.63-0.89)***	0.90(0.82-0.99)**
South	1.00(0.91-1.10)	0.78(0.68-0.90)***	0.93(0.86-0.99)*
West	1.00(0.90-1.11)	0.69(0.58-0.81)***	0.89(0.81-0.97)***

Abbreviations: HCV, Hepatitis C virus; LIS, low-income subsidy; HIV, human immunodeficiency virus;

^a Urban residence is defined as living in a metropolitan area based on Rural-Urban Continuum Codes.

^b The Charlson score is an index that predicts mortality based on 19 conditions in claims over the past 12 months.

* <.10, ** <0.05; * <0.01

Appendix Table 4. Results from regression requiring patients to be alive at least 6 months after the initiation of a therapy

Characteristics	Adjusted Odds Ratio (95% Confidence Interval)		
	Subgroup analysis		All patients (N=81,647)
	with LIS (N=58,442)	without LIS (N=23,205)	
<i>Low Income Subsidy</i>	-	-	0.92(0.76-1.11)
<i>Female</i>	1.16(1.08-1.25)***	1.01(0.92-1.12)	1.11(1.05-1.18)***
<i>Age group (years)</i>		Reference	
<65		Reference	
65-70	1.13(1.03-1.24)***	1.02(0.86-1.21)	1.09(1.01-1.18)**
70-75	1.07(0.93-1.24)	0.91(0.74-1.12)	1.01(0.90-1.13)
>75	1.00(0.81-1.23)	0.99(0.80-1.23)	1.02(0.89-1.17)
<i>Race/Ethnicity</i>		Reference	
White		Reference	
Black	1.05(0.97-1.14)	1.50(1.29-1.75)***	1.15(1.06-1.24)***
Hispanic	1.02(0.89-1.18)	1.59(1.01-2.51)**	1.08(0.94-1.25)
Other	1.09(0.93-1.28)	0.98(0.76-1.27)	1.08(0.94-1.23)
<i>Income (ZIP median)</i>		Reference	
Lowest tertile		Reference	
Middle tertile	0.91(0.81-1.02)	1.00(0.78-1.28)	0.93(0.83-1.03)
Highest tertile	0.94(0.86-1.02)	1.02(0.84-1.24)	0.95(0.88-1.03)
<i>Education (ZIP % college)</i>		Reference	
Below mean		Reference	
Above mean	1.03(0.93-1.13)	1.07(0.90-1.26)	1.04(0.96-1.12)
<i>Residing in urban area^a</i>	1.05(0.95-1.16)	1.02(0.84-1.23)	1.04(0.95-1.14)
<i>Cirrhosis Status</i>		Reference	
No Cirrhosis		Reference	
Compensated Cirrhosis	1.78(1.64-1.94)***	1.86(1.59-2.17)***	1.81(1.67-1.95)***
Decompensated Cirrhosis	1.84(1.64-2.07)***	1.91(1.53-2.38)***	1.86(1.67-2.08)***
<i>Co-morbidities</i>			
Charlson score ^b	1.02(1.01-1.04)**	1.01(0.99-1.04)	1.02(1.01-1.03)**
HIV infection	1.02(0.88-1.18)	0.87(0.61-1.24)	0.98(0.86-1.11)
Drug/Substance use disorder	1.22(1.14-1.31)***	1.03(0.90-1.18)	1.17(1.10-1.25)***
Kidney disease	1.23(1.13-1.35)***	1.23(1.07-1.41)***	1.23(1.15-1.33)***
Anemia	1.01(0.93-1.09)	1.00(0.89-1.13)	1.01(0.94-1.08)
Lung disease	1.16(1.08-1.25)***	1.26(1.11-1.43)***	1.18(1.11-1.26)***
Cancer	0.99(0.88-1.11)	1.03(0.88-1.21)	1.01(0.92-1.11)
Cardiovascular disease	0.92(0.84-1.01)*	0.98(0.85-1.12)	0.94(0.87-1.02)
Dementia	1.22(1.05-1.43)***	1.27(1.01-1.61)	1.23(1.07-1.40)***
Psychiatric disease	1.05(0.97-1.13)	1.16(1.01-1.33)	1.08(1.01-1.15)**
Diabetes mellitus	0.95(0.88-1.02)	0.92(0.80-1.04)	0.94(0.88-0.99)*
Cataract or glaucoma	0.93(0.85-1.03)	0.91(0.81-1.04)	0.93(0.86-0.99)*
Arthritis	0.95(0.88-1.02)	1.02(0.91-1.15)	0.97(0.91-1.04)
End-stage renal disease	1.22(1.01-1.46)**	1.23(0.89-1.71)	1.22(1.04-1.44)**
<i>Region</i>		Reference	
Northeast		Reference	
Midwest	1.02(0.89-1.15)	0.74(0.52-1.04)*	0.92(0.79-1.06)
South	1.02(0.92-1.14)	0.77(0.59-1.01)*	0.93(0.83-1.06)
West	1.00(0.86-1.17)	0.68(0.48-0.96)**	0.89(0.75-1.04)

