The Comparative Clinical Effectiveness and Value of Novel Combination Therapies for the Treatment of Patients with Genotype 1 Chronic Hepatitis C Infection

A Technology Assessment

Final Report

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About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. ICER receives funding from government grants, non-profit foundations, health plans, provider groups, and health industry manufacturers. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at www.icer-review.org

About CTAF

The California Technology Assessment Forum (CTAF) – a core program of ICER – reviews evidence reports and provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CTAF seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care. CTAF is supported by a grant from the Blue Shield of California Foundation.

The CTAF Panel is an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy, all of whom meet strict conflict of interest guidelines, who are convened to evaluate evidence and vote on the comparative clinical effectiveness and value of medical interventions. More information about CTAF is available at www.ctaf.org

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Abbreviations used in this report

AASLD:	American Association for the Study of Liver Diseases
AEs:	Adverse events
AST/ALT:	aspartate aminotransferase/alanine aminotransferase
ASV:	Asunaprevir
CDC:	Centers for Disease Control and Prevention
CHC:	Chronic hepatitis C
CI:	Confidence interval
CMS:	Centers for Medicare & Medicaid Services
CPI:	Consumer Price Index
CTAF:	California Technology Assessment Forum
DARE:	Database of Abstracts of Reviews of Effects
DAA:	Direct-acting antiviral agent
DCV:	Daclatasvir
DR:	Discontinuation rate
FDA:	US Food and Drug Administration
HCC:	Hepatocellular carcinoma
HCV:	Hepatitis C virus
HR:	Hazard ratio
ICER:	Incremental cost-effectiveness ratio
IFN	Interferon
LDV:	Ledipasvir
NDA:	New drug application
NR:	Not reported
NS:	Not significant
OR:	Odds ratio
P:	Pegylated interferon
PBO:	Placebo
PMPM:	Per-member per-month
PR:	Pegylated interferon plus ribavirin
Q8:	Taken every 8 hours
QALY:	Quality-adjusted life year
R:	Ribavirin
RCT:	Randomized Controlled Trial
SMV:	Simeprevir
SOF:	Sofosbuvir
SVR:	Sustained virologic response
SVR12:	SVR at 12 weeks
US:	United States
WTP:	Willingness-to-pay
3D:	Paritaprevir, ritonavir, ombitasvir, and dasabuvir

Abstract

On December 18, 2014, the California Technology Assessment Forum (CTAF) held a meeting to review the newest treatments for genotype 1 hepatitis C infections. Invited experts participating in two policy roundtables discussed clinical considerations, along with innovative payment and pricing approaches for specialty drugs.

CTAF reviewed the comparative ***clinical effectiveness*** of four all-oral, direct-acting antiviral (DAA) combination therapies: simeprevir + sofosbuvir, ledipasvir/sofosbuvir (LDV/SOF), daclatasvir + sofosbuvir, and paritaprevir/ritonavir/ombitasvir + dasabuvir with ribavirin (R), as well as three single-DAA regimens: simeprevir + pegylated interferon (P) and R, sofosbuvir + R, and sofosbuvir + PR. The CTAF Panel voted that there was sufficient evidence to demonstrate that multiple-DAA therapy is clinically superior to single-DAA therapy or PR alone but that there was insufficient evidence to distinguish clinical effectiveness among the multiple-DAA therapies.

ICER's ***cost-effectiveness analysis*** found that, at a 12-week cost of $94,500, LDV/SOF regimens for treatment-naïve and treatment-experienced patients met commonly accepted thresholds of $50,000-$100,000 per additional quality-adjusted life year gained. A strategy of treating patients at all fibrosis stages rather than waiting to treat patients until they reached fibrosis levels F3 or F4 also met commonly accepted cost-effectiveness thresholds. Estimating potential total costs for Medi-Cal and the California Department of Corrections, ICER's ***budget impact analysis*** showed: 1) an initial cost of $3 billion to treat all patients known to be infected with hepatitis C genotypes 1, 2, and 3 with the most effective therapies; and 2) that even after 20 years, less than half of this initial cost would be offset by savings from reduced liver complications. This analysis also found that a price range of $34,000-$42,000 for new regimens would be required to allow treatment of all individuals with known infections while keeping per-member-per-month (PMPM) cost increases to 0.5%-1%, the maximum increase many insurers considered manageable without special measures.

All CTAF Panel members voted that LDV/SOF represents either a reasonable or high care value. However, given concerns regarding the magnitude of the potential budget impact, ten of 12 CTAF panelists voted that LDV/SOF therapy represents an overall low value to the health care system.

Roundtable participants discussed the desirability of expanding hepatitis C treatment given the simplified dosing regimens and greater safety of new agents. However, it was noted that high costs and the need to identify and treat those most in need of care may still require efforts to prioritize treatment for patients with more advanced liver disease and those at high risk of infecting others. Roundtable participants discussed the controversy over the pricing of new therapies, identifying several mechanisms that could be included as part of strategies to manage pricing and payment for high-cost therapies. Participants also stressed the need for improved dialogue between manufacturers, payers, patients, and other stakeholders to ensure that future therapies of high care value can be made more affordable to the health care system.

Executive Summary

Background

On December 18, 2014, the California Technology Assessment Forum (CTAF) held a public meeting to discuss the comparative clinical effectiveness and value of new interferon-free combinations of direct-acting antiviral (DAA) drugs for the treatment of chronic hepatitis C, genotype 1, the most common genotype in the United States. Our prior assessment in March 2014 evaluated single DAA drugs used with pegylated interferon and/or ribavirin. Since that review, the FDA has approved three new therapies that each combine DAAs and do not require the use of either interferon or ribavirin. On October 10, 2014, the FDA approved the combination of ledipasvir/sofosbuvir; on November 5, 2014, the FDA approved the combination of simeprevir + sofosbuvir. On December 19, the day after the CTAF public meeting, the FDA approved the combination of paritaprevir/ritonavir/ ombitasvir + dasabuvir with or without ribavirin.[a] One other combination therapy (daclatasvir + sofosbuvir) was submitted for FDA approval and its clinical effectiveness included in this review.[b]

Chronic hepatitis C is a common infection that is a major cause of chronic liver disease, liver failure, and hepatocellular carcinoma (HCC), and it is the leading indication for liver transplantation in the Western world.[1] Prior to 2011, the combination of pegylated interferon and ribavirin (PR) was the standard of therapy for the treatment of chronic hepatitis C. Fewer than half of patients with genotype 1 clear the virus from their bloodstream entirely and maintain a sustained virologic response (SVR) 24 weeks after the end of treatment with PR. PR therapy can be difficult, however, as both interferon and ribavirin can cause severe fatigue and body aches, and in some cases, dangerous levels of anemia, neutropenia, and/or thrombocytopenia.[2] The 2011 introduction of first-generation DAA protease inhibitors boceprevir and telaprevir resulted in substantially improved SVR rates in many patients when combined with PR. This improvement came with new challenges including significant additional side effects and drug-drug interactions as well as stringent dosing requirements and high pill burdens for patients.[3] In 2013, the FDA approved the second generation of DAAs, simeprevir and sofosbuvir, which in combination with PR increased SVR rates with shorter duration of therapy and fewer adverse events. Since the March 2014 CTAF review on hepatitis C therapies, investigators have published promising results on several interferon-free therapies that combine two or more DAAs.

As highlighted in the prior CTAF assessment, the new drugs are expensive, with new combination therapies costing approximately $65,000 to $190,000 per course of therapy depending on treatment duration.[4,5] Because chronic infection with HCV is relatively common, this translates into

[a] Since this therapy was not FDA-approved and no estimates were available on its projected cost when the modeling was performed or presented at the CTAF public meeting on December 18, 2014, this regimen was not included in the economic analysis.

[b] For the same reasons listed in the previous footnote, this regimen was not included in the economic analysis.

an enormous potential budget impact for federal, state, and private health insurers. Because of the tension between the potential cost-effectiveness of these new agents (i.e., their "care value") and their budgetary impact (i.e., "health-system value"), ICER developed a detailed cost-effectiveness model to provide a more robust analysis of the benefits and costs of the new agents for the current assessment.

Evidence Review

This assessment addresses the following questions: 1) among patients with genotype 1 hepatitis C infections, what is the comparative clinical effectiveness of combinations of two or more DAAs compared to each other, as well as to single DAA therapy used in combination with interferon and ribavirin in the achievement of SVR as a surrogate for the prevention of longer-term sequelae of chronic liver disease; and 2) what is the comparative value of the new therapies and alternative population treatment strategies (i.e., treat all vs. treat only patients with advanced liver disease). The purpose of this assessment is to help patients, providers, and payers address these important questions and to support dialogue needed for successful action to improve the quality and value of health care for patients with hepatitis C.

This evidence review of treatments for genotype 1 differs from the March 2014 CTAF review in analyzing four clinically relevant subgroups shown in Table ES1 below and derives summary estimates for SVR and discontinuation rates (DR) in each group by treatment regimen listed in Table ES2 below.

Table ES1: Clinical Subgroups

Treatment-naïve / non-cirrhotic	Treatment-naïve / cirrhotic
Treatment-experienced / non-cirrhotic	Treatment-experienced / cirrhotic

Table ES2: Therapies Considered in this Assessment

Brand Name	Generic Name	Abbreviation	Pharmaceutical Company
FDA-approved comparators from prior review			
Olysio + PR	Simeprevir + PR	SMV + PR	Janssen and Medivir AB
Sovaldi + PR	Sofosbuvir + PR	SOF + PR	Gilead Sciences
Sovaldi + R	Sofosbuvir + R	SOF + R	Gilead Sciences
FDA-approved combinations since prior review			
Olysio + Sovaldi	Simeprevir + sofosbuvir	SMV + SOF	Janssen + Gilead Sciences
Harvoni	Ledipasvir/sofosbuvir	LDV/SOF	Gilead Sciences
Combinations pending FDA approval at the time of this review (12/18/14)			
Daklinza + Sovaldi	Daclatasvir + sofosbuvir	DCV + SOF	Bristol-Myers Squibb + Gilead Sciences
3D	Paritaprevir/ritonavir/ ombitasvir + dasabuvir	3D	AbbVie

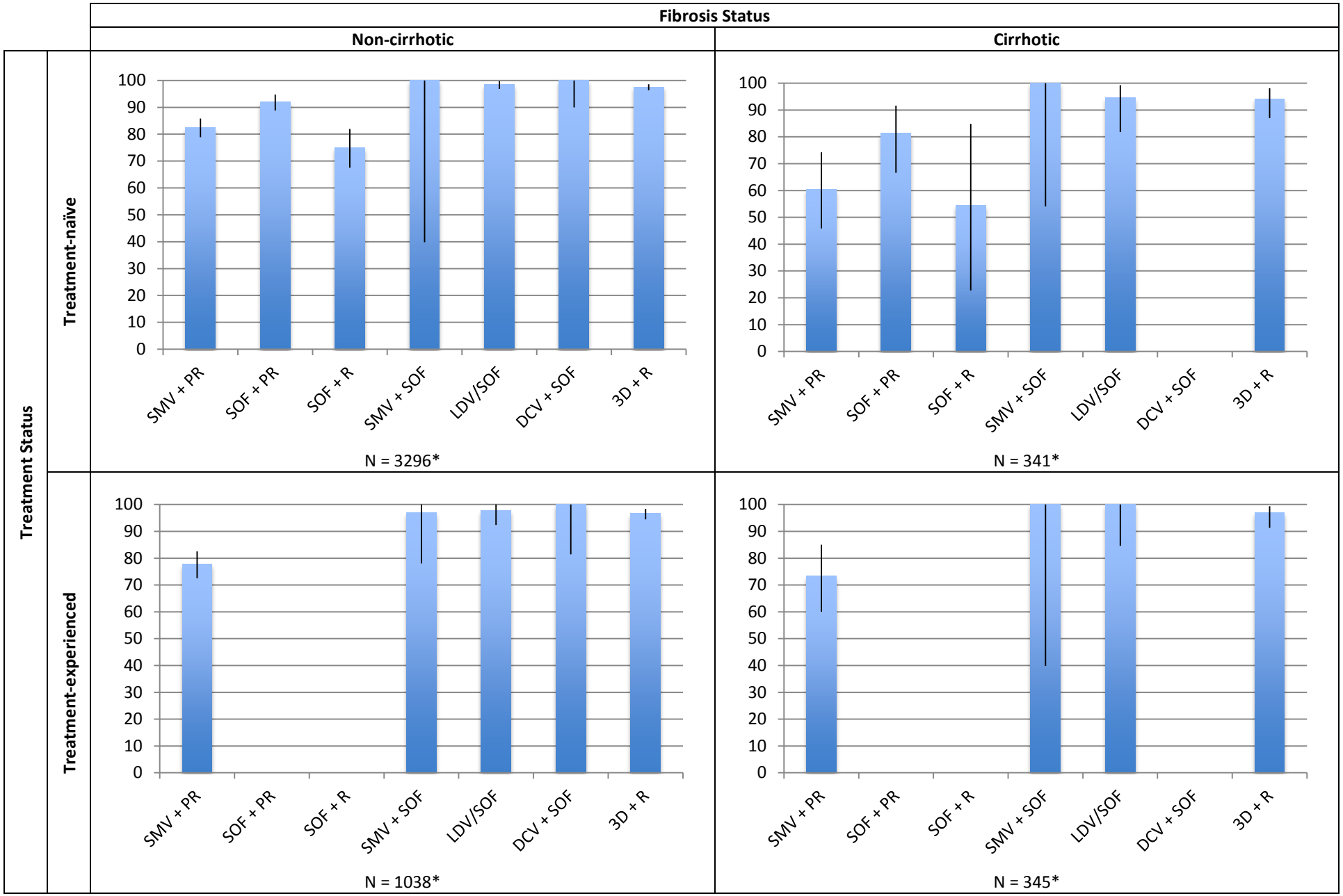
We included all prospective randomized trials and cohorts that reported SVR12 or SVR24 in HCV genotype 1 infected populations. The SVR results for each of the regimens by clinical subgroup are shown in Figure ES1 on page ES4. The evidence on the clinical effectiveness of the all-oral DAA combination treatment regimens compared to second-generation single DAA regimens appears consistent in all four major treatment subgroups. Among treatment-naïve patients without cirrhosis, the SVR12 for simeprevir or sofosbuvir combined with interferon and/or ribavirin is between 75% and 92%, whereas the SVR12 for DAA combination therapy (i.e., SMV + SOF, LDV/SOF, DCV + SOF, 3D) is higher, ranging from 95% to 100%. Among treatment-naïve patients with cirrhosis, the SVR12 for single DAA therapy ranges from 55% to 81% compared to 67% to 95% for DAA combination therapy. For treatment-experienced patients, the SVR12 for single DAA therapy is about 75% for both cirrhotic and non-cirrhotic patients and is 95% to 100% for DAA combination therapy.

