

Cost Burden of Hepatitis C Virus Treatment in Commercially Insured Patients

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The arrival of direct-acting antivirals (DAAs) started a new era of treatment for patients with chronic hepatitis C virus (HCV) infection.¹⁻³ An estimated 80 million to 150 million individuals worldwide, including about 3 million to 4 million in the United States, have chronic HCV infection.^{4,5} If left untreated, chronic HCV infection can lead to cirrhosis, liver failure, and hepatocellular carcinoma^{6,7}; it is the leading cause of liver transplantation and death from liver disease.^{2,8}

Sofosbuvir (Sovaldi), approved by the FDA in late 2013, was the first DAA indicated for treatment of HCV as part of an interferon-free regimen. In clinical trials, 12 weeks of treatment with sofosbuvir-based regimens achieved a sustained virologic response (“cure” or undetectable HCV RNA 12-24 weeks after therapy) rate of approximately 90% in patients with HCV. These regimens show much-improved tolerability and safety compared with poorly tolerated interferon-based therapy regimens that resulted in virologic response in only 20% to 30% of patients.⁹⁻¹¹ Recurrent viremia (detectable HCV RNA at follow-up week 24 after achieving sustained virologic response) is extremely rare with sofosbuvir and ledipasvir/sofosbuvir (Harvoni) (12/3004 [0.4%] patients across 11 phase 3 trials¹²). Furthermore, adherence rates for DAAs are substantially higher than for interferon-based therapy (99.8% vs 36%-60%).^{13,14} Studies indicate that new DAAs are cost-effective in patients with HCV genotypes 1 through 5 at a threshold of \$100,000 per quality-adjusted life-year.^{15,16} Since 2013, 8 other DAAs for HCV have been approved¹⁷ (eAppendix Figure 1 [eAppendix available at ajmc.com]).

The availability of DAAs helped to fuel the discourse about ever-rising spending on pharmaceuticals, driven by spending on specialty medications like DAAs.^{18,19} The published wholesale acquisition cost of sofosbuvir was \$1000 per day in 2014 (or \$84,000 for a 12-week course), with additional spending for required concomitant treatments. A single tablet of ledipasvir/sofosbuvir was available at a published price of \$1125 (\$63,000, \$94,500, and \$189,000 for an 8-, 12-, and 24-week course, respectively).²⁰ Although the high prices of specialty drugs are widely recognized, there were enormous concerns that demand for expensive DAAs

ABSTRACT

OBJECTIVES: New direct-acting antivirals (DAAs), introduced in late 2013, are effective for treating chronic hepatitis C virus (HCV) infection but may pose substantial financial burden on patients and health insurers. We examined HCV medication use and costs in a commercially insured population.

STUDY DESIGN: Retrospective cohort study.

METHODS: We used claims data for 3091 individuals with HCV infection (2012-2015). Outcomes included HCV medication use, inflation-adjusted out-of-pocket (OOP) and health plan spending, and predictors of receiving new DAAs.

RESULTS: Cumulatively, 9% of members with a diagnosis of HCV were treated with HCV medications in 2012 and this increased to 32% in 2015. Of 3091, 589 received new DAAs and 80% (n = 465) completed a 12-week treatment regimen. After new DAAs became available, average annual health plan spending on HCV medications increased from \$2869 to \$16,504 per HCV-diagnosed member (relative change, 475%; 95% CI, 352%-598%), and OOP spending increased from \$41 to \$94 (relative change, 131%; 95% CI, 15%-247%). Age [being aged 50-64 years [adjusted odds ratio (aOR), 2.13; 95% CI, 1.29-3.53] and being ≥65 years [aOR, 2.01; 95% CI, 1.14-3.55] compared with being <30 years] and having liver cirrhosis [aOR, 3.34; 95% CI, 2.64-4.21] were positively associated with receiving new DAAs, and a diagnosis of alcohol abuse [aOR, 0.70; 95% CI, 0.53-0.92] was negatively associated with receiving new DAAs.

CONCLUSIONS: The proportion of a commercially insured population with HCV infection who were treated with HCV medications doubled within 2 years following availability of new DAAs. Member OOP spending was kept low while the health plan bore 99% of the cost of HCV medications. During our 2-year follow-up, we did not observe financial benefits to the health plan of the cure of HCV infection by new DAAs.

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TAKEAWAY POINTS

- ▶ New direct-acting antivirals (DAAs) are effective for treating chronic hepatitis C virus (HCV) infection but may pose substantial economic burden on patients and health insurers.
- ▶ The proportion of a commercially insured population with HCV infection who were treated with HCV medications doubled within 2 years following availability of new DAAs.
- ▶ In this health plan, member out-of-pocket spending was kept low while the health plan bore 99% of the cost of HCV medications. In our 2-year follow-up period, we did not observe financial benefits to the health plan of the cure of HCV infection by new DAAs.

for treatment of a prevalent condition might “bust” the health system budget.^{21,22} Concerns about budgetary impact and the need to contain pharmaceutical spending growth led payers to restrict initial access to DAAs to patients with higher liver fibrosis scores. However, even restricted subsidized access to DAAs could translate into substantial pharmaceutical spending for healthcare payers and/or out-of-pocket (OOP) spending for patients. In a commercially insured population with HCV infection, we examined the utilization of HCV medications, and health plan and member spending on them, both before and after the first availability of DAAs.

METHODS

Setting and Data Source

Harvard Pilgrim Health Care (HPHC) is a commercial health plan serving approximately 1.25 million members²³ in Connecticut, Maine, Massachusetts, and New Hampshire; of these, about 700,000 members are fully insured with pharmacy data accessible to HPHC. Through prior authorization policies, HPHC, like many other health plans, initially restricted access to new DAAs to members with more advanced disease. Criteria for approval in 2014 and 2015 included age at least 18 years; a diagnosis of genotype 1/1b, 2, 3, 4, 5, or 6; liver disease staging within the past 3 years; evidence of stage 2 or greater hepatic fibrosis; being in the care of a gastroenterologist, infectious disease specialist, or hepatologist; and provider attestation that the patient was not currently participating in illicit substance abuse or alcohol abuse, or that the patient was receiving substance or alcohol abuse counseling services as an adjunct to HCV treatment (**eAppendix Table 1**). Once ledipasvir/sofosbuvir entered the market in 2014, it was the preferred medication in this health plan over other DAAs unless appropriate clinical justification was provided.

The study population consisted of fully insured HPHC members. We identified a rolling cohort of individuals who had at least 1 claim with an HCV diagnosis code (*International Classification of Diseases, Ninth Revision [ICD-9]* code 070.44, chronic hepatitis C with hepatic coma; or 070.54,²⁴ chronic hepatitis C without hepatic coma)²⁵ between January 1, 2012, and September 30, 2015 (end of the ICD-9 coding era), and had evidence of pharmacy utilization (to ensure membership in a plan that included pharmacy coverage). We then grouped individuals by calendar year according to their periods of enrollment. Individuals were included in calendar year totals if they

had at least 1 day of enrollment in that year; individuals could thus contribute to multiple years during their enrollment. We analyzed medical and pharmacy claims from January 1, 2012, through December 31, 2015.

Outcome Measures

We first calculated numbers of patients receiving at least 1 dispensing of old and/or new medications for HCV by calendar year

and the total number of days supplied for each medication. Old HCV medications were boceprevir (Victrelis), telaprevir (Incivek), interferon and peginterferon, and ribavirin. New HCV medications included in our analysis were interferon-free regimens: daclatasvir dihydrochloride (Daklinza), ledipasvir/sofosbuvir (Harvoni), simeprevir sodium (Olysio), sofosbuvir (Sovaldi), ombitasvir/paritaprevir/ritonavir (Technivie), and ombitasvir/paritaprevir/ritonavir/dasabuvir sodium (Viekira Pak). Our analysis did not include elbasvir/grazoprevir (Zepatier), sofosbuvir/velpatasvir (Epclusa), sofosbuvir/velpatasvir/voxilaprevir (Vosevi), and glecaprevir/pibrentasvir (Mavyret) because they were approved by the FDA after the end of our study period.

