

# Adoption of New Agents and Changes in Treatment Patterns for Hepatitis C: 2010-2014

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**C**hronic hepatitis C virus (HCV) is an infection that affects nearly 3.2 million individuals in the United States.<sup>1</sup> HCV is associated with increased risk of developing liver cirrhosis, hepatocellular carcinoma, liver failure, and death.<sup>2</sup> Over the past 2 decades, the mainstay of treatment of HCV has been interferon alfa and ribavirin, but the treatment causes numerous adverse events, including influenza-like symptoms, depression, cytopenia, hemolytic anemia, fatigue, pruritus, and rash.<sup>3,4</sup> It also requires long treatment duration (typically 48 weeks), and results in an average low cure rate—defined by sustained viral response (SVR)—of less than 50%.<sup>5,6</sup> Additionally, many patients are not eligible for, or cannot tolerate, interferon-based treatment.<sup>7,8</sup> As a result of these challenges, until recently, only 10% to 30% of adults with chronic HCV received treatment.<sup>9</sup> Since 2011, significant advances have been made among the options for treatment of chronic HCV.

The new generation of medications, such as ledipasvir/sofosbuvir (Harvoni), sofosbuvir (Sovaldi), and simeprevir (Olysio), increase SVR to over 90% and shorten the treatment period to 12 to 24 weeks.<sup>10-14</sup> The incidence and severity of adverse events are also lower in these new agents.<sup>11,15</sup> Considering the efficacy, safety, tolerability, and convenience, these new treatment regimens are recommended by the clinical practice guidelines developed by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America in collaboration with the International Antiviral Society–USA.<sup>16</sup> There is hope that these new medications may increase the historically low treatment rate in patients with chronic HCV; however, to date, little is known about how these new treatments have been adopted into practice and what their impact has been on patients' receipt of treatment. In this study, we sought to examine whether the introduction of new HCV medications was associated with an increased treatment rate, espe-

## ABSTRACT

**Objectives:** A number of new hepatitis C virus (HCV) medications have become available in the United States, but little is known about how these treatments have been adopted into practice and their financial burden on patients. The aim of this study was to examine whether the introduction of new HCV medications was associated with changes in treatment rates and out-of-pocket (OOP) costs.

**Study Design:** Retrospective analysis of administrative claims data from Optum Labs Data Warehouse.

**Methods:** We performed a retrospective analysis using a large, US commercial insurance database to identify 56,116 adults with chronic HCV between January 1, 2010, and December 31, 2014. Logistic regression was performed to calculate patients' predicted probability of being treated before and after the new medications became available.

**Results:** A total of 5436 (9.7%) of patients with HCV received treatment during an average of 1.8 years of follow-up. In the last quarter of 2014, 0.1% of patients with HCV received interferon/ribavirin as the primary treatment; no one received boceprevir or telaprevir, 1.1% received sofosbuvir combined with simeprevir, 1.4% received sofosbuvir or simeprevir alone, and 2.0% received ledipasvir/sofosbuvir. The introduction of new medications was significantly associated with an increased treatment rate, from 5.4% to 6.8% ( $P < .001$ ). The increase was high among elderly patients and patients with liver transplant, liver cancer, and liver disease or cirrhosis. The median OOP costs of patients receiving new regimens were relatively low (\$112-\$340), but great variations existed.

**Conclusions:** At the end of 2014, patients were almost exclusively using new therapies, which was associated with increased treatment rate, especially among patients who may need urgent treatment but are intolerant or ineligible for interferon-based regimens.

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cially among the elderly and patients with other complex chronic conditions who are likely to be ineligible for or intolerant of previous regimens.

A secondary aim of this study was to estimate the financial burden of HCV treatment on patients. The cost of the newest agents has been very controversial, with estimates ranging from \$66,000 per person for simeprevir to \$84,000 for sofosbuvir per person for a 12-week course of treatment.<sup>17</sup> The high costs of the new drug regimens have raised significant concerns about insurance plan affordability and cost sharing for patients. Little is known about the patients' cost sharing; therefore, this study aimed at describing out-of-pocket (OOP) costs of patients undergoing different treatments.

## METHODS

### Data Source

We conducted a retrospective analysis of administrative claims data from Optum Labs Data Warehouse (OLDW), which includes privately insured and Medicare Advantage enrollees throughout the United States. The database contains health information on over 100 million enrollees over the last 20 years from geographically diverse regions across the United States, with greatest representation from the South and Midwest.<sup>18</sup> The included health plans provide claims for professional (eg, physician), facility (eg, hospital), and outpatient prescription medication services.<sup>19</sup> The Mayo Clinic Institutional Review Board exempted this study from approval as it represents research on preexisting, deidentified data.

### Study Population

We identified all adults (18 years or older) who were diagnosed with chronic HCV between January 1, 2010, and December 31, 2014. Patients were considered to have chronic HCV if they had at least 1 chronic HCV diagnosis (*International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)* codes: 070.44 and 070.54), or at least 2 unspecified HCV diagnoses (*ICD-9-CM*: 070.70, 070.71 and V02.62) on different dates. Patients entered the cohort once they had at least 12-month continuous enrollment in medical and drug health plans and at least 1 HCV diagnosis during these 12 months. Due to the changes in enrollment and disenrollment in health plans, patients entered and left the cohort at different times. The date of entry was defined as the index date, and the 12 months prior to the index date was defined as baseline.