Abbreviations: HCV, Hepatitis C virus; LIS, low-income subsidy; HIV, human immunodeficiency virus

^a Urban residence is defined as living in a metropolitan area based on Rural-Urban Continuum Codes.

^b The Charlson score is an index that predicts mortality based on 19 conditions in claims over the past 12 months.

* <.10, ** <0.05; * <0.01

eAppendix Table 5. Results from regression by ribavirin use

Characteristics	Adjusted Odds Ratio (95% Confidence Interval)				
	Subgroup Analysis				All patients (N=82,411)
	with LIS (N=58,735)		without LIS (N=23,321)		
Regimen with ribavirin (N=11,538)	Regimen without ribavirin (N=47,197)	Regimen with ribavirin (n=4,519)	Regimen without ribavirin (n=18,802)	Regimen with ribavirin (N=16,057)	
<i>Low Income Subsidy</i>	-	-	-	-	0.95(0.78-1.15)
<i>Female</i>	1.16(1.02-1.32)**	1.16(1.07-1.27)***	0.93(0.76-1.15)	1.02(0.90-1.16)	1.10(0.98-1.22)*
<i>Age group (years)</i>					
<65				Reference	
65-70	1.14(0.96-1.35)	1.13(1.02-1.25)**	1.14(0.88-1.49)	0.98(0.82-1.18)	1.11(0.96-1.28)
70-75	1.06(0.79-1.41)	1.08(0.92-1.27)	1.07(0.74-1.53)	0.84(0.69-1.03)*	1.04(0.83-1.29)
>75	0.71(0.48-1.04)*	1.09(0.84-1.41)	1.15(0.80-1.65)	0.94(0.75-1.19)	0.93(0.73-1.19)
<i>Race/Ethnicity</i>					
White				Reference	
Black	1.06(0.90-1.24)	1.06(0.96-1.17)***	1.94(1.43-2.62)***	1.40(1.16-1.68)***	1.24(1.07-1.44)***
Hispanic	1.21(0.95-1.54)	0.98(0.80-1.20)	0.96(0.39-2.34)	1.87(1.11-3.17)**	1.19(0.94-1.51)
Other	1.01(0.76-1.35)	1.17(0.97-1.41)	1.30(0.89-1.90)	0.87(0.63-1.21)	1.07(0.84-1.36)
<i>Income (ZIP median)</i>					
Lowest tertile				Reference	
Middle tertile	0.83(0.68-1.02)*	0.95(0.83-1.08)	0.96(0.64-1.42)	1.10(0.80-1.49)	0.87(0.73-1.05)
Highest tertile	0.94(0.81-1.10)	0.94(0.84-1.04)	0.86(0.64-1.16)	1.14(0.90-1.45)	0.93(0.81-1.06)
<i>Education (% college)</i>					
Below mean				Reference	
Above mean	1.13(0.97-1.32)	0.99(0.88-1.11)	0.94(0.70-1.25)	1.08(0.88-1.32)	1.08(0.94-1.23)
<i>Residing in urban area^a</i>	1.04(0.90-1.21)	1.07(0.94-1.21)	0.99(0.73-1.34)	1.06(0.86-1.31)	1.03(0.90-1.17)
<i>Cirrhosis Status</i>					
No Cirrhosis				Reference	
Compensated					
Cirrhosis	1.12(0.95-1.31)	2.10(1.91-2.31)***	1.15(0.90-1.46)	2.16(1.8-2.58)***	1.13(0.99-1.29)*