We assessed the percentage market share (ie, percentage of pharmaceutical spending) for HCV medications overall and for individual products. Among the cohort of HCV-diagnosed individuals, we calculated OOP and health plan spending for medical and pharmacy (HCV and non-HCV medications) services per member per month and per year. OOP spending included co-payments, coinsurance, and deductible amounts. We also calculated OOP spending among users of both old and new HCV medications.

Covariates

Demographic characteristics, derived from enrollment files, included age at time of first HCV diagnosis in the study period, gender, and health plan type (Medicare or commercial). Geographic measures of race/ethnicity, median household income, and education were derived from the 2015 American Community Survey 5-year estimates (2011-2015)²⁶ based on an individual's zip code. We classified members as residing in white, black, Hispanic, or other neighborhoods based on living in neighborhoods with 66% or more persons of the given race/ethnicity. We classified members from areas that did not fall into one of the race/ethnicity categories as residing in mixed race/ethnicity neighborhoods. We categorized median neighborhood household incomes in our study cohort in quartiles from lower to higher incomes. We classified members as residing in areas of high, middle, or low education level (ie, <15%, 15%-24.9%, or >25% of residents in the neighborhood areas with below-high-school education levels, respectively). Clinical characteristics (advanced liver disease, mental illness, and physical illness other than liver disease; see **eAppendix Table 2** for codes) were derived from claims data using the same diagnosis code–based definitions as previous research.^{24,27}

Analysis

We used time series plots to display trends in market share of individual new HCV medications and per-member per-month OOP and health plan spending. Spending was adjusted to 2015 US dollars using the Consumer Price Index.²⁸ We tested for trend in yearly rates using time series regression with a significance level of $P < .05$. We used pre–post analysis to examine changes in spending per HCV-diagnosed member before (2012–2013) and after (2014–2015) the availability of new DAAs. In our generalized estimating equations model,^{29,30} we used marginal effects methods to calculate mean adjusted baseline and follow-up spending as well as absolute and relative changes. Our models adjusted for annual changes in member-level covariates (age, sex, median household income, race/ethnicity [black/white], any advanced liver disease, HIV, any substance abuse, any mental illness, and any physical illness) and for enrollment length using offset in the negative binomial distribution. Finally, we used univariate and multivariate logistic regression models to identify demographic and clinical predictors of receiving new HCV medications. We fit a parsimonious multivariate model including variables that were statistically significant at $P < .05$ in univariate analyses and retaining key demographic and clinical variables regardless of statistical significance (sex, income, education, race/ethnicity, any mental illness, any physical illness). All analyses were carried out using SAS software version 9.3 (SAS Institute; Cary, North Carolina) and STATA 14 (StataCorp; College Station, Texas). The study was approved by the HPHC Institutional Review Board.

RESULTS

Table 1 describes study cohort characteristics, and **eAppendix Figure 2** presents a cascading flowchart for construction of the cohorts. A total of 3091 HPHC members had at least 1 claim with an HCV diagnosis between January 1, 2012, and September 30, 2015, and evidence of pharmacy utilization during the study. The average age of the cohort was 52 years, and 66% were male. Almost one-fourth of the cohort lived in neighborhoods with median incomes below \$51,835, and 78% lived in predominantly white and 78% in high-education neighborhoods.

Between 2012 and 2015, 1501 prior authorization applications for new HCV medications were submitted to the health plan. A total of 690 (46%) were approved. Lack of clinical supporting information or not meeting the fibrosis score criterion were the most common reasons for denial. A total of 164 appeals were received; of these, 53 applications (32%) were subsequently approved.

Table 2 summarizes prevalent use of both old and new HCV medications by year and medication. The proportion of members with treatment for chronic HCV infection increased from 9% in 2012 to 20% in 2015. Overall, 32% of the cohort received HCV medications during the study. A total of 589 members received new HCV medications. Of these, 79% ($n = 465$) members had sufficient supply to complete 12 weeks of new DAA therapy (another 41 individuals

TABLE 1. Cohort Characteristics (N = 3091)

General Characteristic	Study Group
Age group in years (at first observed HCV diagnosis), ^a n (%)	
<30	292 (9.5)
30–49	615 (19.9)
50–64	1923 (62.2)
≥65	261 (8.4)
Age in years, mean (SD)	52.0 (12.6)
Sex, n (%)	
Female	1058 (34.2)
Male	2033 (65.8)
Median household income, ^b n (%)	
Quartile 1 (\$15,558–\$51,835)	762 (24.6)
Quartile 2 (\$51,849–\$70,248)	775 (25.1)
Quartile 3 (\$70,313–\$85,762)	753 (24.4)
Quartile 4 (\$85,798–\$199,599)	774 (25.0)
Missing	27 (0.9)
Race/ethnicity, ^b n (%)	
White	2398 (77.6)
Black	46 (1.5)
Hispanic	0 (0.0)
Other	0 (0.0)
Mixed	624 (20.2)
Missing	23 (0.7)
Education, ^b n (%)	
Low	164 (5.3)
Middle	484 (15.7)
High	2420 (78.3)
Missing	25.0 (0.7)
Enrollment	
Number of months enrolled per member, median	34.0
Number of months enrolled per member, mean (SD)	31.8 (15.1)
Plan type, n (%)	
Medicare (Medicare HMO, Medicare indemnity)	123 (4.0)
Commercial (EPO, HMO, POS/indemnity PPO)	2968 (96.0)
Comorbid diagnoses, ^a n (%)	
Advanced liver disease (any)	878 (28.4)
Hepatic decompensation	546 (17.7)
Liver cirrhosis	693 (22.4)
Liver transplant	105 (2.8)
HIV	92 (3.0)
Substance abuse (any)	879 (28.4)
Substance abuse (alcohol)	532 (17.2)
Substance abuse (opioids)	384 (12.4)
Substance abuse (other drugs)	503 (16.3)
Any mental illness, ^a n (%)	1349 (43.6)
Severe mental illness	298 (9.6)
Major and other depression	820 (26.5)

(continued)

TABLE 1. (Continued) Cohort Characteristics (N = 3091)

General Characteristic	Study Group
Other mental illness	1011 (32.7)
Physical illness other than liver disease (any), ^a n (%)	1374 (44.5)
Chronic pulmonary disease	753 (24.4)
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	423 (13.7)
Metastatic solid tumor	59 (1.9)
Congestive heart failure	192 (6.2)
Myocardial infarction	69 (2.2)
Diabetes, uncomplicated	541 (17.5)
Diabetes, complicated	240 (7.8)

EPO indicates exclusive provider organization; HCV, hepatitis C virus; HMO, health maintenance organization; ICD-9, International Classification of Diseases, Ninth Revision; POS, point of service; PPO, preferred provider organization.

^aCohort members had at least 1 claim with ICD-9 code 070.44 or 070.54 in any of 10 diagnosis fields during the study period (1/1/2012-12/31/15); comorbid diagnoses are defined based on occurrence of at least 1 claim with a relevant ICD-9 code during the study period.

