Annals of Internal Medicine ORIGINAL RESEARCH

Cost-Effectiveness and Budget Impact of Hepatitis C Virus Treatment With Sofosbuvir and Ledipasvir in the United States

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Background: Sofosbuvir and ledipasvir, which have recently been approved for treatment of chronic hepatitis C virus (HCV) infection, are more efficacious and safer than the old standard of care (oSOC) but are substantially more expensive. Whether and in which patients their improved efficacy justifies their increased cost is unclear.

Objective: To evaluate the cost-effectiveness and budget impact of sofosbuvir and ledipasvir.

Design: Microsimulation model of the natural history of HCV infection.

Data Sources: Published literature.

Target Population: Treatment-naive and treatment-experienced HCV population defined on the basis of HCV genotype, age, and fibrosis distribution in the United States.

Time Horizon: Lifetime.

Perspective: Third-party payer.

Intervention: Simulation of sofosbuvir–ledipasvir compared with the oSOC (interferon-based therapies).

Outcome Measures: Quality-adjusted life-years (QALYs), incremental cost-effectiveness ratios (ICERs), and 5-year spending on antiviral drugs.

Results of Base-Case Analysis: Sofosbuvir-based therapies added 0.56 QALY relative to the oSOC at an ICER of $55 400 per additional QALY. The ICERs ranged from $9700 to $284 300 per QALY depending on the patient's status with respect to treatment history, HCV genotype, and presence of cirrhosis. At a willingness-to-pay threshold of $100 000 per QALY, sofosbuvir-based therapies were cost-effective in 83% of treatment-naive and 81% of treatment-experienced patients. Compared with the oSOC, treating eligible HCV-infected persons in the United States with the new drugs would cost an additional $65 billion in the next 5 years, whereas the resulting cost offsets would be $16 billion.

Results of Sensitivity Analysis: Results were sensitive to drug price, drug efficacy, and quality of life after successful treatment.

Limitation: Data on real-world effectiveness of new antivirals are lacking.

Conclusion: Treatment of HCV is cost-effective in most patients, but additional resources and value-based patient prioritization are needed to manage patients with HCV.

Primary Funding Source: National Institutes of Health.

Ann Intern Med. 2015;162:397-406. doi:10.7326/M14-1336 **www.annals.org**
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More than 3 million persons are chronically infected with hepatitis C virus (HCV) in the United States, and most of them are undiagnosed (1, 2). Infection with HCV is the leading cause of hepatocellular carcinoma (HCC) and is the most common indication for liver transplantation (3). In 2011, the economic burden associated with chronic HCV infection in the United States was $6.5 billion (4).

The recent approval of 3 new drugs—sofosbuvir, a first-in-class, once-daily HCV RNA polymerase inhibitor; simeprevir, a once-daily protease inhibitor; and sofosbuvir plus ledipasvir, the first oral combination therapy—by the U.S. Food and Drug Administration (FDA) marked the beginning of a new era for HCV treatment (5–7). Until then, the old standard of care (oSOC) was based on peginterferon and ribavirin with or without boceprevir and telaprevir. With the advent of the new drugs, HCV treatment can for the first time be provided without interferon-based therapy, which is associated with considerable toxicity (8). As a result, many patients who were unable to tolerate previous therapies are now eligible for HCV treatment. These agents are superior, with sustained virologic response (SVR) rates greater than 95% in most patients and shorter duration of treatment and fewer adverse effects than the oSOC (9, 10).

To guide clinicians, the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America jointly published a practice guideline with new recommendations for HCV treatment as a Web document with plans for ongoing updates (11). These recommendations include FDA-approved as well as off-label drug combinations of sofosbuvir and ledipasvir.

Enthusiasm for the new drugs has been dampened by their cost: Sofosbuvir is currently priced at $1000 per day and sofosbuvir–ledipasvir at $1125 per day. The total cost of treatment can be as high as $150 000 per patient. The high price of sofosbuvir has drawn criticism from patient advocates (12), U.S. lawmakers (13), the World Health Organization (14), and private payers (15), especially given that its manufacturing cost is $200 for 12-week treatment (16). Challenged with the budget needed to treat all patients with HCV, at least 35 U.S. states have restricted these treatments to Medicaid

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Context

Newly approved drug regimens for hepatitis C virus (HCV) treatment seem more efficacious and safer than older regimens but are expensive.

Contribution

In a cost-effectiveness analysis, combination therapy with sofosbuvir and ledipasvir reduced HCV-related complications and was cost-effective for most patients. However, its use would cost an additional $65 billion over the next 5 years while offsetting only $16 billion of the overall cost of HCV care.

Caution

Not all data came from large randomized trials.

Implication

If prices remain at current levels, government and private providers will need additional financial resources or will need to prioritize patients for HCV treatment.

patients with advanced-stage disease (17). Similarly, private payers require prior authorization. With more than a million patients needing HCV treatment in the next 3 to 5 years in the United States, the high price of these drugs will substantially affect the budget of private payers and government (18). Treatment cost may, therefore, become the primary barrier to HCV eradication (19, 20).

The manufacturer contends that sofosbuvir-based treatment provides good value (21). However, it remains unclear whether and in which patients the improved benefits of new therapies justify the increased cost compared with the oSOC. In addition, the total spending on new drugs required to treat a large number of patients with HCV is not known. Therefore, the objective of our study was to evaluate the cost-effectiveness and budget impact of sofosbuvir–ledipasvir from a third-party payer's perspective.