Due to the very similar high levels of SVR12 achieved by all DAA combination therapies, and the lack of head-to-head trials, there is inadequate evidence to distinguish the overall effectiveness of the various DAA combination therapies. At the time of the review, only two combinations had FDA approval (SMV + SOF, LDV/SOF). Two of the combinations (SMV + SOF, DCV + SOF) have been studied among very few patients, and the confidence intervals around the estimates for their SVRs are wide. For the patient population with cirrhosis, the confidence intervals are wide for all four of the new DAA combinations. Furthermore, since these data come from single arm studies, in which everyone enrolled in a trial receives the experimental therapy, selection bias may explain some of the observed differences among the SVR point estimates.

Adverse effects are an important part of comparative clinical effectiveness, but there were very few discontinuations from therapy in any of the studies due to adverse events, and the rate of serious adverse events was similarly low. When patient characteristics require longer therapy with ribavirin (sofosbuvir + R for 24 weeks, 3D + R for 24 weeks), the adverse event rates were higher.

Pragmatic randomized trials or high-quality observational studies in real world settings will be essential for evaluating the comparative effectiveness of the combination DAA therapies and to see if the SVR rates achieved in clinical trials are replicated in usual care settings.

Figure ES1: SVR and 95% Confidence Intervals for the Primary DAA Regimens in Four Clinical Subgroups



* — N values represent the total number of patients in the represented studies for each clinical subgroup

Care Value Analysis: Cost-Effectiveness Model

In collaboration with academic faculty at the UCSF School of Medicine, we developed a decision-analytic multistate Markov model[125] to determine the cost-effectiveness of six treatment regimens for HCV genotype 1 marketed in the US as of the December 18, 2014 CTAF public meeting date. The model calculated the net costs, health benefits, and incremental cost-effectiveness ratios (ICERs) of these therapies. It was also designed to determine how these ICERs change if treatment is delayed to a more advanced stage of disease as compared to treating people at all disease stages. We thus aimed to address two key policy or program questions with regard to HCV therapy:

- **Comparing regimens**: Which regimens are most cost-effective? Specifically, what is the incremental cost-effectiveness of more expensive and effective regimens?
- **Comparing population treatment strategies:** What is the cost-effectiveness of treating all individuals, as compared with waiting to treat at more advanced disease stages?

The model produced lifetime discounted quality-adjusted life years (QALYs) and costs to calculate ICERs. Costs, QALYs gained, incremental costs, and incremental QALYs were calculated for each regimen in comparison with the next least costly regimen. The ICER for each regimen's "treat all" strategy also was calculated against "treat at F3, F4" (i.e., treat only when patients have advanced fibrosis or cirrhosis) in order to assess the cost-effectiveness of a universal treatment approach versus a prioritized one.

For the cost models, we examined PR alone, as well as sofosbuvir in combination with other drugs (i.e., SMV, LDV, R, PR). We did not include daclatasvir or the 3D regimen in these analyses, as these therapies were not yet FDA-approved by the CTAF meeting date, and no estimates were available on their projected cost. In the base-case analysis, we found that LDV/SOF regimens for treatment-naïve and treatment-experienced patients demonstrated incremental cost-effectiveness ratios that easily met commonly accepted thresholds, producing ICERs ≤$20,000 per QALY gained regardless of the comparison. In multivariable sensitivity analyses, approximately 98% of the simulations yielded an acceptable cost-effectiveness ratio at a willingness to pay threshold of $50,000 per QALY gained, suggesting that the finding that LDV/SOF is cost-effective at that threshold is robust.

Our analysis also found that, while treating patients at all fibrosis stages was more expensive in comparison to waiting to treat until patients reached F3 or F4, it was also more effective. For example, treating all naïve patients with LDV/SOF 8/12 (according to viral load and fibrosis stage) or LDV/SOF 12 (all patients get 12 weeks of therapy) produced ICERs <$40,000 per QALY gained in comparison to treating only at F3/F4. Among treatment-experienced patients, differences in effectiveness were more pronounced, with more than two years of quality-adjusted life expectancy gained for single DAA sofosbuvir-based regimens relative to PR alone (generating ICERs of $10,000-$20,000 per QALY gained). Comparisons of the "treat all" vs. "treat at F3, F4" approaches in the treatment-experienced subgroup generated more costs (in part because single DAA sofosbuvir-

based regimens are longer) but still produced estimates of cost-effectiveness of ~$50,000 per QALY gained.

Health System Value Analysis

We assessed the clinical benefits and potential budgetary impact of new hepatitis C therapy from the perspective of the state Medi-Cal and Department of Corrections programs over three periods of follow-up: one, five, and 20 years after treatment initiation. As with the cost-effectiveness analyses, the regimen of interest for genotype 1 was the LDV/SOF strategy (8/12 weeks for treatment-naïve, 12/24 weeks for treatment-experienced), as this represents the cost-effective strategy that is currently available and most likely to receive widespread use in this population. For each of these time points, we used outputs from the care value model to inform expected numbers (per 1,000 treated) of patients experiencing HCV-related complications (cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant) and dying of HCV-related causes. Findings for the performance of LDV/SOF vs. PR are presented in Table ES3 on the next page.

LDV/SOF produces incremental clinical benefits very soon after treatment initiation; for example, compared with PR alone, LDV/SOF prevents approximately six cases of cirrhosis and two HCV-related deaths per 1,000 patients treated in the first year alone. Benefits are more fully realized at later time points; at five years, LDV/SOF would avert 44 cases of cirrhosis (15 of which would be decompensated), five cases of HCC, and 17 HCV-related deaths per 1,000 treated. Cost offsets would total approximately 7% of incremental treatment costs. At 20 years, there would be a nearly six-fold reduction in the incidence of cirrhosis, HCC incidence would be reduced by more than half, and 140 HCV-related deaths would be averted per 1,000 treated. More than 25% of treatment costs would be offset by these reductions.

We then combined these results with findings from the March 2014 CTAF review for genotypes 2 and 3[180] to assess the one-, five-, and 20-year budgetary impact of adopting LDV/SOF for genotype 1 and the most effective therapies available for genotypes 2 and 3 (SOF + R for 12 weeks for genotype 2 and 24 weeks for genotype 3). The number of individuals with chronic hepatitis C in Medi-Cal and the California Department of Corrections was recently estimated to total 93,000.[177]

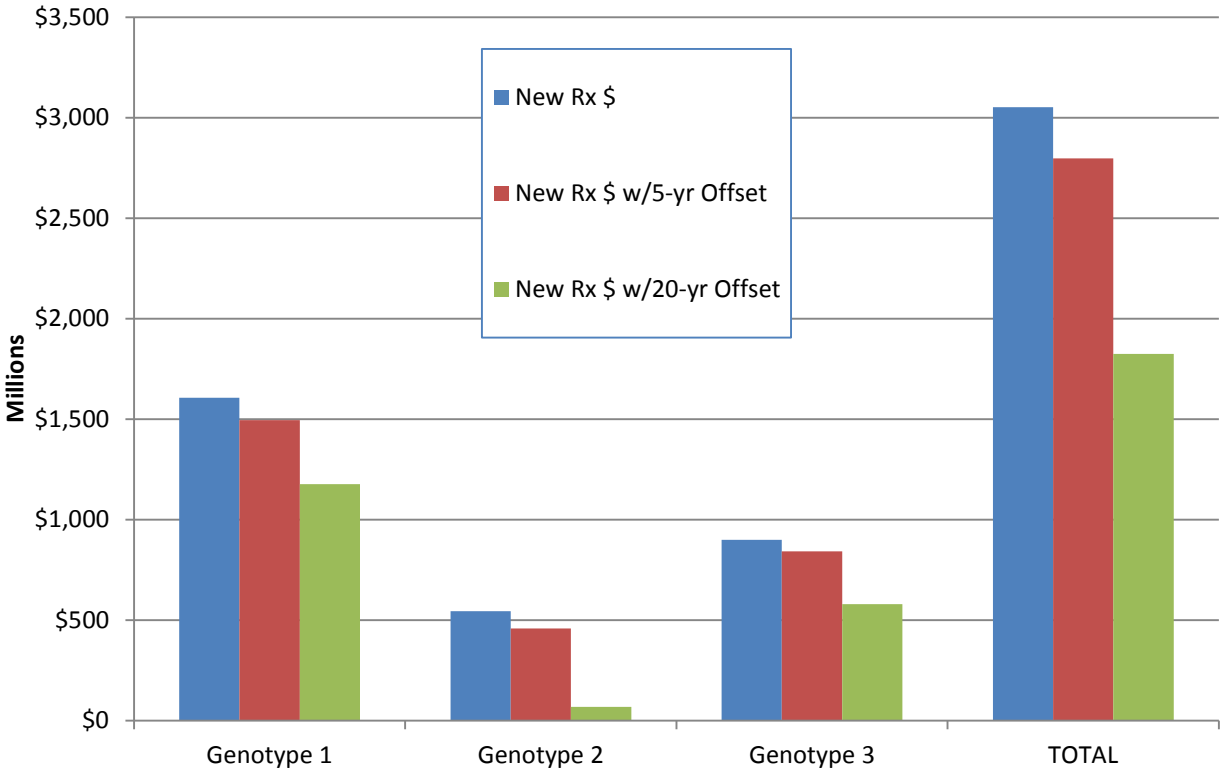
Our model suggests that full uptake of new HCV treatments among known-infected patients would increase costs by approximately $1.6 billion, $545 million, and $901 million for genotypes 1, 2, and 3 respectively (see Figure ES2 on page ES8), resulting in a total increase of $3 billion, or $33 PMPM. This represents a 5% increase over the base per-member per-month (PMPM) Medi-Cal costs of $611.[179] Cost offsets after five years would total $254 million, reducing net expenditures modestly to $2.8 billion. More substantial offsets after 20 years ($1.2 billion) would reduce net expenditures further to $1.8 billion (see section 7 of the report for sensitivity analyses).