### Take-Away Points

- At the end of 2014, patients were almost exclusively using the new hepatitis C medications that were made available since 2013.
- New therapies increased treatment rate, especially among patients who may need urgent treatment but are intolerant or ineligible for previous interferon-based regimens. However, the treatment rate among young and relatively healthy patients decreased.
- The median out-of-pocket costs of patients receiving new regimens were relatively low (\$112-\$340), but there were great variations and the mean costs were high (\$1982-\$2127).

We excluded patients who received any HCV treatment at baseline. A detailed flowchart illustrating the cohort creation process can be found in [eAppendix Figure 1](#) (eAppendices available at [www.ajmc.com](http://www.ajmc.com)).

### Outcomes

The primary outcome of interest was whether patients received any HCV treatment and which treatment they received. We followed the patients from the index date until they were no longer enrolled in the health plans or until end of the study period (December 31, 2014). We assessed 6 treatment regimens available during the study period: 1) interferon/ribavirin, 2) boceprevir (Victrelis), 3) telaprevir (Incivek), 4) simeprevir or sofosbuvir (not combined), 5) simeprevir and sofosbuvir (combined), and 6) ledipasvir/sofosbuvir (see [eAppendix Table 1](#) for the generic names, brand names, Current Procedural Terminology, Version 4 (CPT-4)/Healthcare Common Procedure Coding System codes, and the FDA approval dates). We separated patients who received the combined sofosbuvir and simeprevir from those who received only 1 of the 2 agents due to highly differing costs. We did not separate patients who received only eprevir from those who received only sofosbuvir, because a single patient in the cohort received simeprevir alone.

Treatment regimens 2 through 4 (from above) include the use of ribavirin and/or interferon. If patients received interferon/ribavirin with another medication at the same time, they were considered receiving the other treatment regimen. For example, if patients received boceprevir with interferon and ribavirin, they were considered to be on the boceprevir regimen. We calculated the percentage of patients receiving treatment, and the percentages of patients receiving each of the 6 regimens per study quarter. Patients were considered being treated or being on a specific treatment regimen during the time from the fill date of a medication through the end of this medication fill (fill date + days of supply – 1). Many patients may be cured after treatment, and patients need to be monitored for at least 12 to 24 weeks to determine whether the treatment

was successful. If the treatment failed, some patients may not be eligible or willing to receive another treatment<sup>11,20</sup>; therefore, most treated patients no longer needed treatment—at least in the short term—so we excluded them from both the numerator and denominator of the percentages after the conclusion of their last treatment. Patients were not counted prior to the index date or after they disenrolled from the health plan.

The secondary outcome was patients' OOP cost, defined as the sum of the deductible and copayment of the medications. All the costs were adjusted to 2014 dollars using the personal consumption expenditures inflation factor.<sup>21</sup> We calculated the descriptive statistics of costs stratified by patients' most recent treatment regimens.

### Statistical Analysis

We used multivariable logistic regression analysis to estimate the predicted probability of receiving treatment prior to and after the new medications became available. We divided patients into 2 groups: 1) "pre-group," which includes patients whose enrollment ended before December 1, 2013, approximately when simeprevir and sofosbuvir became available; and 2) "post group," which includes patients who had enrollment on or after December 1, 2013. In this analysis, we excluded 1565 patients who were in the post group but finished treatment prior to December 2013.

Other covariates included demographics and socioeconomic characteristics at index date (ie, age, gender, race, household income, and residence region), baseline comorbidities, Charlson-Deyo Comorbidity Index (CDI),<sup>22</sup> and the length of follow-up. We adjusted for comorbidities that can influence patients' treatment decisions, including depression (*ICD-9-CM* codes: 296.2x, 296.3x, 311), liver cancer (*ICD-9-CM*: 155.0, 155.2), liver disease or cirrhosis (*ICD-9-CM*: 571.2, 571.5, 571.6, 571.8, 571.9), and liver transplant (*ICD-9-CM*: V42.7, 996.82; *ICD-9-CM* procedure: 50.5, 50.51, 50.59; CPT-4 codes: 47135, 47136). The CDI was used to assess a patient's overall comorbidity burden. Statistically significant interactions between the main independent variable and other covariates (ie, age, gender, region, and comorbidities) were also included in the model. All analyses were conducted using SAS 9.3 (SAS Institute Inc, Cary, North Carolina) and Stata 13.1 (Stata Corp, College Station, Texas).

## RESULTS

From January 1, 2010, to December 31, 2014, we identified 56,116 patients with both a diagnosis of chronic HCV and no receipt of any treatment at baseline. Patients'

demographic, socioeconomic, and health characteristics, stratified by their most recent treatment regimens, are presented in **Table 1**. The mean age was 55.4 years; the majority of the cohort were male (59.8%) and white (63.3%); 13.4% of patients had depression at baseline, 2.0% had liver cancer, 17.2% had liver disease or cirrhosis, and 1.6% had liver transplant. Compared with patients who were not treated, patients who received new treatment regimens were generally older and had more comorbidities, whereas patients who received the old therapies were younger and had fewer comorbidities.