METHODS

We developed a Markov-based, individual-level, state-transition model, MATCH (Markov-based Analyses of Treatments for Chronic Hepatitis C), that simulated the clinical course of patients with HCV who received antiviral treatment. We used a weekly cycle length to advance time in the model. The structure of the model was based on our previously published and validated Markov cohort model (22, 23).

Base-Case Population

Our base-case population comprised HCV-infected patients in the United States. We defined a total of 120 patient profiles based on patients' treatment history (naive or experienced), interferon tolerance (yes or no [for treatment-naive patients only]), HCV genotype (1, 2, 3, or 4), sex (male or female), and METAVIR fibrosis score (F0 [no fibrosis], F1 [portal fibrosis without septa], F2 [portal fibrosis with few septa], F3 [numerous septa without fibrosis], or F4 [cirrhosis]) (24). We also assigned baseline ages according to fibrosis score by using a validated simulation model of the HCV disease burden in the United States (**Table 1** of the **Supplement**, available at www.annals.org) (25).

Treatment

For each of the 120 patient profiles, we simulated 2 scenarios: treatment using the oSOC and treatment with sofosbuvir–ledipasvir (**Table 1**) (11). We used efficacy data from the following recent clinical trials of sofosbuvir and ledipasvir in treatment-naive, treatment-experienced, and interferon-intolerant patients: ION-1 (26), ION-2 (10), ION-3 (27), NEUTRINO (9), FISSION (9), VALENCE (28), POSITRON (29), FUSION (29), and the Egyptian Ancestry study (30). We defined treatment ineligibility due to interferon intolerance as presence of 1 or more of the following conditions: bipolar disorder, anemia (hemoglobin level <100 g/L), pregnancy, or neutropenia (neutrophil count $<0.750 \times 10^9$ cells/L) (31). For efficacy data from comparator groups, we used either the aforementioned clinical trials (when the study included the oSOC) or published studies of protease inhibitors and peginterferon–ribavirin (32–40). The duration of treatment in our model varied between 8 and 48 weeks depending on treatment group, HCV genotype, and treatment history. We also included the possibility of early treatment discontinuation because of adverse events or clinical futility rules (for the oSOC only).

Natural History of HCV Infection

Patients who did not achieve SVR transitioned into the natural-history phase of the model, which was defined by using Markov health states. Patients could start in one of the Markov states defined on the basis of the degree of liver fibrosis (F0 to F4) (**Appendix Figure 1**, available at www.annals.org) and could develop decompensated cirrhosis, HCC, or both; receive a liver transplant; or die of a liver-related cause. Those who achieved SVR were assumed to transition into normal health status only if they did not have cirrhosis (stage F4). In patients with cirrhosis, we assumed that disease progressed even after achievement of SVR, although at a slower rate (41).

Data Sources for Transition Probabilities

We used a published meta-regression analysis to estimate fibrosis progression from stage F0 to F4 (**Table 2** of the **Supplement**) (42), which was dependent on the patient's baseline fibrosis score, HCV genotype, duration of HCV infection, sex, and age at HCV acquisition (42). We estimated disease progression in cirrhosis and decompensated cirrhosis from published observational studies (**Table 3** of the **Supplement**) (43, 44). Patients developing decompensated cirrhosis or HCC were eligible to receive a liver transplant (22, 45, 46) and had higher mortality (47). All patients were at higher risk for

Table 1. Treatment-Related Variables for Cost-Effectiveness Analysis of Sofosbuvir-Based Therapies and the oSOC

HCV Treatment, by Treatment History and Genotype	Reference	Regimen	Treatment Duration, *wk*	SVR Rate, %		Discontinuation Rate, %	Probability of Anemia, %	Duration of Anemia, *wk*
				No Cirrhosis	Cirrhosis			
Treatment-naive, interferon-tolerant patients								
Genotype 1								
SOF-LDV	26, 27	SOF-LDV	8*	97	–	1	1	1
		SOF-LDV	12*	96	97	1	1	2
oSOC	32, 33	BOC-PEG-RBV	28–48	67	52	28–42	49	15–21
		TEL-PEG-RBV	24–48	75	62	21	37	12
Genotype 2								
SOF-based	9	SOF-RBV	12	97	83	1	8	4
oSOC	9	PEG-RBV	24	81	62	11	11	8
Genotype 3								
SOF-based	28	SOF-RBV	24	94	92	2	11	7
oSOC	37	PEG-RBV	24	70	49	7	16	8
Genotype 4								
SOF-based	9	SOF-PEG-RBV	12	98	85	2	21	4
oSOC	36	PEG-RBV	48	58	32	7	16	18
Treatment-naive, interferon-intolerant patients†								
Genotype 1								
SOF-LDV	26, 27	SOF-LDV	8*	97	–	1	1	1
		SOF-LDV	12*	96	97	1	1	2
Genotype 2								
SOF-based	29	SOF-RBV	12	92	94	2	13	4
Genotype 3								
SOF-based	28	SOF-RBV	24	93	92	2	11	7
Genotype 4								
SOF-based	30	SOF-RBV	24	93	93	1	11	7
Genotypes 1–4								
oSOC	–	No treatment	–	0	0	–	–	–
Treatment-experienced patients								
Genotype 1								
SOF-LDV	10	SOF-LDV	12	95	–	0	0	–
		SOF-LDV	24	–	99	0	1	4
oSOC	38–40	BOC-PEG-RBV	36–48	58	52	27–33	41–47	16–19
		TEL-PEG-RBV	48	70	58	23–36	30	12
Genotype 2								
SOF-based	29	SOF-RBV	12	96	60	1	11	4
oSOC	34	PEG-RBV	24	65	51	7	16	8
Genotype 3								
SOF-based	28	SOF-RBV	24	85	60	2	11	7
oSOC	34	PEG-RBV	24	60	47	7	16	8
Genotype 4								
SOF-based	–‡	SOF-PEG-RBV	12	69	69	10	21	4
oSOC	34	PEG-RBV	48	31	24	40	16	14

BOC = boceprevir; HCV = hepatitis C virus; LDV = ledipasvir; oSOC = old standard of care; PEG = peginterferon; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response; TEL = telaprevir.