Table ES3: Clinical Outcomes (per 1,000 Patients Treated) and Costs for LDV/SOF and PR Therapy over One, Five, and 20 Years of Follow-up

	Liver-Related Complications				HCV	*Costs (per patient, $)*		
Timeframe/Regimen	**Cirrhosis**	**Decompensation**	**HCC**	**Transplant**	**Death**	**Treatment**	**Other**	**Total**
1 Year								
PR	6.8	3.5	1.8	0.0	5.4	$34,966	$1,636	$36,602
LDV/SOF	0.8	0.6	1.2	0.0	3.4	$84,341	$696	$85,037
Difference (LS-PR)	*(5.9)*	*(3.0)*	*(0.6)*	*0.0*	*(2.0)*	*$49,375*	*($940)*	*$48,435*
5 Years								
PR	34.8	18.7	11.9	0.4	35.3	$34,966	$6,681	$41,647
LDV/SOF	6.1	3.4	6.7	0.3	18.7	$84,341	$3,260	$87,601
Difference (LS-PR)	*(28.8)*	*(15.3)*	*(5.1)*	*(0.1)*	*(16.5)*	*$49,375*	*($3,421)*	*$45,954*
20 Years								
PR	120.9	66.8	45.3	4.9	248.8	$34,966	$23,442	$58,409
LDV/SOF	21.5	11.8	23.0	1.5	109.1	$84,341	$10,214	$94,555
Difference (LS-PR)	*(99.4)*	*(55.0)*	*(22.3)*	*(3.3)*	*(139.7)*	*$49,375*	*($13,229)*	*$36,146*

LS-PR: Difference between LDV/SOF and PR therapy

Figure ES2: Budgetary Impact of New Hepatitis C Treatments in the Medi-Cal/Department of Corrections Hepatitis C Population in California, with and without Cost Offsets from Reduced Liver-related Complications



Drug Pricing to Meet Per-Member Per-Month Benchmarks

PMPM increases of 0.5%-1% in a given year were used in this report as a range of potential budget impact that, when exceeded, are likely to drive specific efforts to manage the costs of a new health care intervention. We examined the incremental drug expenditures at which PMPM increases of 0.5% and 1% would be met for genotype 1, the patient subpopulation of interest in this review. Based on the assumed baseline PMPM in this analysis ($611) as well as the size of the population to be treated (approximately 33,000 patients in the Medi-Cal/Department of Corrections population in California if 50% of genotype 1 patients present for treatment), a course of treatment with a new agent would need to be priced at $34,000 - $42,000 to meet the 0.5% and 1% thresholds respectively.

We also conducted a hypothetical analysis of the number of treatment-naïve Medi-Cal/Department of Corrections patients who could be treated without exceeding these thresholds, based on the current wholesale acquisition costs of LDV/SOF (approximately $63,000 and $95,000 for 8 and 12 weeks, respectively). Only two-thirds of these patients (approximately 16,500 of the 26,000 patients with known infections) could receive treatment at these prices if the one-year PMPM increase were to be held to less than 1%, leaving nearly 10,000 Medi-Cal/Department of

Corrections patients without access to new therapy. When considering a 0.5% threshold for PMPM increase (≤$3.06), less than half of eligible patients (12,600 of 26,000) could be treated at current prices. In contrast, if the population of treatment-naïve genotype 1 patients is restricted to those with F3 and F4 stage disease (n=~6,700), LDV/SOF could replace historical PR therapy in *all* of these patients at current prices and remain under the 1% threshold for PMPM increase. When considering a 0.5% increase in PMPM ($3.06), LDV/SOF could replace PR in 91% of F3/F4 patients (n=~6,100) at current prices.

Summary

Our findings have important implications for patients, physicians, and payers. Specifically, model results suggest that the introduction of LDV/SOF for both treatment-naïve and treatment-experienced individuals would confer substantial clinical benefits in comparison to historical treatment standards and even in relation to other sofosbuvir-based regimens. While the use of this new regimen would increase treatment costs, such use appears to be cost-effective by conventional standards. However, the additional expenditures required to treat all patients with genotype 1 infection (even if only 50% of them are aware of their infection) are substantial; when added to the additional expenditures required for genotypes 2 and 3, this represents a per-member per-month premium increase that is five-fold higher than frequently-discussed manageable thresholds for new interventions. It is clear that patients, physicians, insurers, and health systems will have to grapple with the budget impact of new, highly effective, and expensive treatments for hepatitis C. Whether this will result in prioritization of clinical care, new contracting and financing mechanisms, evolving market dynamics, or policy actions remains to be seen.

CTAF Votes on Comparative Clinical Effectiveness and Value

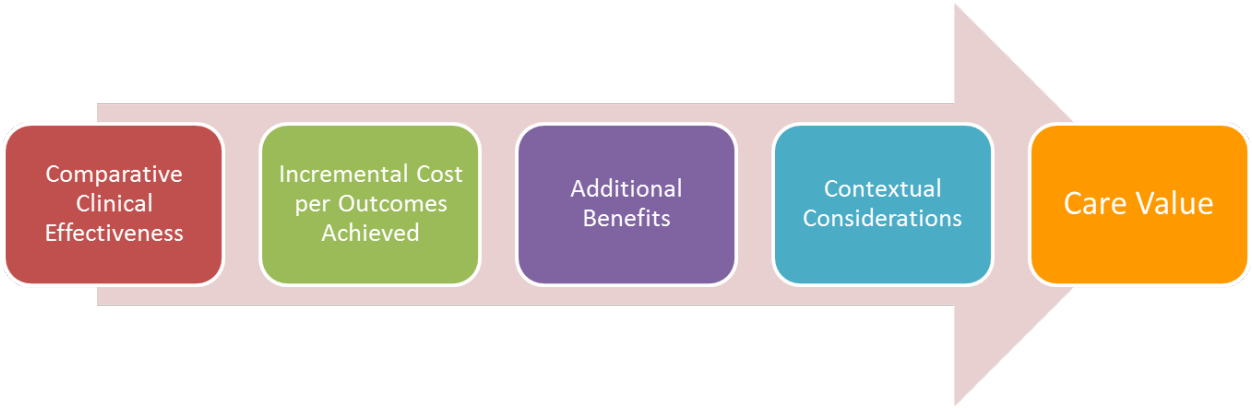
During CTAF public meetings, the CTAF Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, a cost analysis of the applications of the medical technologies or treatments under examination, and the supplementary information presented. Because any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to CTAF Panel, serve as a resource to the CTAF Panel during their deliberation, and help form recommendations with CTAF on ways the evidence can be applied to policy and practice. At each meeting, after the CTAF Panel vote, a policy roundtable discussion is held with the CTAF Panel, clinical experts, and representatives from provider groups, payers, and patient groups.

At the December 18, 2014 meeting, the CTAF Panel discussed issues regarding the application of the available evidence to help patients, providers, and payers address the important questions related to the newest, all-oral treatments for hepatitis C. Following the evidence presentation and

public comments, the CTAF Panel voted on key questions concerning the comparative clinical effectiveness and comparative value of the newest treatments for hepatitis C.

In its deliberations and voting related to value, the CTAF Panel made use of a new value assessment framework with four different components of *care value*, which they considered in assigning an overall rating of low, reasonable, or high care value. The four components of care value are comparative clinical effectiveness, incremental cost per outcomes achieved, additional benefits, and contextual considerations regarding the illness or therapy. Once they made an overall assessment of care value considering these four components, the CTAF panel then explicitly considered the affordability of the newest, all-oral hepatitis C treatments in assessing health system value as low, reasonable, or high (see Figures ES3 and ES4 below).

Figure ES3. Care Value Framework



***Care value* is a judgment comparing the clinical outcomes, average per-patient costs, and broader health effects of two alternative interventions or approaches to care.**

The CTAF Panel was asked to vote whether interventions represent a "high," "reasonable," or "low" care value vs. a comparator from the generalized perspective of a state Medicaid program.

Figure ES4. Health System Value Framework

***Health system value* is a judgment of the affordability of the short-term budget impact that would occur with a change to a new care option for all eligible patients, assuming the current price and payment structure.**

Usually, the care value and the health care system value of an intervention or approach to care will align, whether it is "high," "reasonable," or "low." But health system value also takes into consideration the short-term effects of the potential budget impact of a change in care across the entire population of patients. Rarely, when the additional per-patient costs for a new care option are multiplied by the number of potential patients treated, the short-term budget impact of a new intervention of reasonable or even high care value could be so substantial that the intervention would be "unaffordable" unless the health system severely restricts its use, delays or cancels other valuable care programs, or undermines access to affordable health insurance for all patients by sharply increasing health care premiums. Under these circumstances, unmanaged change to a new care option could cause significant harm across the entire health system, in the short-term possibly even outweighing the good provided by use of the new care option itself.

To consider this possibility, CTAF reviews estimates of the potential budget impact for a change in care as measured by the estimated increase in "per-member-per-month" health care premiums that would be needed to fund a new care option in its first year of use were all eligible patients to be treated.

Comparative Clinical Effectiveness

1. For patients with genotype 1 chronic hepatitis C infection, is the evidence adequate to demonstrate that clinical outcomes with *ledipasvir/sofosbuvir* are superior to those provided by treatment with *pegylated interferon plus ribavirin*?
   CTAF Panel Vote: 12 yes (100%) 0 no (0%)
2. For patients with genotype 1 chronic hepatitis C infection, is the evidence adequate to demonstrate that clinical outcomes with *ledipasvir/sofosbuvir* are superior to those provided by treatment with *sofosbuvir plus pegylated interferon plus ribavirin*?
   CTAF Panel Vote: 10 yes (83%) 2 no (17%)
3. For patients with genotype 1 chronic hepatitis C infection, is the evidence adequate to demonstrate that clinical outcomes with *ledipasvir/sofosbuvir* are superior to those provided by treatment with *simeprevir plus sofosbuvir*?[c]
   CTAF Panel Vote: 1 yes (8%) 11 no (92%)
4. For patients with genotype 1 chronic hepatitis C infection, is the evidence adequate to demonstrate that clinical outcomes with *ledipasvir/sofosbuvir* are superior to those provided by treatment with *3D + R (combination of paritaprevir, ritonavir, ombitasvir, and dasabuvir with ribavirin)*?
   CTAF Panel Vote: 1 yes (8%) 11 no (92%)

[c] At the meeting after the automated voting was completed, two panel members indicated that they voted for a different option than they had intended. As a result, the votes shown here differ from those shown on-screen at the meeting.

Value

5. If yes to question 1, given the prices presented in the report, what is the care value of *ledipasvir/sofosbuvir* vs. *pegylated interferon plus ribavirin*?[d]
   CTAF Panel Vote: 6 high (50%) | 6 reasonable (50%) | 0 low (0%)

6. Assuming no changes to pricing or to payment mechanisms, if a policy strategy to treat all known infected patients was adopted, what would be the health system value of *ledipasvir/sofosbuvir* for a state Medicaid program?
   CTAF Panel Vote: 0 high (0%) | 2 reasonable (17%) | 10 low (83%)

Policy Roundtable Discussion and Key Policy Recommendations

Following its deliberation on the evidence and subsequent voting, the CTAF Panel engaged in moderated discussions with two Policy Roundtables. The first focused on clinical and coverage considerations related to treatment with the newest, all-oral hepatitis C treatments; the second focused on specialty drug pricing and payment, examining the affordability concerns raised by the newest hepatitis C drugs as a case of a more general policy challenge faced by the US health care system. The main recommendations from the discussion are summarized below, and the rationale for these recommendations is presented in the body of the report beginning on page 81. The policy roundtable discussions with the CTAF Panel reflected multiple perspectives and opinions, and therefore, none of the recommendations below should be taken as a consensus view held by all participants.

Clinical Considerations Policy Roundtable

1. Because the newest treatment regimens avoid the need for interferon and therefore are associated with far fewer side effects, there is growing hope among patients and many clinical experts and policy makers that treatment can be expanded to all patients who seek treatment for hepatitis C. Treating all who desire treatment will be costly, however, and in many care settings, there are still infrastructure and financial constraints that highlight the importance of giving priority to identifying patients with advanced liver fibrosis or who are at high risk of infecting others and bringing them into treatment as quickly as possible.

2. Given that the newest treatment regimens are much simpler and have fewer side effects than older treatment regimens, physician groups and payers should consider allowing non-specialist physicians to prescribe them.

[d] See footnote c on the previous page

3. Patients with hepatitis C and their families need guidance and support through the treatment process.

4. Patients and their families, as well as payers, experience the financial impact resulting from the high cost of these new hepatitis C treatments.

Specialty Drug Pricing and Payment Policy Roundtable

1. Hepatitis C deserves a focused, national strategy for treatment and financing.

2. Given the growing trend of effective but expensive new therapies like the new treatments for hepatitis C, inflammatory diseases, and cancer, a variety of mechanisms should be explored so that patients can benefit from treatments of high care value in a manner that also ensures high health system value.

3. Payers should develop transparent approaches for identifying pragmatic thresholds for incremental cost-effectiveness and budget impact that represent both reasonable care and health system value. Efforts to establish and justify price points for new therapies should require dialogue among payers, providers, manufacturers, and other stakeholders.

As a follow-up to the public meeting and as a complement to this report, an action guide for each of three groups (patients, clinicians, and payers/policymakers) will be developed and distributed to interested parties and available on the CTAF website.