^bWe used data from the American Community Survey (2011-2015) to classify members by neighborhood (zip code) income quartile. We classified members as residing in white, black, Hispanic, or other neighborhoods based on living in neighborhoods with 66% or more persons of the given race/ethnicity. We classified members from areas that did not fall into one of the race/ethnicity categories as residing in mixed race/ethnicity neighborhoods. We used members' neighborhood characteristics as a proxy for education (below-high-school education levels of <15%, 15%-24.9%, or >25%) and classified members as residing in areas with a high, middle, or low education level, respectively.

had medication availability that exceeded their enrollment period, but we were unable to determine duration of treatment).

eAppendix Figure 3 shows the market share of individual DAAs based on spending on HCV medications. Sofosbuvir (accounting for 68%) and ledipasvir/sofosbuvir (86%) were the most commonly used medications in 2014 and 2015, respectively. There was little use or no use of ombitasvir/paritaprevir/ritonavir, daclatasvir, ombitasvir/paritaprevir/ritonavir/dasabuvir, and simeprevir in this population. **eAppendix Figure 4** shows the market share of individual DAAs based on numbers of patients treated.

eAppendix Table 3 and **eAppendix Table 4** present average and median (with interquartile range) annual spending per HCV-diagnosed member, respectively. Following availability of new DAAs, average annual health plan spending on HCV medications increased from \$2869 to \$16,504 per HCV-diagnosed member (**Table 3**). In adjusted pre-post analyses, the absolute change was \$13,635 per member per year (95% CI, \$11,708-\$15,562) and the relative change was 475% (95% CI, 352%-598%). Medical spending for HCV-diagnosed members by the health plan remained stable over time. Overall, the health plan contributed more than 99% of the spending on HCV medications both before and after the availability of new DAAs. The **Figure [A]** illustrates monthly trajectories of health plan spending per HCV-diagnosed member.

In this health plan, old HCV medications were generally on a lower tier of the pharmacy formulary (with an average co-payment of \$27 per 30-day dispensing) whereas new DAAs were in a higher tier (with an average co-payment of \$36 per 30-day dispensing).

Some DAAs were “preferred” agents (eg, ledipasvir/sofosbuvir), thus coinsurance was not applied to these medications, keeping these medications more affordable than other specialty medications. Following availability of new DAAs, average yearly OOP spending on HCV medications increased from \$41 to \$94 per HCV-diagnosed member in the study population, with about 32% of members receiving HCV medications. In adjusted pre-post analyses, the absolute change was \$53 (95% CI, \$9-\$97) per member per year and the relative change was 131% (95% CI, 15%-247%). Medical OOP spending did not change significantly following availability of new DAAs. The **Figure [B]** illustrates trends in monthly OOP spending trajectories per HCV-diagnosed member.

When we restricted analysis to only those receiving HCV medications, average annual OOP spending on HCV medications fell from \$636 to \$570 per user following availability of new DAAs, but this was not statistically significant (**Table 3**). In adjusted pre-post analyses, the absolute change was -\$66 (95% CI, -\$147 to \$16) per user per year and the relative change was -10% (95% CI, -22% to 1.5%).

Table 4 presents multivariate regression results on predictors of receiving new DAAs. We found that age (being aged 50-64 years [adjusted odds ratio (aOR), 2.13; 95% CI, 1.29-3.53] and being ≥65 years [aOR, 2.01; 95% CI, 1.14-3.55] compared with being <30 years) and having liver cirrhosis (aOR, 3.34; 95% CI, 2.64-4.21) were positively associated with receiving new HCV medications. A diagnosis of alcohol abuse was negatively associated with receipt of new DAAs (aOR, 0.70; 95% CI, 0.53-0.92).

DISCUSSION

Our longitudinal study examined treatment of HCV infection in a commercially insured population before and after the initial availability of new and highly effective, but costly, DAAs. HCV medication uptake increased substantially following availability of new DAAs, which is not surprising given their high sustained virologic response rates and improved tolerability and safety compared with old HCV medications. In our study, almost 80% of individuals who initiated new DAAs may have completed a 12-week treatment regimen recommended for sustained virologic response, which is associated with lower risk of liver cancer and reductions in longer-term liver-related deaths or liver transplants.³¹⁻³³ In our analysis, the identified predictors of receiving new DAAs largely reflected provider prescribing practice and insurance coverage policies for new DAAs at that time.

About half of the prior authorization applications were initially denied; failing to meet the fibrosis score requirement and missing clinical supporting information were the 2 main reasons for denial during the study period. When new DAAs first became available, severity of liver disease was a commonly used eligibility criterion for coverage with the intent to provide access to these expensive DAAs to the subgroup of patients with the highest immediate clinical need while managing resources.^{34,35} Following DAA treatment of

(CONTINUED ON PAGE E385)

TABLE 2. Use of Old and New HCV Treatments Among Patients With Chronic HCV Infection, 2012-2015

HCV Medications	2012		2013		2014		2015	
	Number of Patients ^a	Days' Supply Dispensed	Number of Patients ^a	Days' Supply Dispensed	Number of Patients ^a	Days' Supply Dispensed	Number of Patients ^a	Days' Supply Dispensed
Total ever enrolled, ^b n	2299	NA	2447	NA	2363	NA	2091	NA
Received HCV medication(s), ^c n (%)	212 (9.2)	NA	89 (3.6)	NA	267 (11.3)	NA	409 (19.6)	NA
Cumulative treated population, n (%)	212 (9.2)		240 (9.8)		415 (17.6)		659 (31.5)	
Old HCV Treatments								
Boceprevir (Victrelis; 200 mg)	35	4536	13	2296	1	56	0	0
Telaprevir (Incivek; 375 mg)	89	5730	21	1372	1	28	0	0
Interferon or peginterferon	210	30,256	84	10,401	62	4901	2	364
Ribavirin (200, 400, 500, 600 mg)	206	29,122	82	8984	160	13,607	103	8425
Ribavirin in combination packs with interferon	0	0	0	0	0	0	0	0
New HCV Treatments								
Daclatasvir dihydrochloride (Daklinza; 30, 60, 90 mg)	0	0	0	0	0	0	4	336
Ledipasvir/sofosbuvir (Harvoni; 90-400 mg)	0	0	0	0	67	3192	355	27,696
Simeprevir sodium (Olysio; 150 mg)	0	0	4	112	51	4062	0	0
Sofosbuvir (Sovaldi; 400 mg)	0	0	9	252	193	16,578	49	4648
Ombitasvir/paritaprevir/ritonavir (Technivie; 12.5-75-50 mg)	0	0	0	0	0	0	0	0
Ombitasvir/paritaprevir/ritonavir/dasabuvir sodium (Viekira Pak; 12.5-75 mg)	0	0	0	0	0	0	2	118

HCV indicates hepatitis C virus; NA, not applicable.

^aNumber of patients ever enrolled in a given year and receiving at least 1 dispensing of an HCV medication in that year.

^bMembers enrolled for at least 1 day in the given year.