A total of 5436 (9.7%) patients in our cohort received HCV treatment during an average of 1.8 years of follow-up. The **Figure** shows the quarterly trend of the percentages of patients who used each of the treatments. In each quarter of 2010, approximately 2.5% to 3% of the patients with chronic HCV were treated using interferon/ribavirin. The use of interferon/ribavirin as the primary treatment gradually decreased from 2.4% in the first quarter of 2010, to 0.10% in the last quarter of 2014. Following the market debut of boceprevir and telaprevir in May 2011, the use of these 2 medications quickly increased. In the last quarter of 2011, 2.5% of patients with HCV received telaprevir and 0.7% received boceprevir, but neither was used in the last quarter of 2014. After simeprevir and sofosbuvir became available at the end of 2013, their use increased and peaked in the second quarter of 2014: 3.3% received 1 of the 2 agents and 1.8% received them together. In the last quarter of 2014, ledipasvir/sofosbuvir became available, and nearly every treated patient was using the new regimens: ledipasvir/sofosbuvir (2.0%), sofosbuvir or simeprevir (1.4%), and sofosbuvir combined with simeprevir (1.1%) (**eAppendix Table 2**).

We also examined the trends of treatment among different subpopulations and found the trend among the elderly (65 years or older) was very different than the rest of the cohort (**eAppendix Figure 2** and **eAppendix Table 3**). Prior to 2014, only 0.5% to 1.5% of elderly patients were on treatment each quarter, but after the new medications became available, the treatment rate tremendously increased. In the last quarter of 2014, the percentage of elderly patients who were being treated was comparable to the overall population (4.4% vs 4.6%).

The predicted probabilities of receiving treatment prior and after new medications became available are shown in **Table 2**. Overall, the treatment rate was estimated to increase from 5.39% to 6.77%, with a significant absolute increase of 1.38%. The absolute increase was greatest among patients who had a past liver transplant (9.11%): from 5.54% to 14.65%. The absolute increase in

■ **Table 1.** Patient Characteristics, Stratified by Treatment Regimen (N = 56,116)