Introduction

This assessment for the California Technology Assessment Forum (CTAF) evaluates the evidence on the comparative clinical effectiveness and value of new interferon-free combinations of direct-acting antiviral (DAA) drugs for the treatment of chronic hepatitis C, genotype 1, which is the most common genotype in the United States. Our March 2014 assessment evaluated single DAA drugs used with pegylated interferon and ribavirin. Since that review, the FDA has approved three new therapies that each combine DAAs and do not require the use of either interferon or ribavirin. On October 10, 2014, the FDA approved the combination of ledipasvir/sofosbuvir; on November 5, 2014, the FDA approved the combination of simeprevir + sofosbuvir. On December 19, the day after the CTAF public meeting, the FDA approved the combination of paritaprevir/ritonavir/ ombitasvir + dasabuvir with or without ribavirin.[e] One other combination therapy (daclatasvir + sofosbuvir) was submitted for FDA approval and its clinical effectiveness included in this review.[f]

Chronic hepatitis C is a common infection that is a major cause of chronic liver disease, liver failure, and hepatocellular carcinoma (HCC), and it is the leading indication for liver transplantation in the Western world.[1] Prior to 2011, the combination of pegylated interferon and ribavirin (PR) was the standard of therapy for the treatment of chronic hepatitis C. Fewer than half of patients with genotype 1 clear the virus from their bloodstream entirely and maintain a sustained virologic response (SVR) 24 weeks after the end of treatment with PR. PR therapy can be difficult, however, as both interferon and ribavirin can cause severe fatigue and body aches, and in some cases, dangerous levels of anemia, neutropenia, and/or thrombocytopenia.[2] The 2011 introduction of first-generation DAA protease inhibitors boceprevir (Victrelis®, Merck & Co.) and telaprevir (Incivek®, Vertex Pharmaceuticals, Inc.) resulted in substantially improved SVR rates in many patients when combined with PR. This improvement came with new challenges including significant additional side effects and drug-drug interactions as well as stringent dosing requirements and high pill burdens for patients.[3] In 2013, the FDA approved the second generation of DAAs, simeprevir and sofosbuvir, which in combination with PR increased the SVR, decreased the duration of therapy and decreased adverse events. Since the March 2014 CTAF assessment of hepatitis C therapies, investigators published promising results on several interferon-free therapies that combine two or more DAAs.

As highlighted in the prior CTAF assessment, the new drugs are expensive, with new combination therapies costing approximately $65,000 to $190,000 per course of therapy, depending on treatment duration.[4,5] Because chronic infection with HCV is relatively common, this translates into an enormous potential budget impact for federal, state, and private health insurers. ICER developed

[e] Since this therapy was not FDA-approved and no estimates were available on its projected cost when the modeling was performed or presented at the CTAF public meeting on December 18, 2014, this regimen was not included in the economic analysis.

[f] For the same reasons listed in the previous footnote, this regimen was not included in the economic analysis.

a detailed cost-effectiveness model to provide a more detailed assessment of the benefits and costs of the new drugs for our new assessment.

This assessment will address the following questions: 1) among patients with genotype 1, what is the comparative clinical effectiveness of combinations of two or more DAAs compared to each other as well as to single DAA therapy used in combination with interferon and ribavirin; and 2) what is the comparative value of the new therapies, including analysis of their care value at the patient level and of their potential health system value when budget impact is also taken into consideration. The purpose of this assessment is to help patients, providers, and payers address these important questions and to support dialogue needed for successful action to improve the quality and value of health care for patients with hepatitis C.

1. Background

1.1 Hepatitis C

The worldwide prevalence of hepatitis C infection is estimated to be between 120 and 170 million.[6] Estimates for the prevalence of hepatitis C in the United States range from 3.0 to 5.2 million people.[7-10] It is the leading cause of liver failure requiring liver transplant.[11]

There are six major genotypes of hepatitis C.[12] The most common genotype in the United States is genotype 1 (70-75%), followed by genotype 2 (13-17%) and genotype 3 (8-12%).[13-18] Genotypes 4 to 6 are uncommon in the United States (1% or less). Knowledge of the viral genotype is important because response to therapy varies by genotype. The new combination therapies considered in this assessment have primarily been studied in genotype 1, and this assessment will focus exclusively on genotype 1.

The majority of patients with chronic hepatitis C infections are asymptomatic and unaware of their infections unless they have been screened. It is estimated that approximately half of patients infected with hepatitis C in the United States are unaware of their infection and that less than 15% have received treatment.[9,19,20] The majority (approximately 76%) of Americans infected with the hepatitis C virus (HCV) were born between the years of 1945 and 1965,[20] and most new cases of HCV infection occur in injection drug users.[186] Both the Centers for Disease Control and Prevention (CDC) and the US Preventive Services Task Force (USPSTF) now recommend hepatitis C screening for all Americans born between 1945 and 1965.[21,22]

The CDC estimates that among 100 people infected with hepatitis C, only 20 to 30 will develop symptoms acutely (see Table 1 on the next page).[121] The symptoms are primarily fatigue, decreased appetite, nausea, and jaundice. Of 100 people infected with hepatitis C, 75 to 85 will remain chronically infected with hepatitis C. [23-25] Between 60 and 70 of these individuals will develop chronic liver disease, and from 5 to 20 will develop cirrhosis over 20 years.[26,27] If untreated, approximately 1 to 5 individuals out of the original 100 infected will die from cirrhosis or liver cancer. The most common causes of death among patients with chronic hepatitis C are drug overdose, HIV, and liver disease.[28-30] This reflects the epidemiology of hepatitis C infection: many are infected through injection drug use, which puts them at risk for both HIV and drug overdose. Evaluation of death certificates and modeling studies suggest that these statistics may underestimate the morbidity and mortality from HCV infection.[122-124]

Table 1. Natural History of Hepatitis C Infection over 20 Years

Condition	Number of individuals
Infection with hepatitis C	100
Develop symptoms	20-30
Remain asymptomatic	70-80
Develop chronic infection	75-85
Develop chronic liver disease	60-70
Develop cirrhosis	5-20
Die from cirrhosis or liver cancer	1-5

As described above, chronic hepatitis C is a slowly progressive disease. Up to 20% of patients develop cirrhosis over 20 to 30 years of infection.[26,27] The risk for cirrhosis may increase with time. One study estimated that the probability of cirrhosis was 16% after 20 years of infection, but increased to 41% after 30 years of infection.[26] Once bridging fibrosis or cirrhosis develops, patients with chronic HCV infection are at risk for the development of hepatocellular carcinoma. Factors associated with an increased risk for progression to cirrhosis include male sex, older age, co-infection with hepatitis B or HIV, obesity, alcohol intake, diabetes, and insulin resistance.[26,27,31-40]

1.2 Definitions

- *Cirrhosis*: progressive scarring of liver tissue that may affect the effectiveness of chronic hepatitis C treatment. Cirrhosis is typically biopsy-proven in clinical trials of chronic hepatitis C therapies.
- *Decompensated cirrhosis:* the presence of cirrhosis plus one or more complications including esophageal varices, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, or hepatocellular carcinoma.
- *Genotype*: a classification of hepatitis C based on genetic material in the RNA strands of the virus. There are six main genotypes, which are further divided into subtypes in some cases.
- *Interferon-ineligible:* patients in whom interferon therapy is contraindicated due to such conditions as anemia, alcohol abuse, advanced or decompensated cirrhosis, or severe psychiatric disorder.
- *Interferon-intolerant:* patients who discontinue interferon therapy prematurely due to side effects.
- *Sustained virologic response (SVR)*: absence of detectable HCV RNA, measured 12-24 weeks following the completion of treatment.
- *Relapse:* recurrence of detectable viral RNA at some point after achieving an undetectable HCV viral load during treatment.

- *Null response:* no reduction of at least 2 $\log_{10}$ in HCV RNA during prior treatment.
- *Partial response:* greater than a 2 $\log_{10}$ reduction in HCV RNA during prior treatment, but never achieving undetectable viral RNA.
- *Treatment-naïve:* not previously treated for chronic hepatitis C infection.
- *Treatment-experienced: o*ne or more previous attempts at treatment of chronic hepatitis C infection. This group may contain a mix of patients who relapsed, those with a partial response, and those with a null response to prior treatment.

The **METAVIR score** is a standardized measure of fibrosis and inflammation seen on a liver biopsy. The fibrosis score ranges from 0 to 4, and the inflammation activity score is measured from 0 to 3.

Fibrosis score:
F0 = no fibrosis
F1 = portal fibrosis without septa
F2 = portal fibrosis with few septa
F3 = numerous septa without cirrhosis
F4 = cirrhosis

Activity score:
A0 = no activity
A1 = mild activity
A2 = moderate activity
A3 = severe activity

The fibrosis score is particularly useful because patients with higher fibrosis scores are more likely to progress to cirrhosis and HCC and may warrant earlier treatment.

The **Ishak scale** is a second commonly reported histologic grading system for liver fibrosis that ranges from 0 to 6.

Ishak Scale
1 = no fibrosis (normal)
2 = fibrous expansion of some portal areas ± short fibrous septa
3 = fibrous expansion of most portal areas ± short fibrous septa
4 = fibrous expansion of portal areas with marked bridging (portal to portal, portal to central)
5 = marked bridging with occasional nodules (incomplete cirrhosis)
6 = cirrhosis

A rough approximation of how the two scoring systems compare is as follows:

Ishak	METAVIR
0	0
1, 2	1
3	2
4, 5	3
6	4

1.3 Treatment of Chronic Hepatitis C Infection

The primary goal of HCV treatment is the prevention of cirrhosis and hepatocellular carcinoma. The combination of pegylated interferon plus ribavirin (commonly referred to as "PR") has until recently been the backbone of treatment for patients infected with HCV. However, patients infected with genotype 1 tend to have a poor response to PR. As noted earlier, the first generation DAAs – the protease inhibitors boceprevir and telaprevir – were approved for treatment of genotype 1 in 2011. The viral clearance rate with first generation triple therapy (boceprevir or telaprevir + PR) is approximately double the cure rate of the combination of interferon and ribavirin alone. The approvals of simeprevir and sofosbuvir in 2013 were based on data demonstrating improved viral clearance rates in genotype 1 with less toxicity and shorter treatment duration. New DAAs and new combinations that eliminate the need for interferon are poised to enter clinical use with the promise of even higher rates of viral clearance, shorter treatment courses, and fewer side effects.

Because the natural history for the development of cirrhosis and HCC is long, treatment success is usually measured by the maintenance of a sustained virologic response (SVR), defined as undetectable serum HCV RNA for at least 24 weeks (SVR24) after the completion of treatment. The FDA changed its guidance for the primary outcome in studies of DAAs to treat chronic hepatitis C to SVR 12 weeks after the end of therapy in October 2013, and SVR12 was the primary outcome for the majority of the recent phase 3 studies of DAAs. SVR is a reasonable, but imperfect measure of a clinical "cure", and it varies somewhat based on when it is measured. For example, the PILLAR trial,[41] a phase 2B trial of simeprevir, reported the number of participants who had undetectable RNA at the end of treatment and at 12, 24, and 72 weeks after treatment. The number of patients with undetectable HCV RNA declined from 336 at the end of treatment to 303 (12 weeks), 300 (24 weeks), and 293 (72 weeks), respectively. Thus SVR12 was a reasonably stable representation of SVR24 (only 3/303 or about 1% relapsed between those two time points). However, relapses did continue over time, with an additional 7/300 (2.3%) relapsing between 24 and 72 weeks of follow-up. One meta-analysis summarized the data on relapse rates among patients treated with PR who achieved SVR12.[42] They found that approximately 6% of patients relapsed between 12 and 24 weeks (SVR12 53% versus SVR24 47%).[42] This may be less of a problem with the newer DAAs, although the data are still limited. A summary of five trials of sofosbuvir-containing regimens found that only 2 of 779 patients achieving SVR12 had detectable viral RNA at 24 weeks (0.3% relapse

rate).[43] In a meta-analysis of long-term outcomes with PR, the percent of patients with long-term viral clearance following SVR24 ranged from 98% to 100%.[44] Comparable data are not yet available for the newer DAA-based regimens.