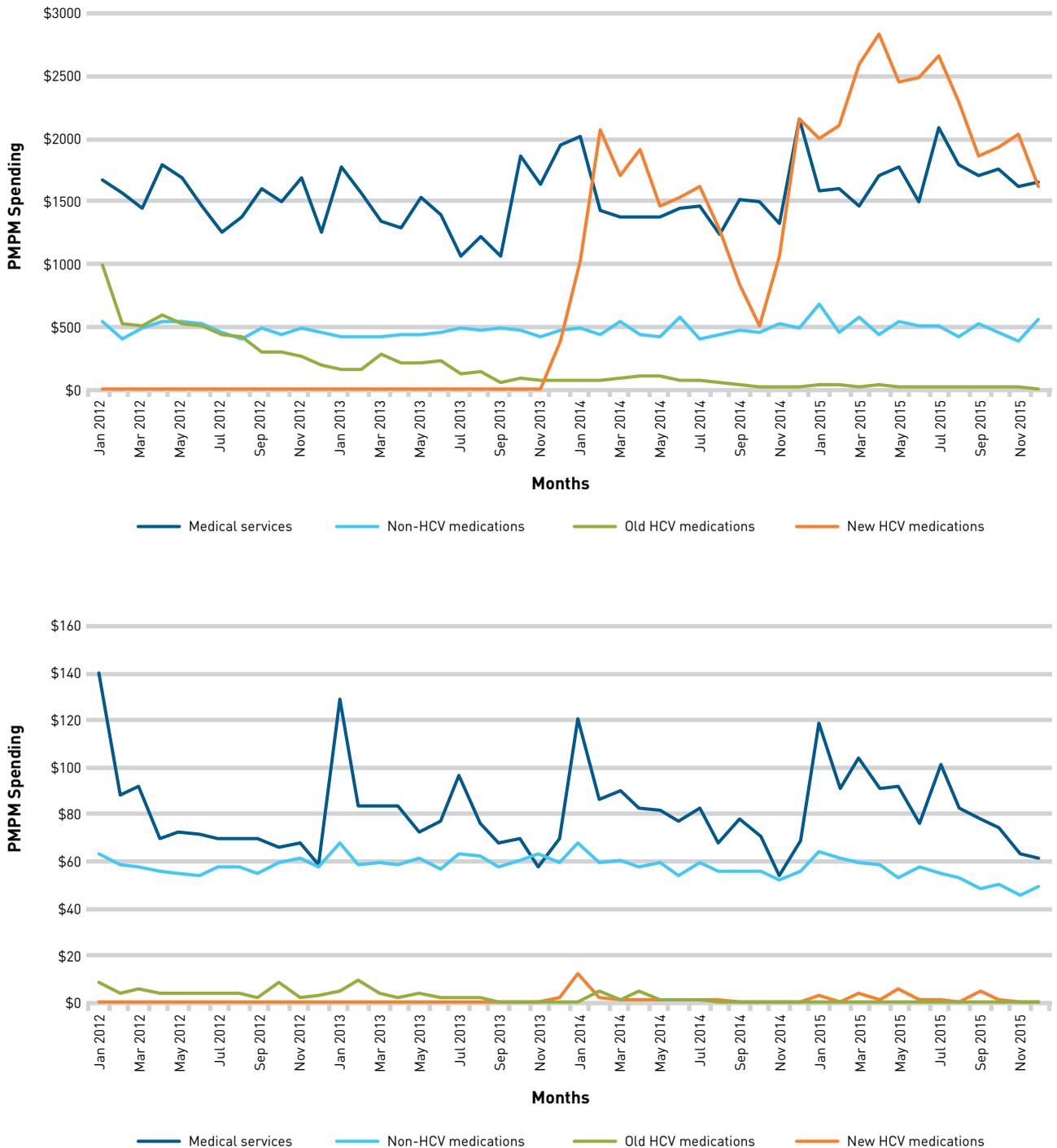
^cReceived at least 1 dispensing of an old or new HCV medication.

TABLE 3. Adjusted Pre-Post Analysis Estimates in Annual Health Plan and OOP Spending per Member With Chronic HCV Infection

	Baseline (2012-2013)	Follow-up (2014-2015)	Absolute Change (95% CI)	Relative Change % (95% CI)
Health plan spending per member with chronic HCV				
Total pharmacy spending	\$6924.88	\$21,110.26	\$14,185.38 [\$12,267.46-\$16,103.31]	204.9 (166.0-243.7)
Pharmacy spending on HCV medications	\$2868.58	\$16,503.62	\$13,635.04 [\$11,708.45-\$15,561.63]	475.3 (352.3-598.4)
Pharmacy spending on non-HCV medications	\$4201.40	\$4763.89	\$562.49 [\$34.17-\$1090.81]	13.4 (0.6-26.2)
Medical spending	\$13,759.92	\$14,377.19	\$617.27 [-\$1019.10 to \$2253.64]	4.5 (-7.7 to 16.7)
Total health plan spending (pharmacy, medical)	\$20,734.00	\$37,201.09	\$16,467.08 [\$13,938.85-\$18,995.32]	79.4 (63.8-95.0)
OOP spending per member with chronic HCV				
Total pharmacy OOP spending	\$583.79	\$626.39	\$42.61 [-\$65.64 to \$151.40]	7.3 (-11.6 to 26.2)
Pharmacy OOP spending on HCV medications	\$40.50	\$93.66	\$53.16 [\$9.06-\$97.27]	131.3 (15.2-247.3)
Pharmacy OOP spending on non-HCV medications	\$564.37	\$529.69	-\$34.68 [-\$80.79 to \$11.44]	-6.1 (-13.9 to 1.6)
Medical OOP spending	\$755.13	\$787.52	\$32.39 [-\$11.46 to \$76.24]	4.3 (-1.6 to 10.2)
Total OOP spending (pharmacy, medical)	\$1325.12	\$1392.40	\$67.28 [-\$45.04 to \$179.60]	5.1 (-3.5 to 13.7)
OOP spending per HCV medication user				
Pharmacy OOP spending for HCV medications	\$636.35	\$570.43	-\$65.92 [-\$147.44 to \$15.61]	-10.4 (-22.2 to 1.5)
Pharmacy OOP spending for non-HCV medications	\$668.19	\$629.02	-\$39.16 [-\$369.76 to \$291.43]	-5.9 (-54.8 to 43.1)
Medical OOP spending	\$962.11	\$843.04	-\$119.07 [-\$254.71 to \$16.58]	-12.4 (-25.2 to 0.5)
Total OOP spending (pharmacy, medical)	\$2221.01	\$2071.79	-\$149.22 [-\$783.68 to \$485.23]	-6.7 (-34.6 to 21.2)

HCV indicates hepatitis C virus; OOP, out-of-pocket.

FIGURE. Inflation-Adjusted Average Monthly Spending Among Individuals With Chronic HCV Infection: (A) Average Medical and Pharmacy Health Plan Spending PMPM and (B) Average Medical and Pharmacy OOP Spending PMPM*



HCV indicates hepatitis C virus; OOP, out-of-pocket; PMPM, per member per month.

*Old HCV medications included were boceprevir (Victrelis), telaprevir (Incivek), interferon and peginterferon, and ribavirin. New HCV medications included were daclatasvir dihydrochloride (Daklinza), ledipasvir/sofosbuvir (Harvoni), simeprevir sodium (Olysio), sofosbuvir (Sovaldi), ombitasvir/paritaprevir/ritonavir (Technivie), and ombitasvir/paritaprevir/ritonavir/dasabuvir sodium (Viekira Pak).

TABLE 4. Predictors of Receiving New HCV Medications (n = 589)

Characteristics	Multivariate Regression Results, aOR (95% CI)
Age group in years (years at first observed HCV diagnosis) ^a	
<30	Reference
30-49	1.61 (0.95-2.72)
50-64	2.13 (1.29-3.53)
≥65	2.01 (1.14-3.55)
Sex	
Female	Reference
Male	1.13 (0.92-1.38)
Median household income ^b	
Quartile 1 (\$15,558-\$51,835)	Reference
Quartile 2 (\$51,849-\$70,248)	0.94 (0.68-1.30)
Quartile 3 (\$70,313-\$85,762)	0.96 (0.68-1.35)
Quartile 4 (\$85,798-\$199,599)	0.92 (0.65-1.29)
Missing	
Race/ethnicity (based on zip code) ^b	
White	Reference
Black	0.95 (0.45-2.04)
Hispanic (n = 0)	–
Other (n = 0)	–
Mixed	0.79 (0.59-1.07)
Education ^b	
Low	Reference
Middle	0.84 (0.54-1.32)
High	0.75 (0.45-1.26)
Enrollment	
Number of months enrolled per member	1.03 (1.02-1.04)
Prior HCV treatment	
Received HCV medication before new DAAs available	0.72 (0.50-1.03)
Comorbid diagnoses ^a	
Hepatic decompensation	0.99 (0.76-1.29)
Liver cirrhosis	3.34 (2.64-4.21)
Status post liver transplant	1.29 (0.80-2.09)
HIV	1.10 (0.65-1.87)
Substance abuse (alcohol)	0.70 (0.53-0.92)
Substance abuse (opioids)	1.12 (0.73-1.70)
Substance abuse (other drugs)	0.84 (0.58-1.22)
Any mental illness ^a	0.85 (0.70-1.04)
Any physical illness other than liver disease ^a	0.77 (0.63-0.94)

aOR indicates adjusted odds ratio; DAA, direct-acting antiviral; HCV, hepatitis C virus; ICD-9, *International Classification of Diseases, Ninth Revision*.