* In treatment-naive patients without cirrhosis, the duration of SOF-LDV depended on the patient's baseline HCV RNA level. Those with a level <6 000 000 IU/mL were considered eligible for 8 wk of treatment; others were considered eligible for 12 wk. In this patient group, 57% were eligible for 8 wk of treatment.

† ≥1 of the following conditions: bipolar disorder, anemia (hemoglobin level <100 g/L), pregnancy, or neutropenia (neutrophil count <0.750 × 10^9 cells/L).

‡ No clinical study evaluated SOF–PEG–RBV in patients with genotype 4 HCV. Therefore, we derived SVR rates for this combination by using data from another study that used SOF–RBV for 24 wk in these patients (30). We assumed that the addition of PEG would increase the SVR rates by 10 percentage points (i.e., from 59% to 69%).

non–liver-related death than the general population; therefore, we adjusted their all-cause mortality with sex-specific hazard ratios (2.58 for men and 1.97 for women) (48–50).

Medical Costs

The model was developed from a third-party payer perspective. All costs were converted to a 2014 baseline by using the Consumer Price Index (51). The weekly costs of sofosbuvir and ledipasvir were $7000 and $875, respectively (52). The weekly costs of peginterferon, ribavirin, boceprevir, and telaprevir were $587, $309, $1100, and $4100, respectively (52). Because most payers receive discounts, we applied the average discount of 11% to all drugs (**Supplement**). We used our previously published study to estimate health state–specific annual costs (22, 53).

Quality-of-Life Weights

We assigned lower quality-of-life (QOL) weights to patients receiving treatment with interferon-based therapies than those receiving all-oral therapies (Table 3 of the Supplement). Patients who developed anemia had a further decrement in QOL for the duration of anemia (54). We assigned health state–specific QOL weights from a previously published study that used the EuroQol-5D instrument (55, 56) and adjusted these weights to the U.S. population norm (Table 4 of the Supplement) (57). We assumed the QOL of patients who achieved SVR to be equivalent to that of the general population (55).

Cost-Effectiveness Analysis

We validated our natural-history model with a recently published multicenter follow-up study of patients with advanced fibrosis and with previously published cost-effectiveness studies (Table 5 of the Supplement) (22, 56, 58, 59). In patients who did not achieve SVR, the predicted 10-year cumulative incidence of decompensated cirrhosis, HCC, and liver-related death plus liver transplantation was within the range of reported values (58). In patients with cirrhosis who achieved SVR and continued to progress, the predicted cumulative incidence of HCC was within the reported range; however, the cumulative incidence of decompensated cirrhosis and liver-related death plus liver transplantation was overestimated, thereby causing the model to underestimate the benefits of new therapies.

For both scenarios, we projected the expected quality-adjusted life-years (QALYs), total lifetime costs, and cost of antiviral drugs. We estimated the incremental cost-effectiveness ratio (ICER) of sofosbuvir–ledipasvir compared with the oSOC. We used a lifetime horizon and discounted all future costs and QALYs at 3% per year. In addition, we projected the cumulative incidence of advanced liver-related complications (decompensated cirrhosis and HCC), liver transplantation, and liver-related deaths.

Budget Impact Analysis

Cost-effectiveness analysis does not provide the impact of new therapies on payers' budgets; therefore, we estimated the budget needed to treat all eligible patients in the United States. Using a validated prediction model of HCV disease burden in the United States (25), we estimated the number of people who will be eligible for treatment in the next 5 years and the resources needed to treat them.

Sensitivity Analysis

We performed 1-way sensitivity analysis to estimate the effects of transition probabilities, QOL weights, and cost inputs on ICERs. To account for lower SVR rates in practice versus clinical trials, we applied a decrement in SVR of 0% to 20% to the oSOC and 0% to 15% to sofosbuvir–ledipasvir (60). We also performed probabilistic sensitivity analysis using 5000 second-order samples of the parameters defined in Table 3 of the Supplement.

Scenario and Subgroup Analysis

Because HCV progresses slowly, payers might not achieve the full benefits of treating patients with HCV with expensive drugs if patients transition to a different payer after treatment. Therefore, we conducted cost-effectiveness analyses for shorter time horizons (10, 20, and 30 years). We also evaluated the cost-effectiveness of sofosbuvir–ledipasvir by fibrosis score (F0 to F4), sex, and 3 age categories (40, 55, and 70 years).

Role of the Funding Source

This study was supported by the National Institutes of Health under award number KL2TR000146. The content is solely the responsibility of the authors and does not represent the views of the National Institutes of Health.