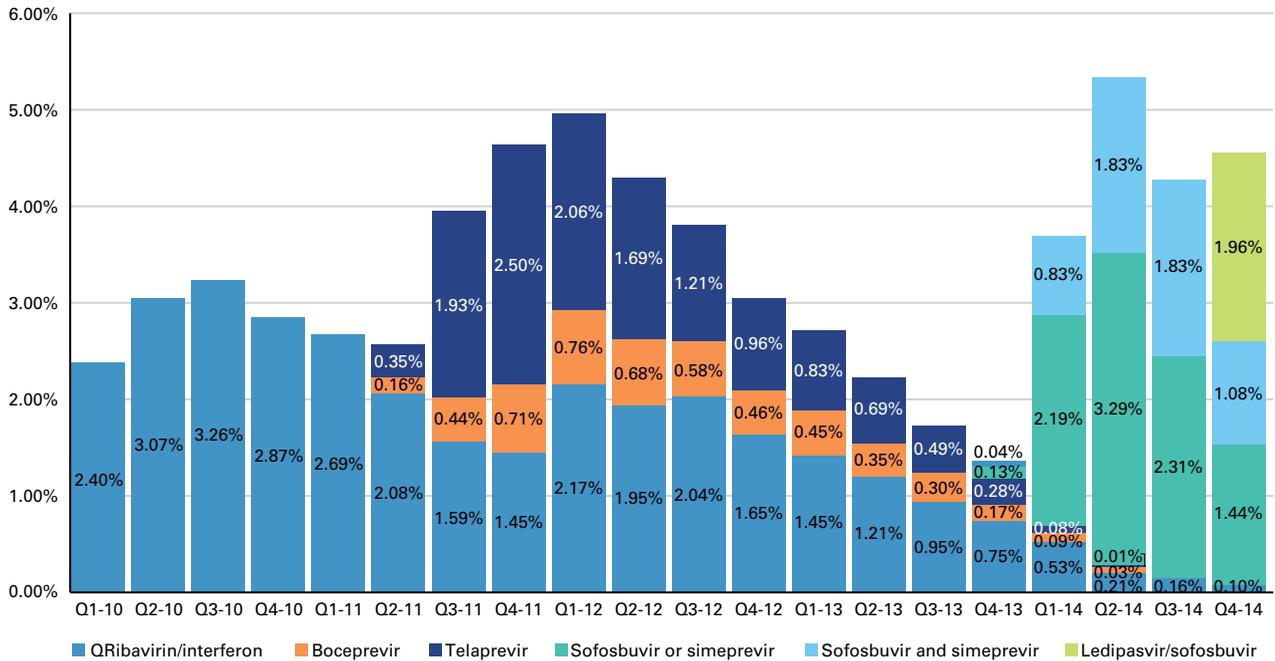
	Ribavirin/ Interferon (N = 1223)	Boceprevir (N = 382)	Telaprevir (N = 1428)	Sofosbuvir or Simeprevir (N = 1153)	Sofosbuvir and Simeprevir (N = 771)	Ledipasvir/ Sofosbuvir (N = 479)	Not Treated (N = 50,680)	Total (N = 56,116)
Age, mean (SD)	51.4 (10.3)	52.9 (9.6)	52.8 (9.5)	55.5 (10.0)	57.2 (8.5)	59.1 (8.7)	55.5 (11.8)	55.4 (11.6)
Age, n (%)								
18-40 years	163 (13.3%)	33 (8.6%)	146 (10.2%)	81 (7.0%)	32 (4.2%)	14 (2.9%)	5152 (10.2%)	5621 (10.0%)
41-50 years	281 (23.0%)	73 (19.1%)	275 (19.3%)	169 (14.7%)	79 (10.2%)	52 (10.9%)	8032 (15.8%)	8961 (16.0%)
51-64 years	709 (58.0%)	253 (66.2%)	935 (65.5%)	728 (63.1%)	532 (69.0%)	279 (58.2%)	27950 (55.1%)	31386 (55.9%)
≥65 years	70 (5.7%)	23 (6.0%)	72 (5.0%)	175 (15.2%)	128 (16.6%)	134 (28.0%)	9546 (18.8%)	10148 (18.1%)
Male, n (%)	756 (61.8%)	241 (63.1%)	905 (63.4%)	731 (63.4%)	493 (63.9%)	296 (61.8%)	30136 (59.5%)	33558 (59.8%)
Race, n (%)								
Asian	54 (4.4%)	11 (2.9%)	31 (2.2%)	44 (3.8%)	19 (2.5%)	13 (2.7%)	2324 (4.6%)	2496 (4.4%)
Black	130 (10.6%)	61 (16.0%)	207 (14.5%)	147 (12.7%)	113 (14.7%)	88 (18.4%)	8112 (16.0%)	8858 (15.8%)
Hispanic	137 (11.2%)	34 (8.9%)	149 (10.4%)	129 (11.2%)	76 (9.9%)	51 (10.6%)	5853 (11.5%)	6429 (11.5%)
Unknown	68 (5.6%)	18 (4.7%)	69 (4.8%)	55 (4.8%)	35 (4.5%)	25 (5.2%)	2537 (5.0%)	2807 (5.0%)
White	834 (68.2%)	258 (67.5%)	972 (68.1%)	778 (67.5%)	528 (68.5%)	302 (63.0%)	31854 (62.9%)	35526 (63.3%)
Household income, n (%)								
<\$40k	264 (21.6%)	72 (18.8%)	246 (17.2%)	236 (20.5%)	154 (20.0%)	130 (27.1%)	12405 (24.5%)	13507 (24.1%)
\$40k-\$49k	84 (6.9%)	28 (7.3%)	117 (8.2%)	83 (7.2%)	58 (7.5%)	37 (7.7%)	4141 (8.2%)	4548 (8.1%)
\$50k-\$59k	110 (9.0%)	36 (9.4%)	115 (8.1%)	93 (8.1%)	55 (7.1%)	54 (11.3%)	3946 (7.8%)	4409 (7.9%)
\$60k-\$74k	112 (9.2%)	52 (13.6%)	146 (10.2%)	119 (10.3%)	87 (11.3%)	46 (9.6%)	5065 (10.0%)	5627 (10.0%)
\$75k-\$99k	187 (15.3%)	43 (11.3%)	212 (14.8%)	168 (14.6%)	103 (13.4%)	50 (10.4%)	6341 (12.5%)	7104 (12.7%)
≥\$100k	316 (25.8%)	119 (31.2%)	471 (33.0%)	311 (27.0%)	249 (32.3%)	95 (19.8%)	11744 (23.2%)	13305 (23.7%)
Unknown	150 (12.3%)	32 (8.4%)	121 (8.5%)	143 (12.4%)	65 (8.4%)	67 (14.0%)	7038 (13.9%)	7616 (13.6%)
Region, n (%)								
Midwest	188 (15.4%)	68 (17.8%)	213 (14.9%)	203 (17.6%)	160 (20.8%)	83 (17.3%)	7787 (15.4%)	8702 (15.5%)
Northeast	215 (17.6%)	82 (21.5%)	352 (24.6%)	306 (26.5%)	196 (25.4%)	170 (35.5%)	12382 (24.4%)	13703 (24.4%)
South	581 (47.5%)	175 (45.8%)	668 (46.8%)	465 (40.3%)	310 (40.2%)	170 (35.5%)	21435 (42.3%)	23804 (42.4%)
Unknown	4 (0.3%)	2 (0.5%)	5 (0.4%)	4 (0.3%)	1 (0.1%)	0 (0.0%)	272 (0.5%)	288 (0.5%)
West	235 (19.2%)	55 (14.4%)	190 (13.3%)	175 (15.2%)	104 (13.5%)	56 (11.7%)	8804 (17.4%)	9619 (17.1%)
Comorbidities, n (%)								
Depression	139 (11.4%)	31 (8.1%)	130 (9.1%)	142 (12.3%)	112 (14.5%)	62 (12.9%)	6898 (13.6%)	7514 (13.4%)
Liver cancer	17 (1.4%)	5 (1.3%)	18 (1.3%)	20 (1.7%)	22 (2.9%)	15 (3.1%)	1025 (2.0%)	1122 (2.0%)
Liver disease or cirrhosis	219 (17.9%)	74 (19.4%)	245 (17.2%)	217 (18.8%)	233 (30.2%)	119 (24.8%)	8526 (16.8%)	9633 (17.2%)
Liver transplant	28 (2.3%)	4 (1.0%)	8 (0.6%)	21 (1.8%)	41 (5.3%)	10 (2.1%)	771 (1.5%)	883 (1.6%)
CDCI score, n (%)								
0	401 (32.8%)	111 (29.1%)	446 (31.2%)	339 (29.4%)	149 (19.3%)	89 (18.6%)	12989 (25.6%)	14524 (25.9%)
1	425 (34.8%)	131 (34.3%)	526 (36.8%)	358 (31.0%)	260 (33.7%)	119 (24.8%)	14571 (28.8%)	16390 (29.2%)
≥2	397 (32.5%)	140 (36.6%)	456 (31.9%)	456 (39.5%)	362 (47.0%)	271 (56.6%)	23120 (45.6%)	25202 (44.9%)
Follow-up, years: mean (SD)	2.5 (1.4)	2.6 (1.2)	2.8 (1.2)	2.2 (1.4)	2.5 (1.5)	2.1 (1.5)	1.7 (1.3)	1.8 (1.4)