^aCohort members had at least 1 claim with ICD-9 code 070.44 or 070.54 in any of 10 diagnosis fields during the study period (1/1/2012-12/31/15); comorbid diagnoses are defined based on occurrence of at least 1 claim with a relevant ICD-9 code during the study period.

^bWe used data from the American Community Survey (2011-2015) to classify members by neighborhood [zip code] income quartile. We classified members as residing in white, black, Hispanic, or other neighborhoods based on living in neighborhoods with 66% or more persons of the given race/ethnicity. We classified members from areas that did not fall into one of the race/ethnicity categories as residing in mixed race/ethnicity neighborhoods. We used members' neighborhood characteristics as a proxy for education (below-high-school education levels of <15%, 15%-24.9%, or >25%) and classified members as residing in areas with a high, middle, or low education level, respectively.

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the highest-risk patients, health plans modified reimbursement restrictions to enable broader access.^{36,37} The requirement of a high fibrosis score was later lifted by many payers,³⁸ including the health plan in our study in 2016. In addition, the study health plan now allows prescribing of DAAs by nonspecialist physicians in consultation with a gastroenterologist, infectious disease specialist, or hepatologist to enhance patient access.³⁹

However, the study health plan still requires providers to attest that the patient is not participating in illicit substance abuse or alcohol abuse, or is receiving substance or alcohol abuse counseling services as an adjunct to HCV treatment (this requirement is to be lifted in 2020). We found that having a diagnosis of substance abuse (specifically, alcohol abuse) was negatively associated with receiving new DAAs, which is not surprising given the reimbursement requirements. Alcohol consumption has been associated with more rapid fibrosis progression.^{40,41} Moreover, the risk of reinfection among HCV-infected individuals who inject drugs could lower the efficient use of finite resources.⁴² This provider attestation requirement aims to ensure that patients are committed to limiting further liver damage and injectable drug use in an effort to prevent reinfection. Nevertheless, clinical guidelines⁴³ suggest that recent or active injectable drug use is not a contraindication to DAAs, as adherence and efficacy rates are comparable between patients who do and do not use injectable drugs. The difference between prescribing restrictions and guideline recommendations possibly reflects, in part, the wedge between cost-effectiveness and affordability considerations.⁴⁴ The availability of more DAAs has facilitated expanded access because of increased market competition, allowing commercial payers like HPHC⁴⁵ to negotiate rebates.²⁰ Interbrand competition⁴⁶ seems to have decreased published prices,⁴⁷ which is unusual before patent expiration (sofosbuvir's patent will be the first to expire in 2028). The budgetary impact of expanded access should be considered in light of potential future cost savings related to treating patients early (eg, costs avoided for treating cirrhosis, liver failure, carcinoma, and liver transplantation).

Among this population of commercially insured patients with HCV, the advent of highly priced DAAs had a relatively small absolute impact on member OOP spending on HCV medications. Following availability of new DAAs, average annual OOP spending on HCV medications across members with this condition increased by about \$53 per member; OOP spending on HCV medications did not change significantly among the subset of patients receiving HCV medications. However, average annual health plan spending on HCV medications per member with HCV increased by 475%, or \$13,635, after the advent of new DAAs. The health plan contributed more than 99% of spending on HCV medications both before and after the availability of new DAAs. Given that the average membership duration is about 2 to 3 years in most commercial health plans,^{48,49} financial benefits following cure of HCV infection by new DAAs (eg, costs avoided for hospitalizations due to progressed disease or liver transplants) might not be realized during the enrollment

span of most members receiving treatment. Indeed, we did not detect changes in medical spending by the health plan for the study population during the median 2.7-year follow-up.

DAA for HCV are only one class of high-priced specialty medications that pose increasing financial burden on patients, providers, payers, employers (because private payers are in many cases simply administering insurance services as decided by employers that self-insure), and society. In 2017, specialty medications accounted for 31% of spending on prescription medications under Medicare, 42% in state Medicaid programs, and 49% among commercial health plans.⁵⁰ Specialty medications come to market at increasingly high prices, often costing more than \$2000 per month per patient.⁵¹⁻⁵³ Increased access to specialty medications will likely lead to higher premiums and/or deductibles, higher member cost sharing, or both, thus threatening affordability and equity in access to healthcare in general and potentially harming health.⁵⁴ These are major concerns for the American public,⁵⁵ and there is “a moral obligation to improve access [to DAAs and other highly effective, highly priced medications] by reforming approaches to drug pricing.”⁵⁶ Payers and employers need to find ways to negotiate prices and streamline access for patients who can benefit most from effective innovations. Alternative payment approaches are being explored in the United States and worldwide. For example, the Louisiana Department of Health has approved a “subscription” or “Netflix” model to pay for HCV treatment for the state’s residents. This model involves a cross-payer coalition in the state: In exchange for subscription fees over a fixed number of years, the drug companies would provide access to HCV therapies and commit to patient and provider outreach efforts to enhance treatment rates.⁵⁷ Australia’s model⁵⁸ involves approximately AUD\$1 billion (US\$766 million) over 5 years in exchange for an unlimited volume of DAAs for HCV from drug companies. Early evidence suggests that such a model may result in lower per-patient prices, broader (or even universal) access to new drugs with certainty about the cost, and increases in market access for pharmaceutical companies with guaranteed revenue over the years of the agreement.⁵⁸

Limitations

Our study has several limitations. First, claims data do not allow for studying outcomes, and a 4-year time window does not capture long-term clinical or financial impact for members or the payer. We did not have information on rebates to the payer or on manufacturer coupons to patients, so we may have overestimated their spending. For HCV medications, pharmaceutical manufacturer coupons are available to lower a member’s cost to \$5 per prescription fill, up to a maximum of 25% of the catalog price of a 12-week regimen.⁵⁹ However, the health plan’s net medication spending increased from 20% to 25% of total healthcare spending between 2011 and 2016, and ledipasvir/sofosbuvir was the health plan’s third most reimbursed product by value, accounting for \$16 million net spending in 2016.⁶⁰ OOP spending included co-payments, coinsurance, and deductible amounts, but we did not have information on premiums. We also did not have information on individuals who did not apply for prior

authorization for DAA treatment nor on those who were denied approval. Given the data available at the time of the analysis, our study provides insights into the early experience of restricted access to DAAs; future research should examine the outcomes of expanded access to DAAs following removal of several reimbursement requirements and the decline of DAA drug prices. Lastly, an important economic component is the operation cost of prior authorization for these medicines, which is beyond the scope of this study. Prior authorization is commonly used to manage specialty medications. Prior authorization can be time-consuming, not only for providers who must complete paperwork but also for the health plan to review applications and adjudicate appeals. Prior authorization has been shown to be costly for all involved,^{61,62} and research is needed to estimate its costs given that more and more products, especially specialty medications, require prior authorization.