RESULTS

The average per-person QALYs for the oSOC and sofosbuvir–ledipasvir were 10.07 and 10.63 (increment, 0.56), respectively (Table 2). The increment in QALYs gained from the use of sofosbuvir–ledipasvir differed substantially by treatment history and presence of cirrhosis (0.44 in noncirrhotic vs. 1.12 in cirrhotic treatment-naive patients and 0.37 in noncirrhotic vs. 0.86 in cirrhotic treatment-experienced patients). Compared with the oSOC, treating 10 000 patients with sofosbuvir–ledipasvir could prevent 600 cases of decompensated cirrhosis, 310 cases of HCC, 60 liver transplantations, and 550 liver-related deaths. The reduction of these adverse end points was greater in patients with cirrhosis than in those without it (Figure 1 of the Supplement). The average per-patient cost of the oSOC ranged from $15 000 to $71 600 depending on HCV genotype and treatment history, whereas the cost of sofosbuvir–ledipasvir ranged from $66 000 to $154 000 (Figure 2 of the Supplement).

Cost-Effectiveness of Sofosbuvir–Ledipasvir

The ICER of sofosbuvir–ledipasvir was $55 400 per additional QALY gained compared with the oSOC (Table 2). Depending on HCV genotype, treatment history, and cirrhosis status, the ICERs ranged from $9700 to $284 300 per QALY. The ICER was $43 000 per QALY in treatment-naive patients versus $79 500 per QALY in treatment-experienced patients (Table 2). The ICERs were lower in patients who were interferon-intolerant ($34 900) than in those who were interferon-tolerant ($48 300) (Table 6 of the Supplement). At a $50 000 willingness-to-pay (WTP) threshold, sofosbuvir–ledipasvir was cost-effective in 82% of treatment-naive and 60% of treatment-experienced patients. The corresponding percentages at a WTP threshold of $100 000 were 83% and 81%, respectively.

Budget Impact for HCV Treatment

A prior analysis found that 1.32 million treatment-naive and 450 000 treatment-experienced persons would be aware of their HCV disease in 2014 and that 510 000 persons would be diagnosed in the next 5 years because of risk-based and birth-cohort HCV

Table 2. Lifetime Cost-Effectiveness of Sofosbuvir-Based Therapies Compared With the oSOC to Treat HCV Infection in 120 Patient Profiles

Variable*	QALYs		Cost, $		ICER, $/QALY	Probability of Cost-Effectiveness†	
	oSOC	SOF-Based	oSOC	SOF-Based		$50 000 WTP Threshold	$100 000 WTP Threshold
Treatment-naive patients							
Genotype 1‡							
No cirrhosis	10.605	11.056	54 052	68 228	31 452	0.77	0.99
Cirrhosis	8.279	9.447	85 170	96 498	9703	0.88	0.95
Genotype 2							
No cirrhosis	10.669	11.041	22 736	78 230	149 463	0.02	0.23
Cirrhosis	8.378	9.161	46 336	95 208	62 428	0.36	0.74
Genotype 3							
No cirrhosis	10.559	11.015	25 134	154 649	284 327	<0.01	0.01
Cirrhosis	8.119	9.354	50 235	167 634	95 083	0.10	0.43
Genotype 4							
No cirrhosis	10.404	11.065	41 742	95 798	81 802	0.09	0.51
Cirrhosis	7.810	9.204	69 357	112 553	30 986	0.62	0.85
Genotypes 1–4							
No cirrhosis	10.608	11.051	48 023	75 276	61 517	0.34	0.88
Cirrhosis	8.277	9.401	77 747	100 989	20 673	0.79	0.92
All	10.035	10.646	55 326	81 593	43 034	0.45	0.89
Treatment-experienced patients							
Genotype 1‡							
No cirrhosis	10.668	11.035	71 605	84 744	35 853	0.72	0.97
Cirrhosis	8.500	9.508	98 456	178 295	79 238	0.18	0.55
Genotype 2							
No cirrhosis	10.648	11.048	26 650	78 161	128 770	0.01	0.20
Cirrhosis	8.380	8.580	48 868	105 046	281 317	0.08	0.08
Genotype 3							
No cirrhosis	10.603	10.917	27 555	156 443	410 548	<0.01	<0.01
Cirrhosis	8.285	8.624	50 300	180 083	382 819	0.03	0.03
Genotype 4							
No cirrhosis	10.215	10.732	45 496	87 245	80 793	0.09	0.56
Cirrhosis	7.796	8.790	69 938	104 102	34 349	0.61	0.85
Genotypes 1–4							
No cirrhosis	10.657	11.026	62 699	88 433	69 707	0.25	0.76
Cirrhosis	8.463	9.324	88 662	168 069	92 302	0.12	0.45
All	10.118	10.608	69 078	107 999	79 457	0.22	0.69
All patients§	10.067	10.631	60 686	91 886	55 378	0.35	0.83

HCV = hepatitis C virus; ICER = incremental cost-effectiveness ratio; LDV = ledipasvir; oSOC = old standard of care; QALY = quality-adjusted life-year; SOF = sofosbuvir; WTP = willingness-to-pay.
* Patients without cirrhosis were defined as those with a METAVIR fibrosis score of F0 to F3. Patients with cirrhosis were defined as those with a score of F4.
† From probabilistic sensitivity analysis.
‡ Treatment based on SOF–LDV.
§ Results estimated by using the weighted average by representative proportion of the HCV population in the United States.

screening (25). Assuming that 63% of treatment-naive and 100% of treatment-experienced patients have insurance coverage (61), we estimated that 1.60 million persons would be eligible for treatment during the next 5 years.