Clinical trial results are typically better than real-world results.[45] Recent data from CVS/Caremark indicate that real world discontinuation rates for sofosbuvir regimens requiring interferon and/or ribavirin may be as high as five times greater than the rates reported in clinical trials.[46] In their data, 10.2% of 738 patients prescribed sofosbuvir + PR discontinued therapy compared to the standard of approximately 2% in the clinical trials. Similarly, 9.0% of 680 patients prescribed sofosbuvir + R discontinued therapy compared to 0-2.0% in the pivotal clinical trials.[46] However, preliminary results from the HCV-TARGET real-world registry, funded through unrestricted grants from a consortium of pharmaceutical companies manufacturing drugs to treat hepatitis C, reported discontinuation rates that were similar to those observed in the clinical trials.[47] In their data, 2.5% of 366 patients prescribed sofosbuvir + PR discontinued therapy compared to 2% in the clinical trials. Similarly, 3.6% of 645 patients prescribed sofosbuvir + R discontinued therapy compared to 0-2.0% in the clinical trials. It is important to note that in the HCV-TARGET registry, 25.7% of the patients treated with sofosbuvir + PR and 52.0% of the patients treated with sofosbuvir + R had not yet completed treatment, so these reported discontinuation rates are likely to be underestimates of the true values.[47]

Treatment of Genotype 1

Pegylated interferon plus ribavirin

Pegylated interferon plus ribavirin (PR) was the primary treatment of HCV for more than 10 years. In clinical trials, the SVR24 for patients with genotype 1 treated with PR ranged from 40% to 50%, but it was about 20% lower in real-world studies in part because of the poor tolerability of PR therapy and because of the special nature of patients willing to participate in clinical trials.[48-50] Interferon requires a weekly injection and commonly causes fatigue (50% to 60%), headache (50% to 60%), myalgias (40% to 55%), and fever (40% to 45%).[51] Other common side effects of PR include anemia (hemoglobin < 10 g/dL) in up to 30% of patients, generalized pruritus (25% to 30%), and psychiatric symptoms such as depression (up to 25%), insomnia, and anxiety (15% to 25%).[51] Ribavirin may cause birth defects, so women of child-bearing age must be on birth control during treatment.

For genotype 1, patients are treated for 48 weeks with once-weekly subcutaneous injections of pegylated interferon and twice-daily oral ribavirin taken with food. Routine monitoring is performed with dose reductions recommended for neutropenia, thrombocytopenia, anemia, depression, and worsening renal function.

Boceprevir and Telaprevir

The first generation protease inhibitors boceprevir and telaprevir were the first two DAAs approved by the FDA. After their approval in 2011, the standard of care for the treatment of genotype 1 became PR in combination with either boceprevir or telaprevir.[52-54] However, the manufacturer of telaprevir discontinued sales in the United States on October 16, 2014 due to declining use after the approval of simeprevir and sofosbuvir. Among treatment-naïve patients in clinical trials, PR plus boceprevir or telaprevir has a SVR24 between 70% and 75%.

Treatment with PR plus either boceprevir or telaprevir is challenging. Patients are required to take either six or 12 pills per day spaced every seven to nine hours with specific dietary restrictions. Both medications increase the risk for severe anemia, which is already common with PR treatment (increased from 30% with PR to 50% with either boceprevir or telaprevir).[51] The combination of PR plus boceprevir or telaprevir is associated with serious adverse event rates between 40% and 50%.[45,51,55] Neither can be used as monotherapy because resistance develops quickly.[56,57] Finally, boceprevir and telaprevir are strong inhibitors of the cytochrome P450 (CYP) 3A4 enzyme, leading to many potential drug interactions with statins, benzodiazepines, colchicine, St. John's wort, anticonvulsants, sulfonylureas, and some reverse transcriptase inhibitors.

Simeprevir and Sofosbuvir

Simeprevir is a NS3/4A protease inhibitor that was approved by the FDA for the treatment of HCV genotype 1 in November 2013. It is a second-generation protease inhibitor (boceprevir and telaprevir were first generation protease inhibitors). Simeprevir has several advantages over the earlier protease inhibitors. It may be taken once a day rather than six to 12 pills divided into doses taken every eight hours. It does not appear to increase the risk for anemia, which is a common, often severe, problem with the first generation protease inhibitors. Simeprevir must be used in combination with PR because viral resistance develops rapidly with monotherapy. Simeprevir is taken once daily with PR for 12 weeks followed by an additional 12 weeks of PR for treatment-naïve patients and patients who relapsed or by an additional 36 weeks of PR for prior partial and null responders (see Table 3 on page 11).

Sofosbuvir is the first drug in the class of HCV NS5B nucleotide analog polymerase inhibitors to be approved. Like the other DAAs, sofosbuvir should not be prescribed as monotherapy. It has been studied in combination with PR, with ribavirin alone, with simeprevir, and in combination with other DAAs that have not yet received FDA approval. Like simeprevir, sofosbuvir only needs to be taken once daily. The details of therapy are guided by genotype, prior treatment status, interferon eligibility, and liver histology. The FDA indication for patients with genotype 1 is sofosbuvir 400 mg daily with PR for 12 weeks; patients who are interferon-ineligible may consider sofosbuvir 400 mg plus R alone for 24 weeks (see Table 3 on page 11). For patients who are HIV co-infected, the treatment is the same as for patients who are not HIV co-infected.

Interferon-free therapy combining more than one DAA for Genotype 1

Boceprevir, telaprevir, simeprevir, and sofosbuvir were the first four DAAs approved by the FDA. More than 30 additional DAAs are in clinical trials. The new drugs attack different targets in the HCV life cycle and include NS3/4A protease inhibitors, nucleoside and nucleotide polymerase inhibitors, non-nucleoside polymerase inhibitors, NS5A inhibitors, and cyclophilin inhibitors. The names and classes of some of the new drugs are summarized in Table 2 on the following page.

At the time of the March 2014 CTAF assessment, preliminary results using several combinations of simeprevir + sofosbuvir with or without ribavirin had been presented at conferences. The study results have now been published, and on November 5, 2014, the FDA approved the combination of simeprevir 150 mg once daily plus sofosbuvir 400 mg once daily without ribavirin for patients with genotype 1 infection (see Table 3 on page 11).[58] Prior to FDA approval, observational studies reported that between 23% and 47% of patients with hepatitis C treated with sofosbuvir-containing combinations were being treated with off-label combinations of simeprevir + sofosbuvir.[46,47]

The FDA approved the combination of ledipasvir/sofosbuvir (LDV/SOF) formulated in a single tablet (Harvoni®) on October 10, 2014. It is taken one pill a day for eight to 24 weeks and is not taken with any additional drugs (see Table 3 on page 11).

Bristol-Meyers Squibb (BMS) has several drug combinations in development. Initial studies show promising results for the combination of daclatasvir + sofosbuvir.[59] BMS has three phase 3 studies of this combination in progress (ALLY 1, 2, and 3).

Table 2: Therapies for Hepatitis C by Class

Brand Name	Generic Name	Internal Name	Pharmaceutical Company
Pegylated Interferon Alfa			
PegIntron	peginterferon alfa-2b		Merck
Pegasys	peginterferon alfa-2a		Genentech
Nucleoside analog			
Ribasphere, Virazole	ribavirin		Genentech
RibaPak	ribavirin		Kadmon
Moderiba	ribavirin		AbbVie
NS3/4A Protease inhibitors			
Incivek	telaprevir		Vertex
Victrelis	boceprevir		Merck
Olysio	simeprevir	TMC435	Janssen and Medivir AB
Sunvepra	asunaprevir	BMS-650032	Bristol-Myers Squibb
n/a	vaniprevir	MK-7009	Merck
n/a	paritaprevir	ABT-450	AbbVie
n/a		MK-5172	Merck
Nucleoside and Nucleotide NS5B Polymerase Inhibitor			
Sovaldi	sofosbuvir	GS-7977	Gilead Sciences
n/a	mericitabine	RG7128	Roche
Non-Nucleotide NS5B Polymerase Inhibitor			
n/a	dasabuvir	ABT-333	AbbVie
n/a		BMS-791325	Bristol-Myers Squibb
n/a		ABT-072	AbbVie
NS5A Inhibitors			
Daklinza	daclatasvir	BMS-790052	Bristol-Myers Squibb
n/a	ledipasvir	GS-5885	Gilead Sciences
n/a	ombitasvir	ABT-267	AbbVie
n/a		GS-5816	Gilead
n/a		MK-8742	Merck
Combination pills			
Harvoni	ledipasvir/sofosbuvir	--	Gilead Sciences

The European Commission approved the use of daclatasvir as part of combination therapy in August 2014, but it has not been approved in the United States. BMS withdrew its application for the combination of asunaprevir + daclatasvir from the FDA in late 2014, but the combination is approved for use in Japan. BMS also has phase 3 studies of the combination of daclatasvir, asunaprevir, and BMS-791325 in progress (UNITY 1, 2, and 3).

In April 2014, AbbVie submitted an interferon-free combination to the FDA of paritaprevir/ritonavir (150/100mg) co-formulated with ombitasvir 25mg, dosed once daily, and dasabuvir 250mg with or without R (weight-based), dosed twice daily. This is known as the "3 DAA" or "3D" regimen. The FDA approved this combination on December 19, 2014, just after the CTAF public meeting.

Many physicians have been monitoring patients with chronic HCV infections but not treating them while waiting for new medical therapies (sometimes referred to as "warehousing"). Treatment rates

have increased since the approval of simeprevir and sofosbuvir, but many patients have been waiting for additional interferon- and ribavirin-free treatments.

Table 3. FDA Indications for New DAAs to Treat Genotype 1

Drug	Genotype	Treatment
Simeprevir	1	• 150 mg daily with PR x **12 weeks** plus PR for an additional **12 to 36 weeks**
Sofosbuvir	1	• 400 mg daily with PR x **12 weeks** • Alternate if interferon (IFN)-ineligible: 400 mg daily with R x **24 weeks**
Simeprevir + sofosbuvir	1	• 150 mg simeprevir with 400 mg sofosbuvir once daily x **12 weeks** for treatment-naïve and treatment-experienced without cirrhosis • 150 mg simeprevir with 400 mg sofosbuvir once daily x **24 weeks** for treatment-naïve and treatment-experienced with cirrhosis
Ledipasvir/ sofosbuvir	1	• 90 mg / 400 mg once daily x **12 weeks** for treatment-naïve with or without cirrhosis and treatment-experienced without cirrhosis • 90 mg / 400 mg once daily x **24 weeks** for treatment-experienced with cirrhosis • Alternate therapy for treatment-naïve patients without cirrhosis and HCV RNA < 6 million IU/ml: 90 mg / 400 mg once daily x **8 weeks**
Ombitasvir / paritaprevir/ ritonavir + dasabuvir	1	• 3D + R x **12 weeks** for genotype 1a without cirrhosis • 3D + R x **24 weeks** for genotype 1a with cirrhosis • 3D x **12 weeks** for genotype 1b without cirrhosis • 3D + R x **24 weeks** for genotype 1ab with cirrhosis

2. Clinical Guidelines

Each of the guidelines referenced below may address multiple hepatitis C genotypes. For the purposes of this review, only information specific to genotype 1 will be included. Websites were accessed on October 27, 2014. Interested parties should check available websites for current clinical guidelines, as they are being updated regularly.

The American Association for the Study of Liver Diseases (AASLD) / Infectious Diseases Society of America (IDSA) / International Antiviral Society – USA (IAS USA) (2014)

http://www.hcvguidelines.org

On January 29, 2014, the AASLD, IDSA, and IAS-USA launched an online guideline for the treatment of chronic hepatitis. The guidelines do not yet include consideration of ledipasvir/sofosbuvir. For genotype 1, current recommendations are 12 weeks of sofosbuvir + PR for interferon-eligible patients, and simeprevir + sofosbuvir ± R for interferon-ineligible patients. Alternative therapies for patients with genotype 1 with genotype 1b or genotype 1a without the Q80K polymorphism are 12 weeks of simeprevir + 24 weeks of PR for interferon-eligible patients and 12 weeks of sofosbuvir + 24 weeks of R for interferon-ineligible patients.

On November 20, 2014, the guidelines were updated to include recommendations on when and in whom to initiate therapy. Recommendations are that highest priority for treatment be given to patients at highest risk for severe complications, including those with advanced liver disease (METAVIR F3 or F4), liver transplant recipients, and patients with severe extrahepatic manifestations of hepatitis C.

The Department of Veterans Affairs (VA)

http://www.hepatitis.va.gov/provider/guidelines/index.asp#S2X

The VA guidelines have not yet addressed the use of ledipasvir/sofosbuvir. For treatment-naïve genotype 1 patients, the current VA recommendations are for 12 weeks of sofosbuvir + PR, with 12 weeks of simeprevir + 24 weeks of PR as an alternative for patients without the Q80K polymorphism. For treatment-naïve patients who are interferon-ineligible, the recommendation for non-cirrhotic patients is 24 weeks of sofosbuvir + R; an alternative treatment for this group and the recommended treatment for interferon-ineligible cirrhotics is 12 weeks of simeprevir + sofosbuvir + R (not FDA-approved at the time the guidelines were published). Treatment-experienced patients who are interferon-eligible are recommended to receive 12 weeks of sofosbuvir + PR. The recommendation for treatment-experienced, interferon-ineligible patients is 12 weeks of simeprevir + sofosbuvir + R (not FDA-approved at the time the guidelines were published). Alternative recommendations for treatment-experienced patients are 12 weeks of simeprevir + 24-48 weeks of PR for patients without Q80K polymorphism, and 12 weeks of

simeprevir + sofosbuvir + R for patients with cirrhosis (not FDA-approved at the time the guidelines were published).

The VA guidelines currently state that it is reasonable to defer treatment in non-cirrhotic patients without significant extrahepatic disease due to the FDA's expected approval of several highly-effective, low side-effect, interferon-free treatments within the next one to two years.