CONCLUSIONS

The proportion of a commercially insured population with HCV infection who were treated with HCV medications doubled within 2 years following availability of new DAAs. These medications can cure a prevalent, potentially fatal, chronic infectious disease, but they have a high price. Based on the experience of a regional commercial health plan, on average, patient OOP spending was kept low while the health plan covered 99% of spending on new HCV medications. In our 2-year follow-up period (similar to the average health plan enrollment spans of commercially insured members), we did not observe financial benefits of the cure of HCV infection by new DAAs. ■

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eAppendix Table 1. 2014-2015 Criteria for approval and denial of reimbursement of hepatitis C medications at Harvard Pilgrim Health Care

Inclusion-criteria common to most medications	
Age	
All medications	18 years old
Diagnosis	
All medications	Chronic hepatitis C genotype 1 or 1b, 2, 3, 4, 5 or 6
Required concomitant therapies	
7 out of 8 medications (not including daclatasvir dihydrochloride (Daklinza))	Ribavirin
Liver disease/liver transplant status	
Daclatasvir dihydrochloride (Daklinza), ledipasvir/sofosbuvir (Harvoni), simeprevir sodium (Olysio), sofosbuvir (Sovaldi), ombitasvir/paritaprevir/ritonavir (Technivie), ombitasvir/paritaprevir/ritonavir/dasabuvir sodium (Viekira Pak)	Patient's liver disease been staged using either an invasive or non-invasive testing method (e.g., liver biopsy confirming METAVIR score, Ishak score, transient elastography (Fibroscan) score, FibroTest/FibroSURE score, or radiological imaging) within the past 3 years
6 out of 8 medications Daclatasvir dihydrochloride (Daklinza), ledipasvir/sofosbuvir (Harvoni), sofosbuvir (Sovaldi), and ombitasvir/paritaprevir/ritonavir/dasabuvir sodium (Viekira Pak))	Evidence of stage 2 or greater hepatic fibrosis: <ul style="list-style-type: none"> • Liver biopsy confirming a METAVIR score of F2, F3 or F4 • Ishak Score ≥ 3 • Transient elastography (Fibroscan) score ≥ 7.5 kPa • FibroTest (FibroSURE) score ≥ 0.48 • Radiological imaging demonstrating cirrhosis (e.g., evidence of portal hypertension or ascites)
4 out of 8 medications	
Other requirements	
All medications	Prescribed by a gastroenterologist, infectious disease specialist, or a physician specializing in the treatment of hepatitis (e.g. hepatologist)
Daclatasvir dihydrochloride (Daklinza), ledipasvir/sofosbuvir (Harvoni), sofosbuvir (Sovaldi) (not mention in 2014), ombitasvir/paritaprevir/ritonavir (Technivie), ombitasvir/paritaprevir/ritonavir/dasabuvir sodium (Viekira Pak)	The provider attested that the patient is not currently participating in illicit substance abuse or alcohol abuse, or that the patient is receiving substance or alcohol abuse counseling services as an adjunct to HCV treatment
5 out of 8*	

Ombitasvir/paritaprevir/ritonavir/dasabuvir sodium (Viekira Pak), ombitasvir/paritaprevir/ritonavir (Technivie), Sofosbuvir (Sovaldi)	Prescriber indicated that treatment with Harvoni would be clinically inappropriate, or that the patient was, or will be, unable to tolerate treatment with Harvoni
--	--

3 out of 8 medications

Exclusion-criteria common to most medications

Liver disease/liver transplant status

Daclatasvir dihydrochloride (Daklinza), ledipasvir/sofosbuvir (Harvoni), sofosbuvir (Sovaldi), ombitasvir/paritaprevir/ritonavir (Technivie), and ombitasvir/paritaprevir/ritonavir/dasabuvir sodium (Viekira Pak)	End stage renal disease, or required dialysis
--	---

5 out of 8 medications

Ombitasvir/paritaprevir/ritonavir (Technivie), Ombitasvir/paritaprevir/ritonavir/dasabuvir sodium (Viekira Pak), Daclatasvir (Daklinza)	Recurrent hepatitis C post liver transplant
--	---

3 out of 8 medications

All medications	Decompensated cirrhosis
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Pre-treatment and response

All medications	Currently taking: a strong inducer of CYP3A (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, or St. John's Wort)
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Other criteria for denial

Boceprevir (Victrelis), telaprevir (Incivek), simeprevir sodium (Olysio), ledipasvir/sofosbuvir (Harvoni)	Co-infection with HIV or hepatitis B or a history of previous solid organ transplant
---	--

4 out of 8 medications

* In 2014 PA for Sofosbuvir (Sovaldi) attestation by a medical professional regarding alcohol or substance abuse was not mentioned and then added in during later years

Notes:

All medications refers to: Boceprevir (Victrelis), telaprevir (Incivek), daclatasvir dihydrochloride (Daklinza), ledipasvir/sofosbuvir (Harvoni), simeprevir sodium (Olysio), sofosbuvir (Sovaldi), ombitasvir/paritaprevir/ritonavir (Technivie), ombitasvir/paritaprevir/ritonavir/dasabuvir sodium (Viekira Pak)

eAppendix Table 2. Codes Used to Create Comorbidities

Comorbidities	Codes
Hepatic decomposition	ICD-9-CM: 070.41, 070.44, 070.49, 070.6, 155.0, 456.0, 456.1, 456.2x, 567.0, 567.2x, 567.8x, 567.9, 570, 572.2, 572.3, 572.4, 572.8, 789.5x
Liver cirrhosis	ICD-9-CM: 571.2, 571.5
Liver Transplant	ICD-9-CM: V42.7, 996.82, ICD-9-CM Procedure: 505
HIV	ICD-9-CM: 042, V08
Substance abuse alcohol	ICD-9-CM: 291.xx, 303.x, 305.0, 535.3, 571.0, 571.1, 571.2, 571.3
Substance abuse opioid	ICD-9-CM: 304.0
Substance abuse other drugs	ICD-9-CM: 292.xx, 304.1, 304.2, 304.3, 304.4, 304.5, 304.6, 304.7, 304.8, 304.9, 305.2, 305.3, 305.4, 305.5, 305.6, 305.7, 305.8, 305.9, 648.3
Severe mental illness	ICD-9-CM: 296.4, 296.5, 296.6, 296.7, 296.8x, 294.0, 294.8, 294.9, 295.x, 296.9x, 297.x, 298.x, 299.8, 299.9
Major and other depression	ICD-9-CM: 296.2, 296.3, 300.4, 311
Other mental illness	ICD-9-CM: 294.1, 296.0, 296.1, 300.0x, 300.1x, 300.2x, 300.3, 300.5, 300.6, 300.7, 300.8x, 300.9, 301.x, 302.x, 306.x, 307.x, 308.x, 309.0, 309.1, 309.2x, 309.3, 309.4, 309.8x, 309.9, 312.xx, 313.xx, 314.xx, 316
Chronic pulmonary disease	ICD-9-CM: 416.8, 416.9, 490.x–505.x, 506.4, 508.1, 508.8
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	ICD-9-CM: 140.x–172.x, 174.x–195.8, 200.x–208.x, 238.6
Metastatic solid tumor	ICD-9-CM: 196.x–199.x
Congestive heart failure	ICD-9-CM: 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x
Myocardial infarction	ICD-9-CM: 410.x, 412.x
Diabetes, uncomplicated	ICD-9-CM: 250.0–250.3
Diabetes, complicated	ICD-9-CM: 250.4–250.9

eAppendix Table 3. Inflation-adjusted average yearly spending per member with chronic hepatitis C virus infection, 2012-2015* (2015 US \$)

	Year 2012	Year 2013	Year 2014	Year 2015
Number of members with chronic hepatitis C, n	2,299	2,447	2,363	2,091
Total months of enrollment among members with chronic hepatitis C, n	25,046	26,087	23,382	18,759
Health plan costs per member with chronic hepatitis C				
Total pharmacy costs	\$7,908.08	\$5,173.66	\$16,217.10	\$24,342.73
Pharmacy costs for HCV medications	\$3,878.63	\$1,482.67	\$12,336.43	\$19,912.88
Pharmacy costs for non-HCV medications	\$4,029.45	\$3,690.99	\$3,880.67	\$4,429.85
Medical costs	\$12,877.68	\$12,127.76	\$12,554.13	\$12,561.32
Total health plan costs (pharmacy, medical)	\$20,785.76	\$17,301.42	\$28,761.23	\$37,904.05
OOP costs per member with chronic hepatitis C				
Total pharmacy OOP	\$568.20	\$547.87	\$548.05	\$575.73
Pharmacy OOP for HCV medications	\$41.48	\$24.64	\$59.11	\$95.98
Pharmacy OOP for non-HCV medications**	\$526.72	\$523.23	\$488.94	\$479.75
Medical OOP	\$655.18	\$663.21	\$661.88	\$669.33