CDCI indicates Charlson-Deyo Comorbidity Index; SD, standard deviation.

treatment rate was also high among patients 65 years or older (4.34%); those with liver cancer (5.47%), liver disease, or cirrhosis (5.15%); and a CDCI score of 2 or more

(2.95%). The predicted probability of receiving treatment significantly decreased among patients aged 18 to 40 years and 41 to 50 years, and patients with a CDCI score of 0%,

**Figure.** Quarterly Trend of Hepatitis C Medications, 2010-2014



-3.54%, -2.24%, and -1.12%, respectively. The increase in treatment rate was greater among male than female (1.75% vs 0.90%), black than white (1.62% vs 1.31%), poor (annual household income <\$40,000) than high-income (>\$100,000; 2.04% vs 0.77%), and patients living in the Midwest and Northeast than those living in the South and West (2.47%, 2.76%, 0.36%, 0.97%, respectively).

**Table 3** shows the OOP costs among the 5436 treated patients. The median OOP costs of patients receiving new regimens were relatively low (\$112-\$340), but there were great variations and the mean costs were high (\$1982-\$2127). Some patients did not pay any cost OOP, whereas others paid as high as \$75,831.

## DISCUSSION

To the best of our knowledge, no contemporary data exists on the trends and patterns of HCV treatment in real-world clinical practice, especially in the new era of HCV treatment since December 2013. Our study is the first to examine the early adoption of new HCV treatment in a large, national, privately insured population. We observed substantial changes in treatment patterns over the past 5 years. The older treatments, ribavirin, interferon, boceprevir, and telaprevir, are essentially obsolete now, with few patients receiving these therapies at the end of 2014. Instead, patients are now almost exclusively using

therapies only made available since 2013, because of the efficacy, safety, and convenience of the new medications.

Our study also found the introduction of new medications was associated with increased treatment rates, especially among those who were older and had other chronic conditions that necessitated urgent treatment. We also observed different patterns of the uptake of new medications among different subpopulations of patients. Although white and high-income patients had the highest treatment rate both before and after the new medications became available, the gaps between white and black and high- and low-income individuals were closing. The Midwest and Northeast seemed to adopt the new treatment more quickly than the South and West. Patients who were young or had few chronic conditions might be less likely to receive care. Due to the high costs of new medications, some insurers developed prior authorization programs and asked physicians to treat only patients who require immediate therapy<sup>23</sup>; this makes it difficult for young and healthy patients to obtain treatment. These patients may also be willing to hold off on treatment, with the expectation that more new HCV medications would become available and the price would drop.

In the cohort, 1948 patients received prescriptions for sofosbuvir, 781 for simeprevir, and 780 for both agents. This translates to 40% of patients receiving prescriptions for sofosbuvir and nearly everyone who received pre-

■ **Table 2.** Adjusted Predicted Probabilities of Receiving Treatment (N = 54,551)