European Association for the Study of the Liver (EASL)

http://www.easl.eu/_clinical-practice-guideline

EASL has also not yet addressed the use of ledipasvir/sofosbuvir in its guidance. The most recent guideline update in April 2014 includes the same regimens for genotype 1 infections as the AASLD and VA guidelines but also includes 12-24 weeks of daclatasvir + PR as an alternative for patients with genotype 1b infections. Interferon-ineligible patients are recommended to receive 24 weeks of sofosbuvir + R, 12 weeks of simeprevir + sofosbuvir ± R, or 12-24 weeks of sofosbuvir + daclatasvir ± R.

EASL recommends that all patients with compensated liver disease due to HCV be considered for treatment and that treatment be prioritized for patients with significant fibrosis (METAVIR F3 or F4) or significant extrahepatic manifestations. EASL states that treatment of patients with METAVIR score F2 is justified. They suggest that treatment for patients with METAVIR scores of F0-F1 may be deferred and that regular assessments be made to assess for disease progression or other reasons to initiate treatment.

National Institute for Health and Care Excellence (NICE)

http://www.nice.org.uk/guidance/conditions-and-diseases/liver-conditions/hepatitis

http://cks.nice.org.uk/hepatitis-c

NICE has nearly completed its technology appraisals of simeprevir and sofosbuvir and is currently developing technology assessments of daclatasvir, faldaprevir, and two combination therapies: ledipasvir/sofosbuvir and paritaprevir/ritonavir/ombitasvir + dasabuvir (3D).

Broader hepatitis C treatment guidelines have not been updated, however, since 2012 and continue to recommend treatment with telaprevir or boceprevir + PR for patients with genotype 1 infection. The NICE website does not indicate when its guideline will be updated.

3. Coverage Policies

Coverage policies of a variety of public and private payers for sofosbuvir, simeprevir, and ledipasvir/sofosbuvir were reviewed on **November 3, 2014**. Interested parties should obtain current, specific coverage policy information from individual payers, as these policies are being updated regularly. Each of the policies may address multiple hepatitis C genotypes, but for the purposes of this review, only policies for genotype 1 will be included. Tables summarizing details of coverage policies are provided in Appendix A and include website links for each payer/drug regimen.

3.1 Ledipasvir/sofosbuvir (Harvoni)

Medicare & Medicaid

No publicly-available coverage policies, prior authorization protocols, or formulary designations for ledipasvir/sofosbuvir were available from CMS or Medi-Cal, California's Medicaid agency.

Regional Private Payers

Health Net (revised October 28, 2014)
https://www.healthnet.com/static/general/unprotected/html/national/pa_guidelines/harvoni_natl.html

Health Net's interim guidelines for ledipasvir/sofosbuvir provide coverage for patients with genotype 1 chronic hepatitis C infections who have not failed previous treatment that included sofosbuvir and who have fibrosis demonstrated by liver biopsy or noninvasive test corresponding to METAVIR score ≥ 2 or biopsy corresponding to Ishak score ≥ 3. Coverage is not available for those with decompensated liver disease.

National Private Payers/Pharmacy Benefit Managers

Aetna (revised October 31, 2014)
http://www.aetna.com/products/rxnonmedicare/data/2014/GI/hepatitis_c.html

Aetna covers ledipasvir/sofosbuvir for patients with genotype 1 chronic hepatitis C infections and compensated liver disease who are treatment-naïve or have failed previous treatment with PR ± any protease inhibitor. Aetna's policy bulletin states that for patients meeting the criteria for ledipasvir/sofosbuvir, its use will be required over other simeprevir or sofosbuvir regimens unless the patient has a contraindication or intolerance to any of its ingredients. Ledipasvir/sofosbuvir is noted as being less costly and/or more effective in achieving SVR than any other simeprevir or

sofosbuvir regimens for previously treated, non-cirrhotic patients. For reauthorization at six weeks of treatment, hepatitis C RNA levels must have declined more than $2\log_{10}$ IU/ml at treatment week four.

Anthem/WellPoint/Express Scripts (revised October 15, 2014)
http://www.anthem.com/provider/noapplication/f0/s0/t0/pw_e225443.pdf?na=pharminfo&

Anthem covers ledipasvir/sofosbuvir for adults with genotype 1 chronic hepatitis C infections and compensated liver disease who are post-liver transplant, have serious extrahepatic manifestations, or have advanced liver disease demonstrated by imaging or biopsy corresponding to METAVIR, IASL, Batts-Ludwig scores ≥ 3 or Ishak score ≥ 4. Ledipasvir/sofosbuvir is not covered for patients with severe renal impairment, patients who have failed prior treatment with sofosbuvir- or ledipasvir-based regimens, and in combination with other NS5A or NS5B inhibitors. Patients must not be actively abusing illicit drugs and/or alcohol, or must be in concurrent substance abuse treatment.

UnitedHealthcare (effective October 15, 2014)
https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Ox_MPUB_Future_Pharmacy/PA_Med_Nec_Harvoni_101414.pdf

UnitedHealthcare limits the use of ledipasvir/sofosbuvir to patients with genotype 1 chronic hepatitis C infections who have advanced liver disease (biopsy or imaging corresponding to METAVIR score ≥ F3 or its equivalent on the Batts-Ludwig, Knodell, or Ishak scales) or have serious extrahepatic manifestations. Patients meeting these criteria may be either treatment-naïve or have previously failed regimens with PR ± any protease inhibitor or sofosbuvir. Patients re-infected with genotype 1 hepatitis C post liver transplant are eligible for treatment with ledipasvir/sofosbuvir. Cirrhotic patients must have stage 4 hepatic fibrosis (METAVIR score of F4 or equivalent). All patients prescribed ledipasvir/sofosbuvir must either have no history of substance abuse or have abstained from illicit drug/alcohol abuse for the past 6 months.

3.2 Sofosbuvir

Sofosbuvir in combination with PR has been covered by most payers included in our review, with three payers requiring a fibrosis score of ≥F3 and one requiring a fibrosis score of ≥F2; Medi-Cal also allowed for treatment of patients with a lower fibrosis score if they have severe extrahepatic manifestations. Coverage for sofosbuvir + R and simeprevir + sofosbuvir ± R was generally limited to patients who were interferon-ineligible. Several payers had limits on sofosbuvir coverage for treatment-experienced patients, often requiring that they not have a previous treatment failure with a regimen inclusive of sofosbuvir. Of the four payers that have released policies on ledipasvir/sofosbuvir since its approval by the FDA in October 2014, Aetna and Health Net have

restricted coverage for SOF + PR, SOF + R, or SMV + SOF ± R to patients with an intolerance or contraindication to either ledipasvir or sofosbuvir.

3.3 Simeprevir

Simeprevir in combination with PR has been covered by most payers included in our review, with two payers requiring a fibrosis score of ≥F3 and one requiring a fibrosis score of ≥F2; Medi-Cal also allowed for treatment of patients with a lower fibrosis score if they have severe extrahepatic manifestations. All but one of the payers excluded coverage for genotype 1a patients with the Q80k polymorphism; UnitedHealthcare (UHC) noted that SMV + PR is not the recommended treatment for these patients and an alternative is encouraged. Several payers had limits on simeprevir coverage for treatment-experienced patients, often requiring that they not have a previous treatment failure with a protease inhibitor. As with sofosbuvir, Aetna and Health Net have restricted coverage for SMV + PR to patients with an intolerance or contraindication to either ledipasvir or sofosbuvir.

3.4 Coverage Policies across Payers

Aetna and Humana's coverage policies did not specify a level of liver fibrosis needed for coverage of these treatments, and CVS/Caremark required a METAVIR score ≥ F3 only for SMV + SOF ± R. Medi-Cal, Anthem, and UHC covered treatment with a fibrosis score of ≥F3; Medi-Cal also allowed for treatment of patients with a lower fibrosis score if they have severe extrahepatic manifestations. Health Net covered these treatments with a fibrosis score of ≥F2 (except for SMV + SOF ± R, for which Health Net has no publicly available policy). As noted above, two of the four payers with ledipasvir/sofosbuvir policies (Aetna and Health Net) have restricted coverage for simeprevir- or sofosbuvir-based regimens to patients with an intolerance or contraindication to either ledipasvir or sofosbuvir.

Coverage for several patient characteristics is summarized below:

- *Treatment-experienced* – for most payers, patients were generally eligible for treatment with a protease or polymerase inhibitor if they had not failed previous treatment with the same type of inhibitor. UHC covered ledipasvir/sofosbuvir for patients who had any previous treatment failure, including sofosbuvir-based regimens. Anthem did not cover simeprevir- or sofosbuvir-based regimens for patients who had failed therapy with any protease or polymerase inhibitor in combination with PR and did not cover LDV/SOF for patients who had failed either LDV or SOF.
- *Decompensated cirrhosis* – most payers covered SOF + R or SMV + SOF ± R if decompensation was the reason for a patient's interferon-ineligibility
- *Hepatocellular carcinoma* – most payers covered SOF + R if for patients who were awaiting liver transplants and required that treatment be discontinued if a liver transplant occurs

- *Post-liver transplant* – most payers covered SOF + PR, SOF + R, or SMV + SOF ± R for patients who had a liver transplant, although CVS/Caremark only covered SMV + SOF ± R for patients who are treatment-naïve post-transplant. Anthem and UHC covered ledipasvir/sofosbuvir for all post-liver transplant patients, Aetna did not cover this treatment, and Health Net did not specify in this category.
- *Severe renal impairment* – generally not covered or not specified for sofosbuvir-based regimens, and generally not specified for simeprevir-based regimens

Several other coverage requirements are summarized below:

- *Treatment discontinuation if HCV RNA levels not reduced* – five of the seven payers required or recommended this for one or more of the DAA drug regimens
- *Specialist to prescribe or consult on these treatments* – three of the seven payers recommended or required this
- *Abuse of illicit drugs and/or alcohol* – Medi-Cal, Anthem, and UHC had requirements related to this, including concurrent substance abuse treatment, toxicology tests, and/or six months of abstinence prior to treatment

4. Previous Systematic Reviews and Technology Assessments

We were unable to identify any systematic reviews or formal technology assessments that address the interferon-free combinations of two or more DAAs considered in this assessment.

4.1 Formal Health Technology Assessments

No formal health technology assessments were identified for the new multiple DAA combinations. However, the Canadian Agency for Drugs and Technologies in Health (CADTH, http://www.cadth.ca) is currently reviewing new DAA agents (among patients with genotype 1 chronic hepatitis C only). Similarly, the National Institute for Health and Care Excellence (NICE, http://www.nice.org.uk) in England is reviewing the new DAAs and has draft guidance on sofosbuvir.

4.2 Systematic Reviews

No published systematic reviews of the newest DAAs were identified.

5. Ongoing Studies

The table on the next four pages summarizes the ongoing and recently completed Phase III and IV trials with at least one arm including the following combinations of two or more DAAs:

1) Simeprevir + sofosbuvir
2) Daclatasvir + sofosbuvir
3) Ledipasvir/sofosbuvir
4) 3D ± ribavirin

We did not include studies focusing exclusively on the treatment of HCV genotypes 2, 3, 4, 5, or 6, or on combinations of drugs that were not considered in this assessment.