Total OOP (pharmacy, medical)	\$1,223.38	\$1,211.08	\$1,209.93	\$1,245.15
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OOP costs per HCV medication user

Individuals with chronic hepatitis C receiving a HCV medication, n	212	89	267	409
Pharmacy OOP for HCV medications	\$449.86	\$677.56	\$523.11	\$490.70
Pharmacy OOP for non-HCV medications	\$588.86	\$614.54	\$552.29	\$548.04
Medical OOP	\$828.57	\$1018.79	\$833.25	\$782.85
Total OOP (pharmacy and medical)	\$1867.30	\$2310.89	\$1908.66	\$1821.59

OOP costs per member not receiving any HCV medication in any of the study years

Individuals not receiving a HCV medication in any of the study years, N	1711	1796	1674	1432
Pharmacy for OOP non-HCV medications	\$507.32	\$514.40	\$470.90	\$455.70
Medical OOP	\$651.06	\$658.15	\$636.31	\$656.80
Total OOP (pharmacy and medical)	\$1158.38	\$1172.55	\$1107.21	\$1112.50

OOP costs per member not receiving any HCV medication in the respective calendar year

Individuals not receiving a HCV	2087	2358	2096	1682
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medication in the calendar year,*** N				
Pharmacy for OOP non-HCV medications	\$520.40	\$519.78	\$480.87	\$463.14
Medical OOP	\$637.57	\$649.79	\$640.05	\$641.73
Total OOP (pharmacy and medical)	\$1157.97	\$1169.58	\$1120.92	\$1104.87

*Test for trend using time series regression. No significant trend detected unless otherwise noted.

** P value <.05

*** Members may have received HCV medication in other study years

eAppendix Table 4. Inflation-adjusted median (25th and 75th percentile) yearly spending per member with chronic hepatitis C virus infection, 2012-2015 (2015 US \$)

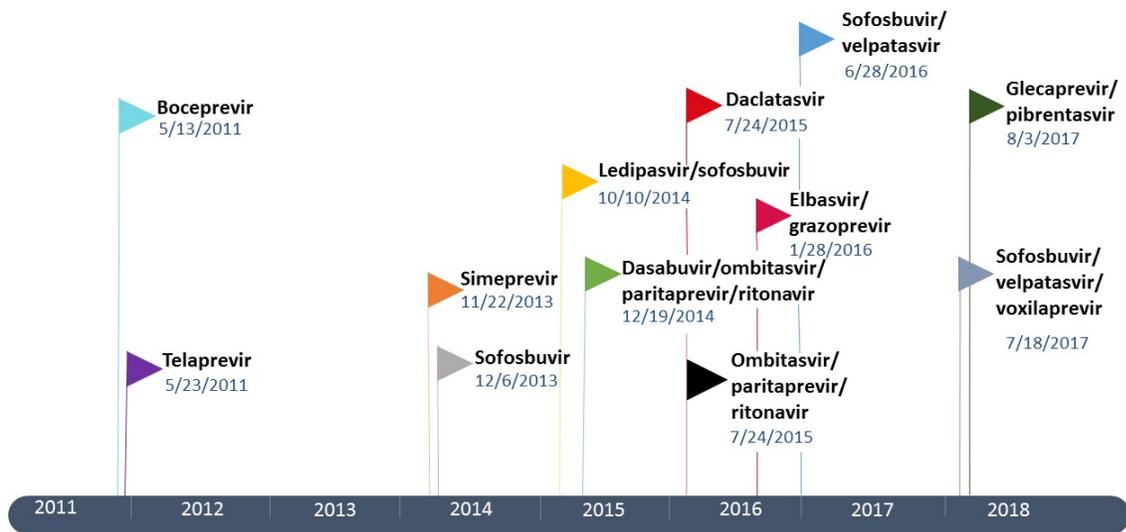
	Year 2012	Year 2013	Year 2014	Year 2015
Number of members with chronic hepatitis C, n	2,299	2,447	2,363	2,091
Total months of enrollment among members with chronic hepatitis C, n	25,046	26,087	23,382	18,759
Health plan costs per member with chronic hepatitis C				
Total pharmacy costs	\$626.72 (\$27.03, \$3,999.67)	\$374.49 (\$13.86, \$2,853.73)	\$527.39 (\$27.66, \$4,746.14)	\$1,067.71 (\$40.27, \$13,135.35)
Pharmacy costs for HCV medications	\$0.00 (\$0.00, \$0.00)	\$0.00 (\$0.00, \$0.00)	\$0.00 (\$0.00, \$0.00)	\$0.00 (\$0.00, \$0.00)
Pharmacy costs for non-HCV medications	\$456.13 (\$21.54, \$2,676.86)	\$332.99 (\$12.19, \$2,426.58)	\$336.43 (\$17.0, \$2,518.64)	\$360.45 (\$18.12, \$2,760.05)
Medical costs	\$3,421.64 (\$1,050.50, \$9,010.23)	\$2,765.38 (\$889.88, \$8,616.72)	\$2,829.19 (\$907.08, \$8,609.88)	\$2,845.45 (\$900.24, \$8,099.82)
Total health plan costs (pharmacy, medical)	\$5,709.59 (\$1,733.92, \$19,552.05)	\$4,660.75 (\$1,425.99, \$15,139.59)	\$5,384.43 (\$1,491.51, \$22,556.99)	\$7,241.43 (\$1,702.32, \$40,444.59)
OOP costs per member with chronic hepatitis C				
Total pharmacy OOP	\$335.17 (\$91.92, \$756.90)	\$293.67 (\$168.17, \$713.20)	\$302.22 (\$81.96, \$701.77)	\$300 (\$89.67, \$702.07)
Pharmacy OOP for HCV medications	\$0.00 (\$0.00, \$0.00)	\$0.00 (\$0.00, \$0.00)	\$0.00 (\$0.00, \$0.00)	\$0.00 (\$0.00, \$0.00)
Pharmacy OOP for non-HCV medications	\$302.78 (\$81.10, \$702.89)	\$283.18 (\$62.93, \$691.90)	\$270.79 (\$71.71, \$660.79)	\$260.00 (\$70.00, \$640.00)
Medical OOP	\$346.04 (\$94.33, \$821.10)			\$300.00 (\$90.00, \$790.00)

		\$314.65 (\$90.3, \$830.67)	\$307.34 (\$97.33, \$823.05)	
Total OOP (pharmacy, medical)	\$829.78 (\$335.22, \$1,654.48)	\$760.40 (\$304.37, \$1,582.45)	\$763.65 (\$307.34, \$1,628.88)	\$778.14 (\$330.00, \$1,598.7)

OOP costs per HCV medication user

Individuals with chronic hepatitis C receiving a HCV medication, n	212	89	267	409
Pharmacy OOP for HCV medications	\$302.78 (\$151.39, \$454.17)	\$241.23 (\$104.88, \$419.53)	\$225.39 (\$97.33, \$338.08)	\$90.00 (\$60.00, \$180.00)
Pharmacy OOP for non-HCV medications	\$415.24 (\$132.46, \$857.87)	\$418.46 (\$110.13, \$887.30)	\$332.96 (\$102.45, \$778.61)	\$339.00 (\$98.76, \$708.42)