	Before December 2013 % (95% CI)	After December 2013 % (95% CI)	Difference % (95% CI)
Overall	5.39% (4.98%-5.79%)	6.77% (6.48%-7.06%)	1.38% *** (0.87%-1.89%)
<b>Age</b>			
18-40 years	7.52% (6.35%-8.69%)	3.98% (3.34%-4.61%)	-3.54% *** (-4.88% to -2.21%)
41-50 years	8.28% (7.35%-9.21%)	6.04% (5.39%-6.68%)	-2.24% *** (-3.39% to -1.10%)
51-64 years	6.93% (6.44%-7.42%)	8.11% (7.70%-8.51%)	1.17% *** (0.52%-1.83%)
≥65 years	1.38% (0.94%-1.82%)	5.72% (5.19%-6.24%)	4.34% *** (3.65%-5.03%)
<b>Gender</b>			
Female	5.15% (4.60%-5.69%)	6.04% (5.65%-6.44%)	0.90% * (0.22%-1.58%)
Male	5.56% (5.09%-6.02%)	7.30% (6.93%-7.67%)	1.75% *** (1.14%-2.36%)
<b>Race</b>			
Asian	3.47% (2.77%-4.18%)	4.51% (3.69%-5.32%)	1.03% *** (0.56%-1.50%)
Black	4.36% (3.83%-4.90%)	5.98% (5.45%-6.50%)	1.62% *** (1.09%-2.14%)
Hispanic	5.30% (4.68%-5.92%)	6.67% (6.02%-7.32%)	1.37% *** (0.81%-1.92%)
White	5.91% (5.47%-6.34%)	7.21% (6.87%-7.56%)	1.31% *** (0.77%-1.84%)
<b>Household income</b>			
<\$40k	4.00% (3.51%-4.49%)	6.04% (5.60%-6.48%)	2.04% *** (1.51%-2.58%)
\$40k-\$49k	4.73% (4.08%-5.38%)	6.16% (5.44%-6.89%)	1.44% *** (0.94%-1.94%)
\$50k-\$59k	6.10% (5.34%-6.86%)	7.52% (6.71%-8.33%)	1.42% *** (0.85%-2.00%)
\$60k-\$74k	5.88% (5.20%-6.55%)	7.13% (6.42%-7.83%)	1.25% *** (0.71%-1.79%)
\$75k-\$99k	6.46% (5.82%-7.11%)	7.49% (6.83%-8.14%)	1.02% *** (0.48%-1.57%)
≥\$100k	7.15% (6.58%-7.71%)	7.91% (7.40%-8.43%)	0.77% ** (0.19%-1.34%)
<b>Region</b>			
Midwest	5.33% (4.49%-6.17%)	7.80% (7.11%-8.48%)	2.47% *** (1.38%-3.56%)
Northeast	4.76% (4.13%-5.39%)	7.52% (6.96%-8.07%)	2.76% *** (1.91%-3.61%)
South	6.09% (5.53%-6.65%)	6.45% (6.05%-6.85%)	0.36% (-0.34% to 1.07%)
West	4.91% (4.23%-5.60%)	5.88% (5.27%-6.49%)	0.97% * (0.05%-1.89%)
<b>Comorbidities</b>			
<b>Depression</b>			
No	5.53% (5.10%-5.97%)	6.82% (6.51%-7.13%)	1.29% *** (0.74%-1.83%)
Yes	4.53% (3.76%-5.30%)	6.45% (5.76%-7.13%)	1.92% *** (0.88%-2.95%)
<b>Liver cancer</b>			
No	5.43% (5.02%-5.84%)	6.73% (6.44%-7.01%)	1.30% *** (0.79%-1.81%)
Yes	3.64% (2.71%-4.58%)	9.11% (7.15%-11.07%)	5.47% *** (4.07%-6.86%)
<b>Liver disease or cirrhosis</b>			
No	5.45% (5.02%-5.88%)	6.20% (5.91%-6.49%)	0.75% * (0.22%-1.28%)
Yes	5.09% (4.39%-5.79%)	10.24% (9.43%-11.05%)	5.15% *** (4.07%-6.23%)
<b>Liver transplant</b>			
No	5.38% (4.98%-5.79%)	6.68% (6.39%-6.97%)	1.30% *** (0.79%-1.81%)
Yes	5.54% (3.39%-7.69%)	14.65% (11.51%-17.78%)	9.11% *** (5.30%-12.92%)
<b>CDCI score</b>			
0	7.58% (6.81%-8.34%)	6.45% (5.95%-6.95%)	-1.12% * (-2.05% to -0.20%)
1	6.90% (6.22%-7.59%)	7.16% (6.65%-7.67%)	0.26% (-0.61% to 1.12%)
≥2	3.76% (3.32%-4.20%)	6.71% (6.31%-7.11%)	2.95% *** (2.34%-3.55%)

CDCI indicates Charlson-Deyo Comorbidity Index.

\*\*\* indicates  $P < .05$ , \*\* indicates  $P < .01$ , and \*\*\*\* indicates  $P < .001$ .

■ **Table 3.** Average Out-of-Pocket Costs per Episode of Care, in 2014 Dollars (N = 5436)<sup>a</sup>

Treatment Regimen	Patients, n	Mean	SD	Minimum	Median	Maximum
Ribavirin/interferon	1223	659.12	1339.39	0.00	255.36	14,874.58
Boceprevir	382	1226.79	1847.93	0.00	604.02	10,488.45
Telaprevir	1428	1325.92	2974.24	0.00	458.21	46,009.58
Sofosbuvir or simeprevir	1153	2027.14	3767.52	0.00	340.00	35,285.16
Sofosbuvir combined with simeprevir	771	2127.33	4484.41	0.00	300.00	75,831.44
Ledipasvir/sofosbuvir	479	1982.38	3317.71	0.00	111.53	32,874.87

SD indicates standard deviation.

<sup>a</sup>If patients received interferon/ribavirin with another medication at the same time, they were considered receiving the other treatment regimen. The out-of-pocket costs included co-payments and deductibles for all hepatitis C medications that a patient received during the study period.

scriptions for simeprevir was treated by the combination of the 2 agents. Although the combination of sofosbuvir and simeprevir was approved by the FDA in November 2014,<sup>24</sup> the off-label use started right after the 2 agents were individually approved. The efficacy and safety of this combination was supported by the combination of simeprevir and sofosbuvir in a trial of patients with HCV infection,<sup>12</sup> and may be attractive for patients who are unwilling or unable to undergo interferon-based regimens. The most recent American guideline includes the combined therapy as one of the recommended regimens.<sup>16</sup> Nearly half the patients receiving the combination had other complex chronic conditions, such as depression (14.5%), liver cancer (2.9%), liver disease or cirrhosis (30.2%), and liver transplant (5.3%). These comorbidities were captured during the 12-month baseline, so it is possible that patients' diseases information was not fully captured. It is also possible that patients developed new conditions during follow-up. Despite the potentially underestimated prevalence of comorbidities, it is clear many patients receiving the combination did not have any severe chronic conditions other than HCV. Interestingly, the payers seemed to cover costs of the combined regimen very well; the average OOP costs were only \$100 higher for the combined regimen than the regimen that was not combined. In fact, the median cost was lower in the combined regimen (\$300 vs \$340).