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Simeprevir + Sofosbuvir					
Simeprevir / Sofosbuvir With or Without Ribavirin (RBV) for Interferon-intolerant or Ineligible (IFN-II) Patients With Chronic Hepatitis C (Phase IV) NCT02214420	Interventional N = not provided	SMV + SOF vs. SMV + SOF + R	• HCV • Interferon intolerant or ineligible	SVR12	August 2015
The SIM-SOF Trial: A Randomized Trial Comparing Simeprevir-Sofosbuvir Versus Peginterferon/Ribavirin/Sofosbuvir for the Treatment of Chronic Hepatitis C Genotype-1a-infected Patients With Cirrhosis (Phase IV) NCT02168361	RCT Open label N = 82	SMV + SOF vs. SOF + PR	• GT 1a • Cirrhosis, compensated	SVR12	Nov 2014
Efficacy and Safety of a 12-Week Regimen of Simeprevir in Combination With Sofosbuvir in Treatment-Naïve or -Experienced Subjects With Chronic Genotype 1 Hepatitis C Virus Infection and Cirrhosis (Phase III) NCT02114151	Cohort, single arm Open-label N = 103	None	• GT 1 • Treatment-naïve and experienced • Cirrhosis, compensated	SVR12	April 2015
Efficacy and Safety of a 12- or 8-Week Treatment Regimen of Simeprevir in Combination With Sofosbuvir in Treatment-Naïve and -Experienced Subjects With Chronic Genotype 1 Hepatitis C Virus Infection Without Cirrhosis (Phase III) NCT02114177	RCT Open-label N = 310	SMV + SOF for 8 weeks Vs. SMV + SOF for 12 weeks	• GT 1 • Non-cirrhotic • Treatment-naïve and experienced	SVR12	April 2015

Daclatasvir + Sofosbuvir					
ALLY-1: Evaluation of Daclatasvir, Sofosbuvir, and Ribavirin in Genotype 1-6 Chronic Hepatitis C Infection Subjects With Cirrhosis Who May Require Future Liver Transplant and Subjects Post-Liver Transplant (Phase III) NCT02032875	Cohort, multiple arm Open label N = 110	None	• GT 1, 2, 3, 4, 5, or 6 • Chronic HCV before or after liver transplantation	SVR12	March 2015
ALLY-2: Evaluation of Daclatasvir Plus Sofosbuvir in Treatment-naïve and Treatment-experienced Chronic Hepatitis C (Genotype 1- 6) Subjects Coinfected With HIV (Phase III) NCT02032888	RCT Open label N = 200	DCV + SOF for 8 weeks vs. DCV + SOF for 12 weeks	• GT 1, 2, 3, 4, 5, or 6 • Treatment-naïve or experienced • HIV-1 co-infection	SVR12	Jan 2015
Ledipasvir/Sofosbuvir					
Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin in Treatment-Naïve and Treatment-Experienced Japanese Subjects With Chronic Genotype 1 HCV Infection (Phase IIIb) NCT01975675	RCT, multiple arm Open Label N = 341	LDV/SOF vs. LDV/SOF + R	• GT1 • Treatment-naïve or experienced • Japanese patients	SVR 12 Major adverse events	Aug 2014 (completed recently)
Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Subjects With Chronic Genotype 1 or 4 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 Co-infection (Phase III) NCT02073656	Cohort, single arm Open label N = 300	None	• GT1 and GT4 • HIV-1 co-infection • Treatment-naïve and experienced	SVR12 Major adverse events	June 2016
Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination in Treatment-Naïve and Treatment-Experienced Subjects With Chronic Genotype 1 HCV Infection (Phase III) NCT02021656	Cohort, single arm Open label N = 360	None	• GT1 • Treatment-naïve and experienced • Korean/Taiwanese patients	SVR12 Major adverse events	June 2017

3D ± R					
MALACHITE-1: Efficacy and Safety of ABT-450/Ritonavir/ABT-267 and ABT-333 Co-administered With and Without Ribavirin Compared to Telaprevir Co-administered With Pegylated Interferon α-2a and Ribavirin in Treatment-Naïve Adults With Chronic Hepatitis C Genotype 1 Virus Infection (Phase III) NCT01854697	RCT Open label N = 314	3D + R vs. 3D vs. Telaprevir + PR	• GT1 • Treatment-naïve • Non-cirrhotic	SVR12	July 2015
MALACHITE-2: Efficacy and Safety of ABT-450/Ritonavir/ABT-267 and ABT-333 Co-administered With Ribavirin Compared to Telaprevir Co-administered With Pegylated Interferon a-2a and Ribavirin in Treatment-Experienced Adults With Chronic Hepatitis C Genotype 1 Virus Infection (Phase III) NCT01854528	RCT Open label N = 150	3D + R vs. 3D vs. Telaprevir + PR	• GT1 • Treatment-experienced	SVR12	July 2015
TURQUOISE-CPB: Safety and Efficacy of ABT-450/Ritonavir/ABT-267 and ABT-333 With Ribavirin in Adults With Genotype 1 Chronic Hepatitis C Virus Infection and Decompensated Cirrhosis (Phase III) NCT02219477	Cohort, multiple arms Open label N = 50	Treatment for 12 vs. 24 weeks	• GT1 • Cirrhosis, decompensated (Child Pugh score 7-9)	SVR12	October 2016
TURQUOISE-I: Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered With Ribavirin (RBV) in Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Human Immunodeficiency Virus, Type 1 (HIV-1) Coinfection (Phase II/III) NCT01939197	RCT Open Label N = 300	Treatment for 12 vs. 24 weeks	• GT1 • HIV-1 Co-infection	SVR12	May 2016
TURQUOSE-III: Safety and Efficacy of Ombitasvir/ABT-450/Ritonavir and Dasabuvir in Adults With Genotype 1b Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (Phase III) NCT02219503	Cohort, single arm Open label N = 50	None	• GT1b • Cirrhosis (Child-Pugh score 5 or 6)	SVR12	Nov 2015

TURQUOISE-IV: Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered With Ribavirin (RBV) in Adults With Genotype 1b Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (Phase III) NCT02216422	Cohort, single arm Open label N = 36	None	• GT1b • Cirrhosis	SVR12	Sep 2015
TOPAZ-I: Long-Term Outcomes With ABT-450/Ritonavir/ ABT-267 (ABT-450/r/ABT-267) and ABT-333 With or Without Ribavirin (RBV) in Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (Phase III) NCT02219490	Cohort, single arm Open label N = 1650	3D ± R, for 12 or 24 weeks	• GT1	All-cause and liver-related death, liver decompensation, liver transplantation, and HCC	Dec 2020
TOPAZ-II: Long-term Outcomes With ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With or Without Ribavirin (RBV) in Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (Phase III) NCT02167945	Cohort, single arm Open label N = 600	3D ± R, for 12 or 24 weeks	• GT1	All-cause and liver-related death, liver decompensation, liver transplantation, and HCC	March 2020
RUBY-I: Safety and Efficacy of Ombitasvir/ABT-450/Ritonavir and Dasabuvir With or Without Ribavirin (RBV) in Treatment-Naïve Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection, With Severe Renal Impairment or End-Stage Renal Disease (Phase III) NCT02207088	Cohort, single arm Open label N = 40	3D vs. 3D + R	• GT1 • Treatment-naïve • Severe or end-stage renal impairment	SVR12	March 2016

6. Evidence Review (Methods & Results)

The goal of this technology assessment is to evaluate the comparative effectiveness and value of new combinations of two or more DAAs in the treatment of chronic HCV genotype 1 infection. We compared the four combination therapies that are expected to be approved by the end of 2014 based on new drug applications (NDAs) to the FDA with the three FDA-approved uses of single DAA therapy with simeprevir or sofosbuvir that were evaluated in our March 2014 assessment (see Table 4 below). There are no randomized or other studies that directly compare the new therapies. The majority of the studies compare different dosing regimens of the same drug combinations to each other but not to older therapies like PR or PR plus one of the first generation protease inhibitors. For our prior review, there were sufficient randomized trials comparing boceprevir, telaprevir, simeprevir, and sofosbuvir to the combination of pegylated interferon and ribavirin (PR) to perform a network meta-analysis. Because there are no randomized trials or other studies directly comparing the interferon-free combinations considered in this review to PR or to each other, it is not possible to perform a network meta-analysis in this review. Instead, we summarize the proportion of patients achieving SVR12 with each new combination and combine them using a meta-analysis of proportions.[183] To allow comparisons with the drug combinations for genotype 1 considered in the prior review, we also calculate new summary estimates for the proportion of patients who achieve SVR using the same methodology. These estimates differ somewhat from those reported in the prior review because of the different method used to produce the summary estimate and because we are now estimating the results in four patient subgroups (naïve, non-cirrhotic; naïve, cirrhotic; experienced, non-cirrhotic; experienced, cirrhotic) rather than two subgroups (naïve, experienced).

Table 4: Therapies Considered in this Assessment

Brand Name	Generic Name	Abbreviation	Pharmaceutical Company
FDA-approved comparators from prior review			
Olysio + PR	Simeprevir + PR	SMV + PR	Janssen and Medivir AB
Sovaldi + PR	Sofosbuvir + PR	SOF + PR	Gilead Sciences
Sovaldi + R	Sofosbuvir + R	SOF + R	Gilead Sciences
FDA-approved combinations since prior review			
Olysio + Sovaldi	Simeprevir + sofosbuvir	SMV + SOF	Janssen + Gilead Sciences
Harvoni	Ledipasvir/sofosbuvir	LDV/SOF	Gilead Sciences
Combinations pending FDA approval at the time of this review (12/18/14)			
Daklinza + Sovaldi	Daclatasvir + sofosbuvir	DCV + SOF	Bristol-Myers Squibb + Gilead Sciences
3D	Paritaprevir/ritonavir/ ombitasvir + dasabuvir	3D	AbbVie

We included all prospective randomized trials and cohorts that reported SVR12 or SVR24 in HCV genotype 1 infected populations. We used fixed effects meta-analysis to summarize the SVR12 and discontinuation rates within each treatment regimen, but any comparison of these summary SVR12 rates between treatments should be made cautiously because differences in the study samples may

explain some of the differences in response rates. To calculate the SVR and discontinuation rates in each individual study, we used the number of patients randomized, even if study subjects were later found to be ineligible, never received treatment, or withdrew consent for the trial. The discontinuation rate includes patients who were lost to follow-up, withdrew consent, or stopped treatment due to adverse events. For our primary analyses, we focused on the four subgroups noted above: treatment-naïve patients with and without cirrhosis and treatment-experienced patients with and without cirrhosis. These represent the primary criteria guiding the choice of therapy for HCV genotype 1.

The Medline database, Embase, Cochrane clinical trials database, Cochrane reviews database, the Database of Abstracts of Reviews of Effects (DARE), the Web of Science, and BIOSIS previews were searched using the key words "simeprevir" OR "sofosbuvir" OR "daclatasvir" OR "ombitasvir" OR "abt-450." The search was performed for the period from 1945 through September 10, 2014. Full details of the search are in Appendix B. The bibliographies of systematic reviews and key articles were manually searched for additional references. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. Because of the paucity of published data, we included meeting abstracts, FDA documents, and press releases as sources of information. For the results of a study to be included in the meta-analysis of SVR, at least one study group must have received a treatment regimen with dosing similar to the likely final FDA dose for the particular indication. We did not treat the data from study abstracts or FDA documents differently from that abstracted from published studies. If both were available, we preferentially used data from the published study.

The search identified 608 potentially relevant references (see Figure 1 on page 27). After elimination of duplicate and non-relevant references, the search identified 54 publications and abstracts describing clinical trials of new DAAs for the treatment of HCV genotype 1. The primary reasons for study exclusion were (a) early dose finding studies, (b) no data on genotype 1, (c) lack of SVR or other clinical outcomes, or (d) reviews and commentaries. Some of the publications reported the results from more than one study. For genotype 1, there were five studies of simeprevir + PR using the dose recommended by the FDA[41,60-63] and an additional four publications describing five studies of a lower dose alternative in Japan.[64-67] There were three studies of sofosbuvir + PR[68-70] and three studies of sofosbuvir + R.[71-73] For combination therapy with sofosbuvir, there was one published study of simeprevir + sofosbuvir,[58] six publications[74-79] and two abstracts[80,81] of ledipasvir/sofosbuvir, and one published study of daclatasvir + sofosbuvir.[59] Evidence on additional combination therapies included six publications on daclatasvir + asunaprevir[82-87] and six publications on paritaprevir (ABT-450)/ritonavir/ombitasvir + dasabuvir, with or without ribavirin (3D ± R).[88-93] In addition, there were 11 publications on other combinations,[94-103] three using the new combinations in HIV co-infected patients,[104-106] and three in patients around the time of liver transplant.[107-109]

We adopted the approach of the ICER Evidence Rating Matrix to evaluate the evidence for each therapy (ICER Evidence Rating Matrix).[110] The quality of individual studies was assessed by