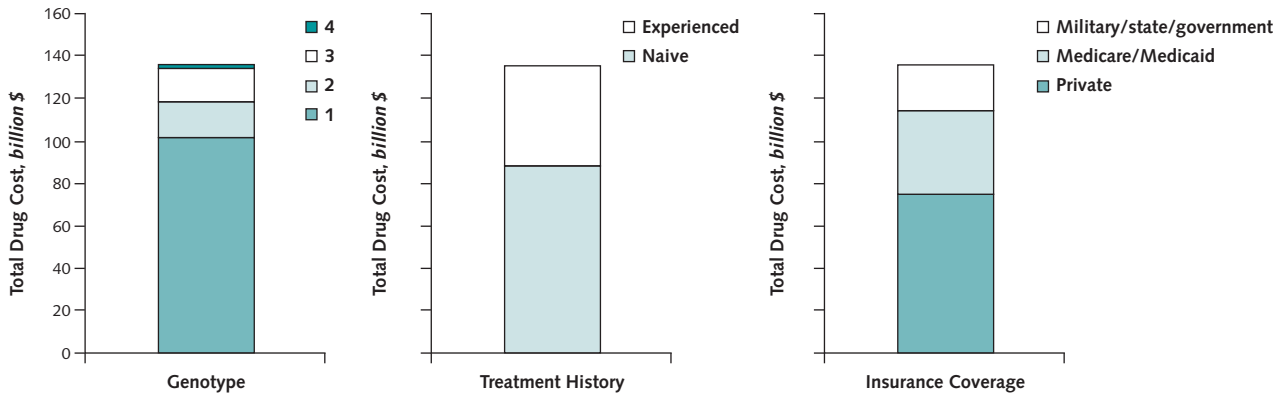
Payers would need $136 billion to cover drug costs for all treatment-eligible patients with HCV during the next 5 years, $61 billion of which would need to be paid by the government (Figure 1). Compared with the oSOC, new drugs would cost an additional $65 billion; the cost offsets from the use of sofosbuvir–ledipasvir would be $16 billion (24% of the additional spending on drugs).

Sensitivity Analysis

Using 1-way sensitivity analysis, we identified the 10 variables that had the largest effect on ICERs (Appendix Figure 2, available at www.annals.org). The ICERs were most sensitive to post-SVR QOL, discounts on sofosbuvir–ledipasvir, decreases in SVR rates from sofosbuvir–ledipasvir, probability of decompensated cirrhosis or HCC in patients with cirrhosis, probability of decompensated cirrhosis after achievement of SVR, and QOL associated with fibrosis stages F0 to F4. Similar trends were observed in treatment-naive and treatment-experienced patients (Figure 3 of the Supplement).

Using probabilistic sensitivity analysis, we estimated that sofosbuvir–ledipasvir was cost-effective, with 35% probability at a $50 000 WTP threshold and 83% probability at a $100 000 threshold (Figure 2). The probabilities of cost-effectiveness were 34% and 79% in treatment-naive patients without and with cirrhosis, re-

Figure 1. Total spending on sofosbuvir–ledipasvir to treat all HCV-infected patients in the United States in the next 5 y.



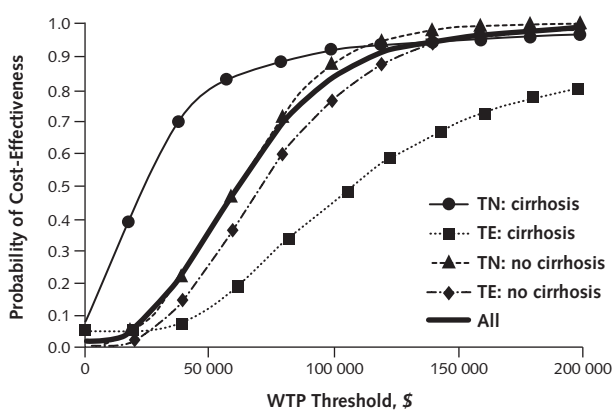
HCV = hepatitis C virus.

spectively, at a $50 000 WTP threshold. In treatment-experienced patients, the corresponding probabilities were 25% and 12%, respectively. The probability of cost-effectiveness for each of the 12 scenarios is provided in Figures 4 through 6 of the Supplement.

Scenario and Subgroup Analysis

The ICERs for sofosbuvir–ledipasvir with 10-, 20-, and 30-year time horizons were $148 500, $82 100, and $66 800, respectively (Tables 7 through 9 of the Supplement). Therefore, the value of sofosbuvir–ledipasvir decreased with shorter time horizons. In addition, age and fibrosis score had substantial effects on the ICERs, ranging from cost-saving to $939 200 (Figure 3 and Figures 7 through 9 of the Supplement). The ICERs in 40-year-old versus 70-year-old patients were $25 000 and $125 900, respectively. In addition, the ICERs were higher in men than in women.

Figure 2. Probability of cost-effectiveness of sofosbuvir–ledipasvir, by WTP threshold.



Results are from probabilistic sensitivity analysis. TE = treatment-experienced; TN = treatment-naive; WTP = willingness-to-pay.