Overall, the OOP costs were affordable for many of the patients who received the new therapies. The median cost for the ledipasvir/sofosbuvir regimen was only \$112—much lower than any previous regimen. Despite the high wholesale prices, due to the effectiveness of treatment as well as the expected reductions in downstream costs associated with averted progression of liver disease, the new standard HCV treatments might be cost-effective in most patients.<sup>25-28</sup> Therefore, some insurers might be willing to cover most of the costs. However, the OOP costs varied a lot among pa-

tients, and some patients had to pay approximately \$35,000 to \$76,000 for the new regimens. In this study, we did not use a multivariable regression model to assess the independent role of new medications on OOP costs. One reason is that new medications are available to broader patient populations than old regimens. Moreover, patients who received newer agents right after the medications became available are often those who had good insurance coverage.

### Limitations

One limitation of this study is that we could not fully capture patients' past treatment history. A patient whose previous treatment failed might make decisions differently regarding whether to receive another treatment and which treatment to receive, compared with a treatment-naïve patient. Although we excluded patients who received treatment at baseline, it is possible some patients may have been treated prior to the baseline or prior to their enrollment in the health plan. However, the percentage of patients who underwent HCV treatment has been very low, especially before 2011, so there should be very few patients in our cohort who were previously treated.

Another limitation is that when estimating the OOP costs, we only considered the medication costs. We did not consider the OOP costs associated with interferon injection performed by providers, so we may have underestimated the costs of the interferon. However, only approximately 1% of claims were injections performed by health professionals. Additionally, the estimated OOP costs may not accurately reflect the costs per treatment regimen. Some patients may receive multiple treatments during follow-up, some may discontinue treatment, not comply with treatment, or their follow-up may end before finishing treatment. We conducted a sensitivity test that included only compliant patients who received a single treatment episode and finished at least 12 weeks of treatment. We excluded patients who received multiple regimens and who had a

very short (<77days) or long treatment period (>365 days), and who had a proportion of days covered less than 80% (eAppendix Table 4). The estimated costs per regimen using this method were similar to the results in Table 3, except for ledipasvir/sofosbuvir. The median costs of ledipasvir/sofosbuvir increased from \$112 to \$180, and the mean increased from \$1982 to \$3030. Because ledipasvir/sofosbuvir became available in October 2014, patients who initiated treatment in November and December 2014 would not be able to finish treatment by the end of the year. Therefore, we did not capture the whole costs for some patients on ledipasvir/sofosbuvir.

## CONCLUSIONS

The new HCV antiviral medications have been quickly adopted into practice; they are associated with increased treatment rates, especially among the elderly and patients with multiple chronic conditions that necessitate urgent treatment, but also make them intolerant or ineligible for previous interferon-based regimens. In this study, we did not include Viekira Pak, another new HCV medication approved by the FDA in December 2014. This new drug, developed by AbbVie Inc, has become a strong competitor of Harvoni and Sovaldi, which were developed by Gilead Sciences Inc. With more new medications available and increasing competition, the changes in treatment patterns and affordability will continue to evolve.

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## eAppendix

**Table 1.** HCV Antiviral Therapy

<b>Generic Name</b>	<b>Brand Name</b>	<b>HCPCS/CPT-4</b>	<b>FDA Approval Date</b>
Interferon alfa-2a	Roferon	J9213	June 1986
Interferon alfa-2b	Intron A	J9214	June 1986
Interferon alfacon-1	Infergen	J9212	October 1997
Peginterferon alfa-2a	Pegasys	S0145	October 2002
Peginterferon alfa-2b	Pegintron	S0146, S0148	January 2001
Ribavirin	CoPegus		December 2002
Ribavirin	Moderiba		January 2014
Ribavirin	Rebetol		June 1998
Ribavirin	Ribapak		May 2012
Ribavirin	Ribasphere		April 2004
Ribavirin	Ribatab		June 1998
Boceprevir	Victrelis		May 2011
Telaprevir	Incivek		May 2011
Simeprevir	Olysio		November 2013
Sofosbuvir	Sovaldi		December 2013
Ledipasvir/sofosbuvir	Harvoni		October 2014
Ombitasvir/paritaprevir/ritonavir/ dasabuvir	Viekira Pak		December 2014

We did not include the 2 new drugs (ie, Harvoni and Viekira Pak) approved after the end of the study period (September 30, 2014).