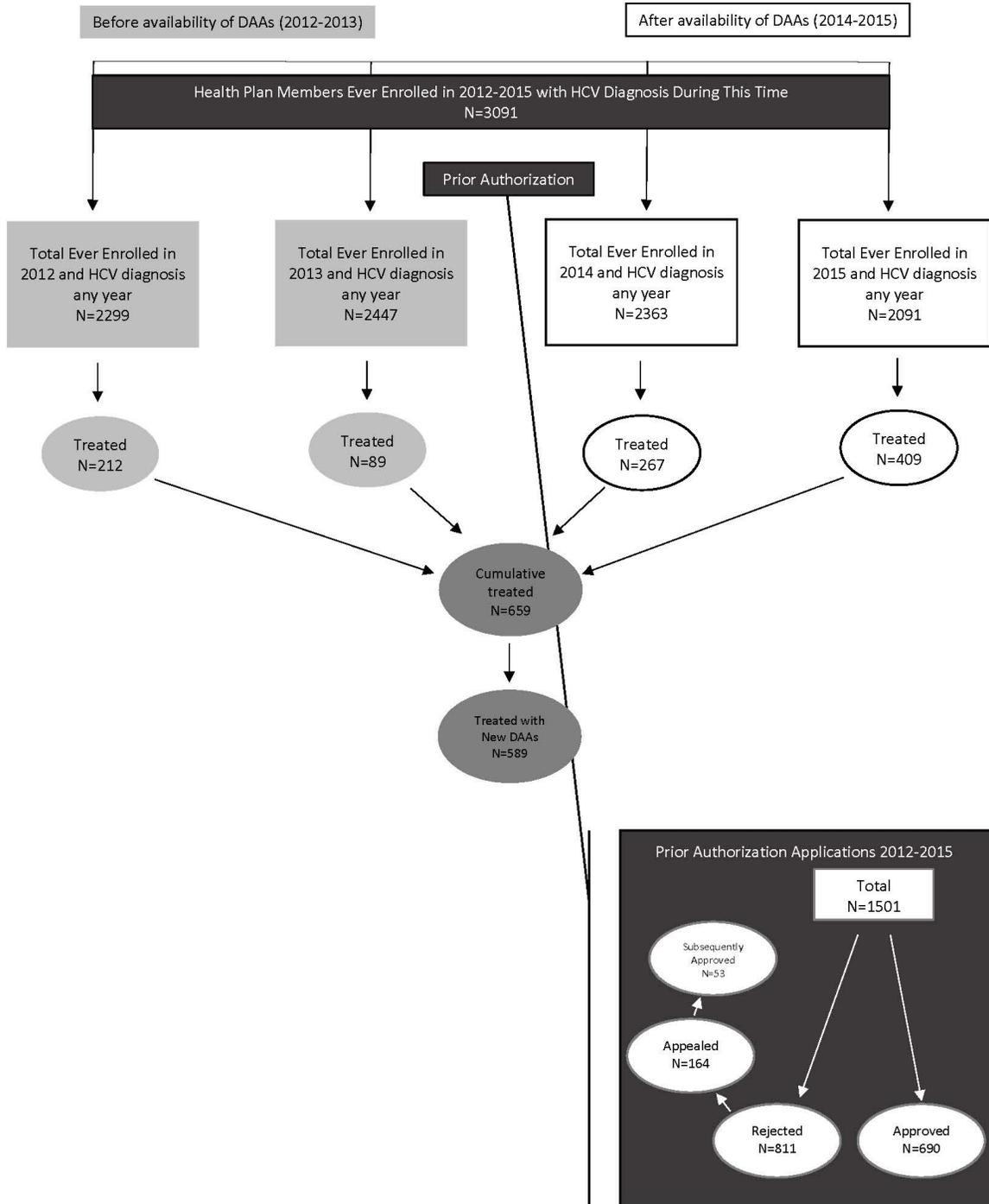
eAppendix Figure 1. FDA approvals of DAAs for hepatitis C



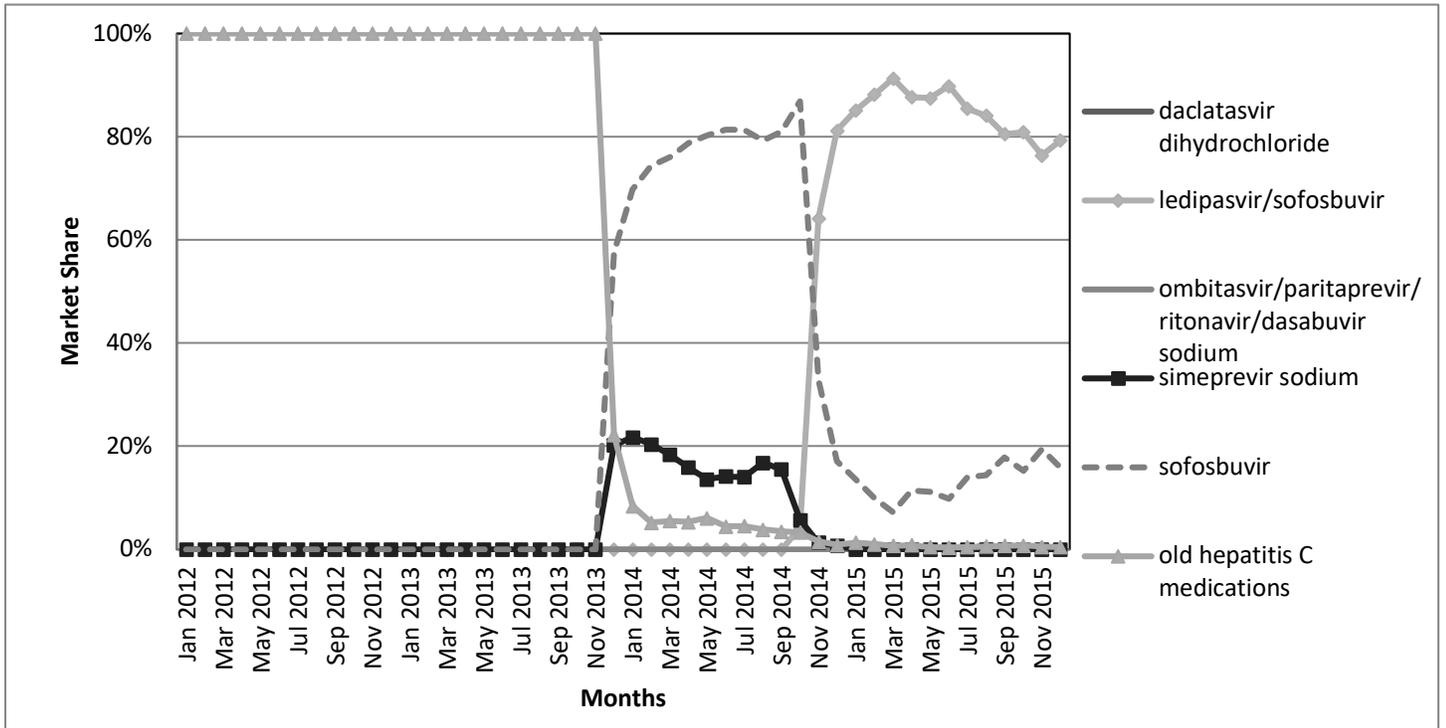
Note: DAAs=direct acting antivirals; FDA=Food and Drug Administration, information from

<https://www.accessdata.fda.gov/scripts/cder/drugsatfda/>

eAppendix Figure 2. Cascading flow chart for the analytical cohort



eAppendix Figure 3. Market share of new DAAs among all hepatitis C medications, based on pharmacy spending



Footnote: Old hepatitis C medications include: boceprevir (Victrelis), telaprevir (Incivek), peginterferon, and ribavirin

eAppendix Figure 4. Market share of individual DAAs based on numbers of patients treated by these medications