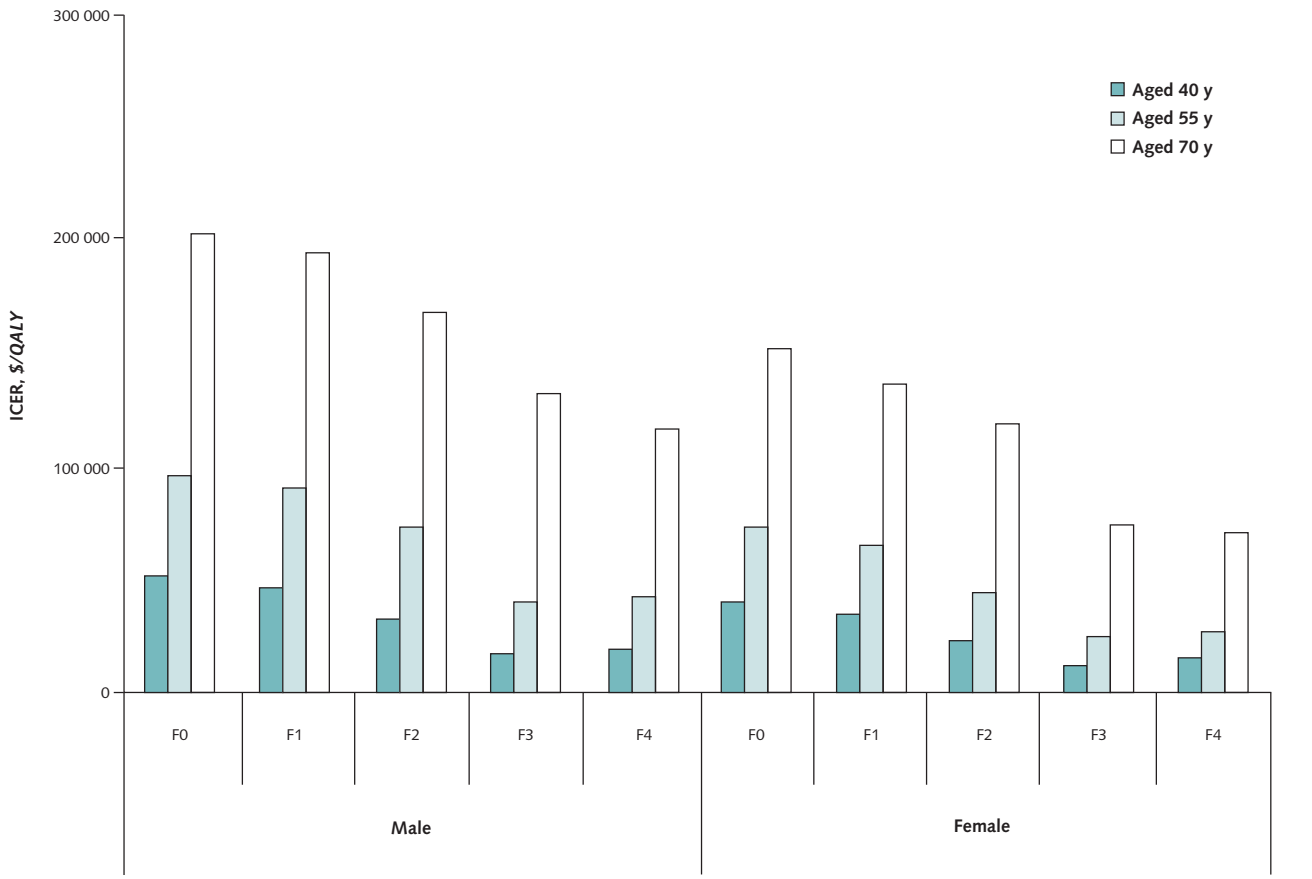
DISCUSSION

The use of sofosbuvir–ledipasvir would substantially reduce the clinical burden of HCV disease. At its current price, this therapy is cost-effective in selected patient groups when a WTP threshold of $50 000 per additional QALY is used. However, at a WTP threshold of $100 000, this therapy is cost-effective in most patients. Sofosbuvir–ledipasvir provides better value for money in patients who have genotype 1 HCV, are in advanced stages of disease, or are younger. Although the reported ICERs are within the range of therapies for other medical conditions in the United States (62–64), the resources needed to treat a large number of eligible patients with HCV infection could be immense and unsustainable. Compared with the oSOC, the downstream cost offsets from using sofosbuvir–ledipasvir would be only 24% of the additional $65 billion spent on this new therapy. Therefore, our analysis does not support the assertion that sofosbuvir–ledipasvir will lead to an overall reduction in the cost of HCV disease at its current price.

To our knowledge, this is the first study to fully evaluate the cost-effectiveness of sofosbuvir–ledipasvir. Earlier cost-effectiveness studies of oral HCV therapies either did not evaluate the current recommendations or made conclusions based on drug prices that were significantly lower than the listed drug prices (65–68). Another report assessed the value of sofosbuvir–simeprevir but did not use modeling to simulate downstream events (69). In contrast, we present a comprehensive and up-to-date analysis of the value of HCV treatment by including 4 major genotypes, interferon tolerance, and treatment history. In addition, we conducted a budget impact analysis, which is especially important given the high price of new antivirals.

The large number of HCV-infected persons needing treatment could place a huge burden on health expenditures, reaching an average of $27 billion per year, which is equivalent to 10% of U.S. prescription drug spending in 2012 (70). A large portion of the treatment

Figure 3. ICERs of sofosbuvir–ledipasvir, by METAVIR fibrosis score (F0 to F4), sex, and age.



ICERs were higher for men because of their higher background mortality. ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

cost will fall on the government. The Patient Protection and Affordable Care Act is expected to increase the number of patients with HCV who are covered under Medicaid (71). In addition, with widespread implementation of birth-cohort HCV screening, many new diagnoses are expected in persons covered under Medicare. Although manufacturers generally provide discounts to most purchasers, current law prohibits Medicare from negotiating drug prices (72). Therefore, treating all patients with HCV with sofosbuvir–ledipasvir at its current price would dramatically affect the financial resources of Medicare and Medicaid.