**Table 2.** Percentages of Patients Receiving Hepatitis C Medication in Each Quarter, From 2010 to 2014 (N = 56,116)

Quarter	Patients, n	Treated	Ribavirin/ Interferon	Boceprevir	Telaprevir	Sofosbuvir or Simeprevir	Sofosbuvir and Simeprevir	Ledipasvir/ Sofosbuvir
Q1-10	6547	2.40%	2.40%	0.00%	0.00%	0.00%	0.00%	0.00%
Q2-10	10461	3.07%	3.07%	0.00%	0.00%	0.00%	0.00%	0.00%
Q3-10	13049	3.26%	3.26%	0.00%	0.00%	0.00%	0.00%	0.00%
Q4-10	14961	2.87%	2.87%	0.00%	0.00%	0.00%	0.00%	0.00%
Q1-11	16743	2.69%	2.69%	0.00%	0.00%	0.00%	0.00%	0.00%
Q2-11	18404	2.58%	2.08%	0.16%	0.35%	0.00%	0.00%	0.00%
Q3-11	19749	3.94%	1.59%	0.44%	1.93%	0.00%	0.00%	0.00%
Q4-11	20763	4.66%	1.45%	0.71%	2.50%	0.00%	0.00%	0.00%
Q1-12	22244	4.99%	2.17%	0.76%	2.06%	0.00%	0.00%	0.00%
Q2-12	23127	4.33%	1.95%	0.68%	1.69%	0.00%	0.00%	0.00%
Q3-12	23597	3.83%	2.04%	0.58%	1.21%	0.00%	0.00%	0.00%
Q4-12	25718	3.07%	1.65%	0.46%	0.96%	0.00%	0.00%	0.00%
Q1-13	24475	2.73%	1.45%	0.45%	0.83%	0.00%	0.00%	0.00%
Q2-13	25187	2.26%	1.21%	0.35%	0.69%	0.00%	0.00%	0.00%
Q3-13	25702	1.74%	0.95%	0.30%	0.49%	0.00%	0.00%	0.00%
Q4-13	26321	1.37%	0.75%	0.17%	0.28%	0.13%	0.04%	0.00%
Q1-14	24666	3.70%	0.53%	0.09%	0.08%	2.19%	0.83%	0.00%
Q2-14	24965	5.37%	0.21%	0.03%	0.01%	3.29%	1.83%	0.00%
Q3-14	24808	4.30%	0.16%	0.00%	0.00%	2.31%	1.83%	0.00%
Q4-14	24380	4.58%	0.10%	0.00%	0.00%	1.44%	1.08%	1.96%

**Table 3.** Percentages of Elderly Patients ( $\geq 65$  years) Receiving Hepatitis C Medication in Each Quarter, From 2010 to 2014 (N = 10,148)

Quarter	Patients, n	Treated	Ribavirin/ Interferon	Boceprevir	Telaprevir	Sofosbuvir or Simeprevir	Sofosbuvir and Simeprevir	Ledipasvir/S ofosbuvir
Q1-10	912	0.88%	0.88%	0.00%	0.00%	0.00%	0.00%	0.00%
Q2-10	1419	1.20%	1.20%	0.00%	0.00%	0.00%	0.00%	0.00%
Q3-10	1779	1.12%	1.12%	0.00%	0.00%	0.00%	0.00%	0.00%
Q4-10	2067	0.87%	0.87%	0.00%	0.00%	0.00%	0.00%	0.00%
Q1-11	2416	0.79%	0.79%	0.00%	0.00%	0.00%	0.00%	0.00%
Q2-11	2723	0.77%	0.66%	0.04%	0.07%	0.00%	0.00%	0.00%
Q3-11	2958	0.91%	0.47%	0.07%	0.41%	0.00%	0.00%	0.00%
Q4-11	3131	1.44%	0.54%	0.26%	0.64%	0.00%	0.00%	0.00%
Q1-12	3641	1.51%	0.55%	0.30%	0.66%	0.00%	0.00%	0.00%
Q2-12	3846	1.25%	0.52%	0.29%	0.44%	0.00%	0.00%	0.00%
Q3-12	4045	0.94%	0.49%	0.15%	0.30%	0.00%	0.00%	0.00%
Q4-12	4603	0.89%	0.50%	0.13%	0.26%	0.00%	0.00%	0.00%
Q1-13	4475	0.87%	0.36%	0.18%	0.34%	0.00%	0.00%	0.00%
Q2-13	4728	0.85%	0.42%	0.21%	0.21%	0.00%	0.00%	0.00%
Q3-13	4945	0.61%	0.26%	0.14%	0.20%	0.00%	0.00%	0.00%
Q4-13	5196	0.46%	0.17%	0.08%	0.13%	0.04%	0.04%	0.00%
Q1-14	4943	2.35%	0.16%	0.00%	0.04%	1.70%	0.45%	0.00%
Q2-14	5172	3.71%	0.10%	0.00%	0.00%	2.22%	1.39%	0.00%
Q3-14	5335	3.22%	0.06%	0.00%	0.00%	1.48%	1.69%	0.00%
Q4-14	5358	4.42%	0.02%	0.00%	0.00%	1.05%	0.86%	2.50%

**Table 4.** Average Out-of-Pocket Costs per Episode of Care, in 2014 Dollars (N = 3292)

<b>Treatment Regimen</b>	<b>Patients, n</b>	<b>Mean</b>	<b>SD</b>	<b>Minimum</b>	<b>Median</b>	<b>Maximum</b>
Ribavirin/interferon	799	787.31	1434.10	0.00	307.64	12641.78
Boceprevir	277	1226.25	1822.54	0.00	623.85	9791.48
Telaprevir	967	1397.08	2894.13	0.00	497.48	34500.96
Sofosbuvir or simeprevir	737	1960.66	3457.43	0.00	345.00	35285.16
Sofosbuvir combined with simeprevir	456	2436.20	5173.40	0.00	300.00	75831.44
Ledipasvir/sofosbuvir	56	3029.97	5415.57	0.00	180.00	32874.87

This table only included compliant patients who received a single treatment episode and finished at least 12 weeks of treatment. We excluded patients who received multiple regimens, and who had very short (<77days) or long treatment period (>365 days), and who had a proportion of days covered less than 80%.

**Figure 1.** Cohort Creation Flowchart