Decompensated					
Cirrhosis	1.30(1.06-1.60)**	2.18(1.89-2.5)***	1.41(0.98-2.03)*	2.21(1.7-2.86)***	1.34(1.10-1.63)***
<i>Co-morbidities</i>					
Charlson score ^b	1.04(1.01-1.08)*	1.02(1.01-1.04)*	1.01(0.96-1.05)	1.02(0.99-1.06)	1.03(1.01-1.06)*
HIV infection	0.81(0.60-1.11)	1.09(0.93-1.27)	0.82(0.45-1.52)	0.88(0.60-1.30)	0.81(0.63-1.05)
Drug/Substance use	1.33(1.18-1.52)***	1.18(1.08-1.29)***	0.91(0.71-1.16)	1.11(0.95-1.29)	1.23(1.10-1.36)***
Kidney disease	1.31(1.10-1.55)***	1.20(1.09-1.32)***	1.59(1.23-2.07)***	1.11(0.94-1.30)	1.39(1.21-1.60)***
Anemia	0.82(0.72-0.93)***	1.11(1.01-1.22)**	0.92(0.70-1.20)	1.08(0.95-1.24)	0.85(0.75-0.95)***
Lung disease	1.16(1.01-1.34)**	1.14(1.05-1.24)***	1.27(1.01-1.63)*	1.24(1.05-1.46)***	1.19(1.05-1.34)***
Cancer	0.89(0.73-1.09)	1.01(0.87-1.17)	0.88(0.67-1.16)	1.07(0.89-1.30)	0.90(0.76-1.06)
Cardiovascular					
disease	0.99(0.87-1.14)	0.89(0.80-0.99)**	0.98(0.79-1.23)	0.97(0.81-1.17)	0.99(0.88-1.11)
Dementia	1.20(0.92-1.57)	1.22(1.02-1.48)**	1.75(1.18-2.58)***	1.00(0.74-1.35)	1.32(1.07-1.63)***
Psychiatric disease	0.96(0.84-1.10)	1.10(1.01-1.20)*	1.45(1.16-1.81)***	1.04(0.90-1.21)	1.09(0.97-1.22)
Diabetes mellitus	0.86(0.74-0.99)**	0.97(0.87-1.07)	1.01(0.82-1.24)	0.87(0.73-1.03)	0.90(0.80-1.01)*
Cataract or					
glaucoma	0.87(0.72-1.04)	0.95(0.85-1.06)	0.86(0.68-1.09)	0.94(0.80-1.10)	0.86(0.74-0.99)*
Arthritis	0.92(0.82-1.02)	0.97(0.89-1.07)	1.04(0.83-1.30)	1.03(0.90-1.18)	0.94(0.85-1.04)
End-stage renal					
disease	1.02(0.74-1.41)	1.28(1.04-1.57)**	1.05(0.61-1.83)	1.23(0.85-1.78)	1.02(0.77-1.36)
<i>Region</i>					
Northeast				Reference	

Midwest	1.28(1.01-1.63)**	0.91(0.78-1.06)	0.87(0.60-1.24)	0.68(0.47-0.99)*	1.14(0.93-1.40)
South	1.15(0.94-1.40)	0.97(0.86-1.11)	0.69(0.50-0.95)**	0.82(0.61-1.10)	0.99(0.83-1.19)
West	1.15(0.92-1.43)	0.94(0.77-1.16)	0.70(0.46-1.08)	0.69(0.48-0.97)**	0.99(0.80-1.23)

Abbreviations: HCV, Hepatitis C virus; LIS, low-income subsidy; HIV, human immunodeficiency virus

^a Urban residence is defined as living in a metropolitan area based on Rural-Urban Continuum Codes.

^b The Charlson score is an index that predicts mortality based on 19 conditions in claims over the past 12 months.

* <.10, ** <0.05; * <0.01