The cost-effectiveness of HCV treatment depends on society's willingness to pay for improvements in health. Unlike most other developed countries, the United States has not adopted an official threshold to determine whether a new intervention is cost-effective (73). The commonly used $50 000 threshold is questionable, and the more appropriate threshold could be between $100 000 and $200 000 (74, 75). However, despite the cost-effectiveness of HCV treatment, our analysis shows that it is unaffordable at the current price. This raises the question of whether the threshold should depend on the available budget and disease prevalence (for example, lower thresholds for treatment of HCV and other common diseases and higher thresholds for treatment of rare diseases).

The cost-effectiveness of HCV treatment also depends on the insurance type. For private payers, which have a median length of patient enrollment of less than 10 years, sofosbuvir–ledipasvir may not be cost-effective. Therefore, a lower drug price may provide better value to private payers. Conversely, for Medicaid, Medicare, and the Veterans Health Administration, which have longer patient enrollment, sofosbuvir–ledipasvir may be cost-effective. Therefore, providing additional resources to these public programs for HCV treatment could provide good value for money.

Our results were highly sensitive to QOL after achievement of SVR. Therefore, further research is needed in patients who achieve SVR with new therapies. The results were also sensitive to discounts on sofosbuvir–ledipasvir, so higher discounts will improve the value of treatment. In addition, the results were sensitive to several baseline patient demographic characteristics (HCV genotype, presence of cirrhosis, treatment history, and age).

Our study has limitations. First, several clinical studies included in our analysis were not randomized and did not directly compare the efficacy of new drugs;

therefore, our study used only the best available evidence on treatment efficacy, which might have high uncertainty because of the low number of patients. We used efficacy data from phase 2 clinical trials when data were not available from either phase 3 trials or meta-analyses, but we performed sensitivity analyses. The use of data from international clinical trials for the U.S. population could have resulted in overestimation of the benefits of new therapies. Our analysis assumed that QOL after achievement of SVR was equivalent to that of a healthy person, which could also have resulted in overestimation of the benefits of new therapies. We also did not model the future possibility of re-treatment with next-generation antivirals because of a lack of these data at the time of our study. Finally, we did not consider changes in the insurance pool as a result of the Patient Protection and Affordable Care Act, which may affect the budget impact of HCV treatment.

In conclusion, the use of sofosbuvir–ledipasvir substantially reduces HCV-related complications and is cost-effective in most patients. However, treating all eligible patients with HCV in the United States would have an immense budgetary impact on both private and government providers. If prices of these regimens remain at current levels, additional resources and value-based patient prioritization will be needed to manage patients with HCV.

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Acknowledgment: The authors thank Elamin Elbasha, PhD, and Scott Cantor, PhD, for constructive comments that improved the quality of the manuscript; Mina Kabiri, MS, and Qiushi Chen for help with data analysis; and Jill Delsigne, PhD, and Diane Hackett for editing the manuscript.

Financial Support: This study was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number KL2TR000146. Dr. Kanwal was supported in part by the Veterans Affairs Health Services Research and Development Center for Innovations in Quality, Effectiveness and Safety (#CIN 13-413).

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-1336.

Reproducible Research Statement: *Study protocol:* Not applicable. *Statistical code and data set:* Available from Dr. Chhatwal (e-mail, JChhatwal@mdanderson.org).

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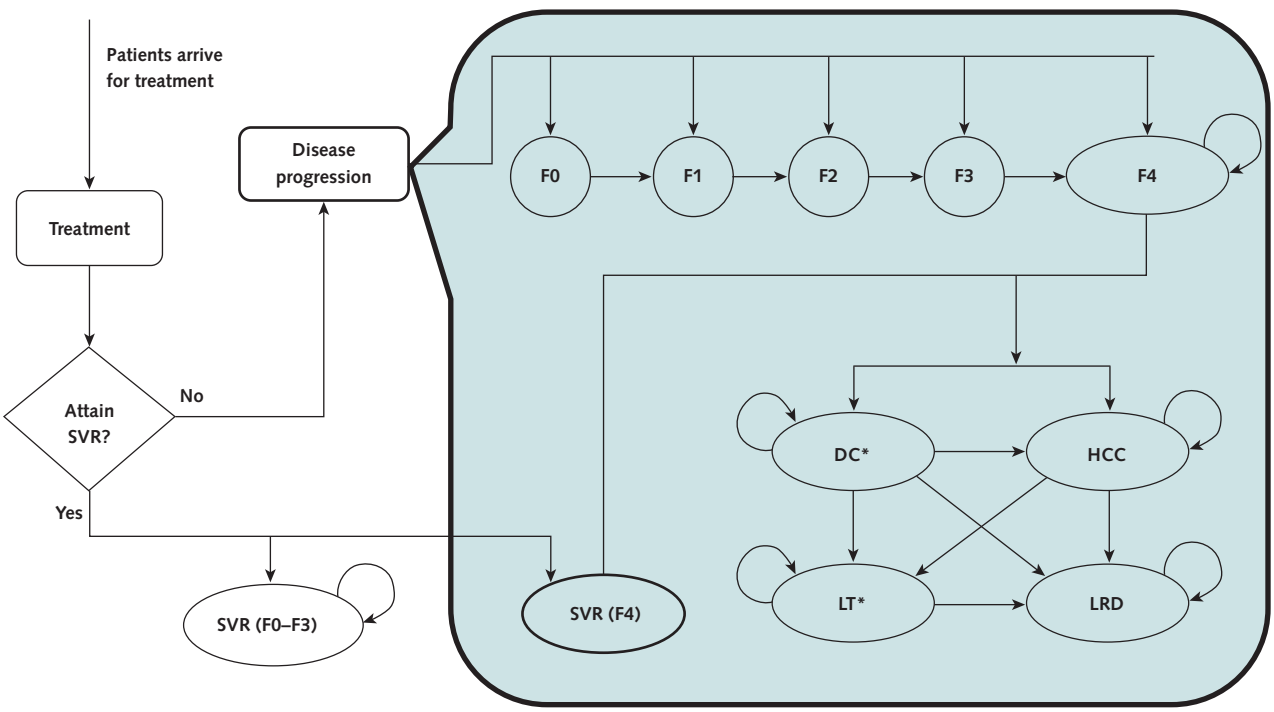
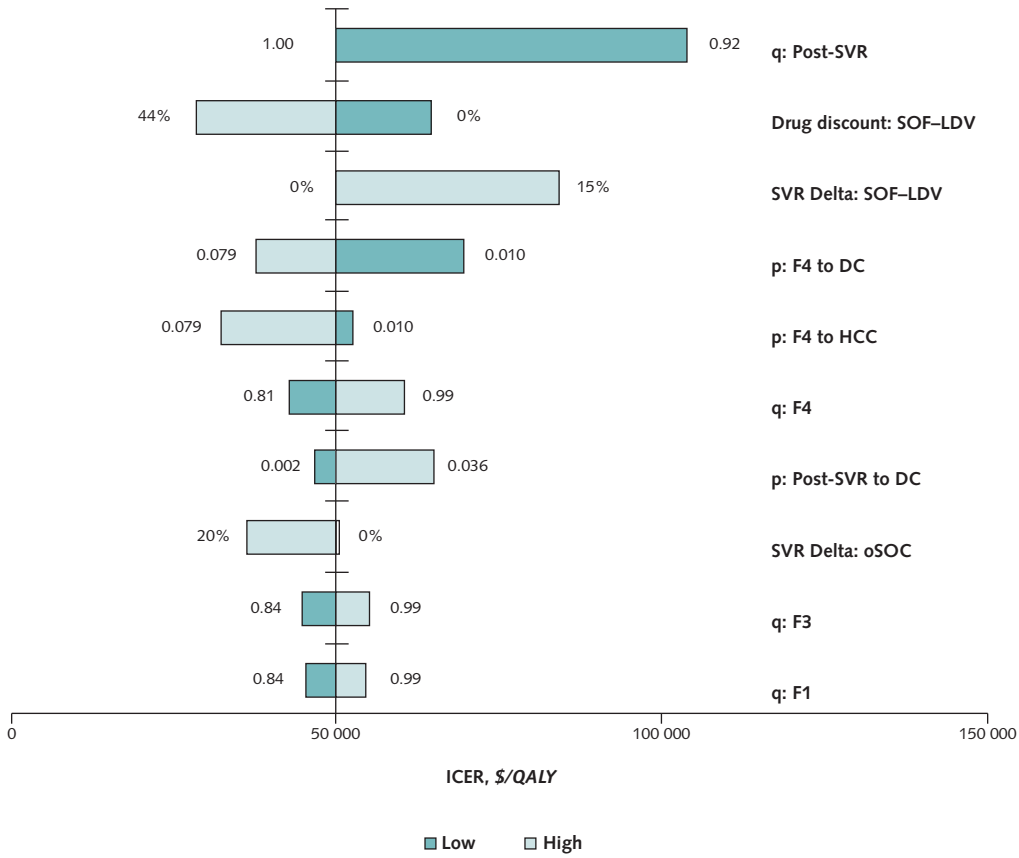
Appendix Figure 1. State-transition diagram of HCV treatment model for a cost-effectiveness analysis of sofosbuvir–ledipasvir.



At a given time, a patient occupies one of the health states represented by the circles or ovals. Arrows between states represent possible transitions based on annual probabilities. As time progresses, patients can transition to another state and acquire cost and health utilities associated with that state. The model stops when all patients transition to the death state. A patient could transition to a death state from any of the other states because of background mortality (these transitions are not shown for clarity). DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; LRD = liver-related death; LT = liver transplantation; SVR = sustained virologic response.
***** The DC and LT states were further divided into first-year and subsequent-year states to account for different mortality rates and costs; however, they are collapsed into 1 state for presentation purposes only.

Appendix Figure 2. One-way sensitivity analysis showing the 10 most sensitive parameters.



DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; ICER = incremental cost-effectiveness ratio; LDV = ledipasvir; oSOC = old standard of care; p: F4 to DC = probability of DC associated with METAVIR fibrosis score F4; p: F4 to HCC = probability of HCC associated with fibrosis score F4; p: Post-SVR to DC = probability of DC in patients with fibrosis score F4 who achieved SVR; QALY = quality-adjusted life-year; q: F1 = QOL weight associated with fibrosis score F1; q: F3 = QOL weight associated with fibrosis score F3; q: F4 = QOL weight associated with fibrosis score F4; QOL = quality of life; q: Post-SVR = QOL after achievement of SVR; SOF = sofosbuvir; SVR = sustained virologic response; SVR Delta: oSOC = reduction in SVR with the oSOC; SVR Delta: SOF–LDV = reduction in SVR with SOF–LDV.