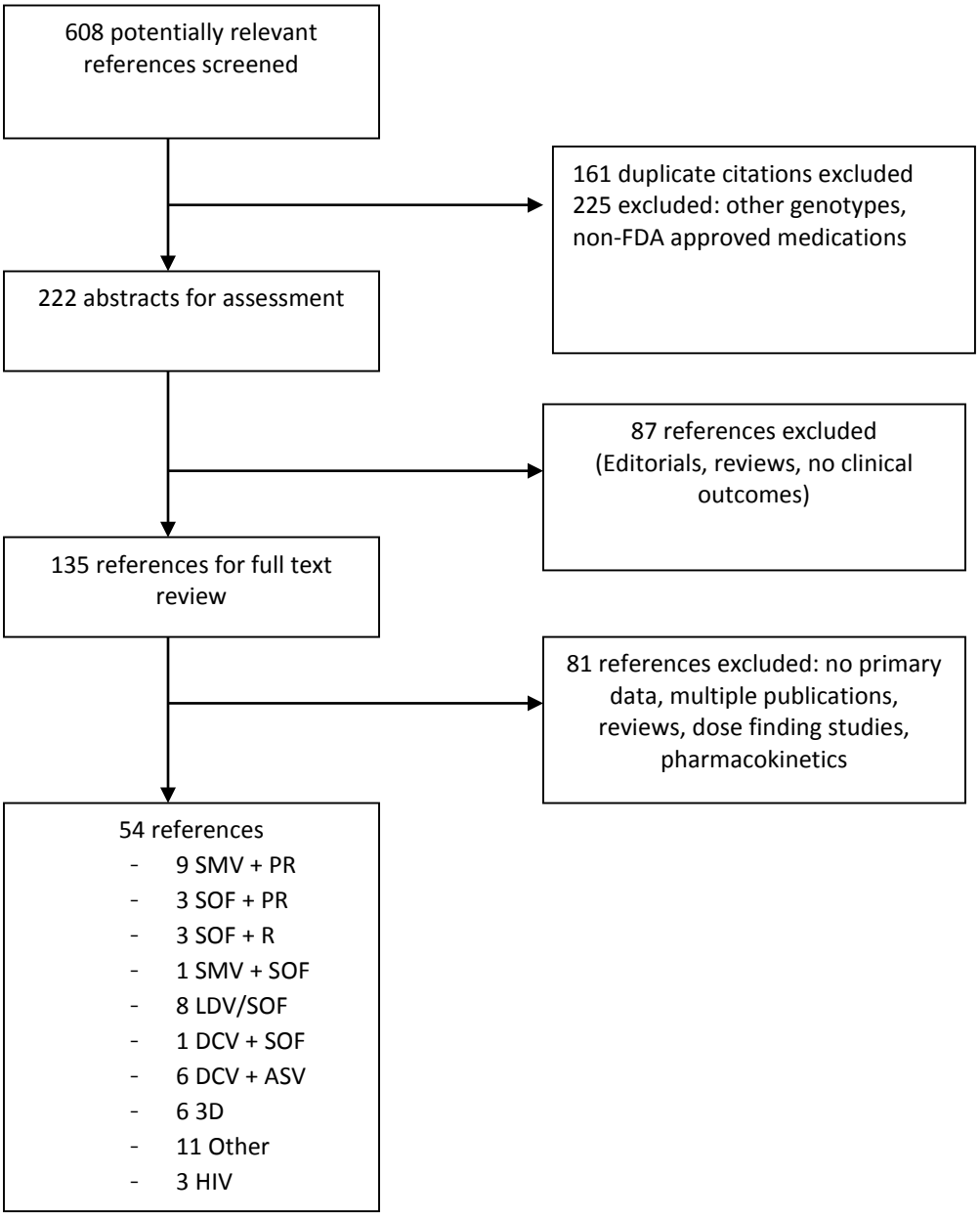
considering the domains listed below, which are adapted from the methods guide of the Agency for Healthcare Research & Quality (AHRQ):

- Similarity of baseline characteristics and prognostic factors between comparison groups
- Well-described methods for randomization and concealment of treatment assignment
- Use of valid, well-described primary outcomes
- Blinding of subjects, providers, and outcome assessors
- Intent-to-treat analysis (all randomized subjects included)
- Limited and non-differential loss to follow-up
- Disclosure of any conflicts of interest

The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.

Figure 1. Selection of Studies for Inclusion in Review



Key Patient Outcomes

The four most important outcomes in chronic HCV infection are the development of decompensated liver cirrhosis, hepatocellular carcinoma, liver transplantation, or death from liver-related causes. Because HCV has such a long natural history (often 20-40 years before the development of cirrhosis and HCC), large randomized trials with long-term follow-up are needed to demonstrate improvement in these outcomes. None of the studies identified in the search evaluated these four outcomes. For new drug evaluation, the primary outcome has been the sustained absence of HCV viral RNA for at least 24 weeks after the end of therapy (SVR24). The FDA

changed its guidance for the primary outcome in studies of DAAs to treat chronic hepatitis C to SVR 12 weeks after the end of therapy in October 2013, and SVR12 was the primary outcome for the majority of the recent phase 3 studies of DAAs.

The vast majority of patients with SVR24 remain HCV free during long-term follow-up. In several studies with five or more years of follow-up, 91% to 100% of patients remained virus free.[111-114] Additionally, patients with SVR24 have marked improvements or normalization of their liver function enzymes as well as improvements in liver histology.[111-116] More importantly, SVR24 has been associated with improvements in quality of life and a reduction in fatigue within months of treatment.[117,118] Recent studies have demonstrated that SVR24 is associated with decreases in decompensated liver disease, hepatocellular carcinoma, liver transplant, and all-cause mortality.[111,119-123] For example, in the HALT-C trial, the investigators prospectively followed 526 patients with advanced fibrosis who received treatment with PR (140 patients with SVR; 386 patients with either non-response, breakthrough, or relapse to therapy) for a median of approximately seven years.[120] The primary outcomes were death, liver transplant, death from liver-related causes, and decompensated liver failure. There was more than an 80% reduction in all clinically important outcomes including death or liver transplantation (HR=0.17, 95% CI: 0.06–0.46), decompensated liver disease or death from liver-related causes (HR=0.15, 95% CI: 0.06–0.38), and incident HCC (HR=0.19, 95% CI: 0.04–0.80).

In a much larger observational study of VA patients using data from their electronic medical records, the benefits of achieving SVR were somewhat lower. Over six years of follow-up, there was a 27% reduction in liver-related complications (HR 0.73, 95% CI 0.66 to 0.82) and a 45% reduction in all-cause mortality (HR 0.55, 95% CI 0.47to 0.64). The VA study compared patients with an undetectable viral load at one point in time following therapy to those with no documentation of an undetectable viral load.[123] Confounding by indication (sicker patients may be more likely to receive treatment) in the VA study may explain some of the difference between it and studies like HALT-C, which compared responders to non-responders in a population of treated patients.

All of the studies linking SVR to clinical outcomes are observational and thus may be subject to residual confounding. In addition, it is important to note that among patients with SVR, those with cirrhosis prior to treatment were still at risk for HCC during follow-up.[111,112,114,119,120,124] Thus, achieving an SVR24 will not prevent the complications of chronic HCV infection for all patients.

6.1 Overview of the Key Studies by Treatment Regimen

This review begins with a summary of the three single DAA treatments reviewed in the March 2014 CTAF assessment, simeprevir and sofosbuvir, because these represent the current standard used to assess the new drug therapies. Then we will review the two new FDA-approved combinations of two DAAs, simeprevir + sofosbuvir and ledipasvir/sofosbuvir. Finally, we will consider the two

additional DAA combinations likely to be approved by the end of 2014, daclatasvir + sofosbuvir and 3D. Tables summarizing the results for the individual studies are in Appendix C. In addition, tables summarizing the results of the combination of daclatasvir + asunaprevir, which was withdrawn from the FDA, can also be found in Appendix C. Following this overview, the summary estimates for each of the seven primary treatment regimens will be compared.

Simeprevir + PR

As described in our prior assessment, there are data available from 10 trials of simeprevir in patients with HCV genotype 1 infections (see Appendix Tables C1 and C2 for details). There are two phase 2 trials (PILLAR, ASPIRE), three phase 3 trials (QUEST-1, QUEST-2, PROMISE), and five Japanese trials (DRAGON, CONCERTO 1-4). The evidence base is remarkable for the large number of randomized trials with an appropriate comparator as a control (8/10 trials). However, the Japanese trials use a lower dose of simeprevir (100 mg rather than 150 mg), so results from those trials do not directly apply to patients in the United States. Without the Japanese trials, 847 patients were randomized to the FDA-approved dose and duration of simeprevir + PR. The quality of the data for simeprevir + PR is higher than that for most of the other therapies, because of the large number of patients randomized and the number of randomized trials with an appropriate comparator. The primary weaknesses of the evidence base for simeprevir + PR is the use of the intermediate outcome, SVR. As noted in the prior review, patients with the Q80k polymorphism have a lower response rate to combination therapy with simeprevir, which decreases the population of patients eligible for simeprevir + PR. For this assessment, we elected to present the SVR results for simeprevir + PR in all patients with genotype 1 infections to allow direct comparisons with the new DAA combinations being evaluated. This underestimates the efficacy of simeprevir + PR in patients without the Q80K polymorphism. Please see our March 2014 assessment for the efficacy estimates in patients without the Q80K polymorphism.

Sofosbuvir + PR

The clinical trial data for sofosbuvir are more complex (see Appendix Tables C3 and C4). There are data available from only three trials of sofosbuvir that included patients infected with genotype 1 (PROTON, ATOMIC, NEUTRINO), and none of the trials included a control group without sofosbuvir. None of the trials compared sofosbuvir to PR plus another active agent, and a total of 391 patients were randomized to sofosbuvir + PR for 12 weeks. The quality of the trials was lower than that for simeprevir because there were no randomized trials comparing sofosbuvir + PR to a prior standard therapy. As with simeprevir, the outcome was SVR, an intermediate outcome. In addition, there are no data on the effectiveness of sofosbuvir + PR in treatment-experienced patients.

Sofosbuvir + R

The evidence base for sofosbuvir + R for 24 weeks is even sparser (see Appendix Tables C5 and C6). Only 54 patients with genotype 1 have been studied in clinical trials. There are no treatment-

experienced patients treated for 24 weeks in the studies and only six patients with cirrhosis treated for 24 weeks. There are no controlled studies, and the outcomes were all intermediate (SVR).

Simeprevir + sofosbuvir

The COSMOS trial is the only published study of the combination of simeprevir + sofosbuvir (see Appendix Tables C7 and C8). The study enrolled 80 treatment-experienced patients with genotype 1 fibrosis stages F0 to F2 (Cohort 1) and treated them with four different combinations: simeprevir + sofosbuvir for 12 weeks; simeprevir + sofosbuvir for 24 weeks; simeprevir + sofosbuvir + ribavirin for 12 weeks; or simeprevir + sofosbuvir + ribavirin for 24 weeks. Only 14 patients in Cohort 1 received the FDA-indicated dose of simeprevir + sofosbuvir for 12 weeks.

The study also enrolled 87 patients with genotype 1 fibrosis stages F3 or F4 (Cohort 2) and treated them with the same four combinations. About half of the patients in Cohort 2 (40/87) were treatment-naïve. Only 10 patients in Cohort 2 had cirrhosis and were treated with the FDA-indicated dose: 24 weeks of simeprevir + sofosbuvir.

Eleven patients did not complete the study (6.5%) and the overall SVR12 was 92% (154/168). The number of patients treated according to the FDA indication was small (n=31, see Appendix Table C8), but their overall SVR12 was high (97%). As with the prior studies, the quality of data is limited by the lack of any appropriate control group, the use of an intermediate outcome, and the level of uncertainty due to the small number of patients studied in each of the key patient subgroups.

Ledipasvir/sofosbuvir

The evidence base is larger for the combination of ledipasvir/sofosbuvir (see Appendix Tables C9 and C10). There are five phase 2 studies and three phase 3 studies. These studies include 841 patients with HCV genotype 1 who received the FDA indicated dose of ledipasvir/sofosbuvir. The SVR12 rates are almost uniformly high (94% to 100%) with the exception of the small ELECTRON 2 trial. The primary methodological concern is the lack of a control group in any of the trials. However, the magnitude of benefit (SVR rate 94% to 100% compared to historical controls of approximately 60%, fewer adverse events) somewhat mitigates this concern.

Daclatasvir + sofosbuvir

There is only a single published trial of daclatasvir + sofosbuvir (see Appendix Tables C11 and C12). The study assigned 167 patients with HCV genotype 1 to one of seven treatment groups, all of which contained daclatasvir + sofosbuvir. They varied by the length of treatment, inclusion of ribavirin, and whether or not the patients had received prior treatment for HCV. There was no control group. Overall, 98% of patients achieved SVR12. There are three ongoing phase 3 trials of the combination of daclatasvir + sofosbuvir.

Daclatasvir + asunaprevir

BMS withdrew the NDA for daclatasvir + asunaprevir from the FDA in late 2014, so this combination will not be considered further in our assessment. Details of the six trials of this two-DAA combination are summarized in Appendix Tables C13 and C14.

3D

The last therapy combines three DAAs (paritaprevir, ombitasvir, and dasabuvir) with ritonavir. The combination has been studied with or without ribavirin. There are data from one phase 2 trial (AVIATOR, 14 groups studied) and six phase 3 studies (PEARL II, PEARL III, PEARL IV, SAPPHIRE I, SAPPHIRE II, and TURQUOISE II). The study results are summarized in Appendix Tables C15 and C16. A total of 1,677 patients were treated with either 12 or 24 weeks of 3D + R and the SVR12 rates ranged from 90% to 100%. Two of the trials had placebo groups (SAPPHIRE I, SAPPHIRE II), but none of the trials had active control groups with PR or a single DAA therapy.

Important Subgroups

HIV co-infection

The data for HIV co-infected patients are sparse but encouraging. Two therapies containing one DAA (simeprevir + PR, sofosbuvir + R) and one dual DAA therapy (ledipasvir/sofosbuvir) have been studied in HIV co-infected patients (see Appendix Tables C17 and C18). For all three of these drug regimens, the SVR12 was approximately the same for HIV co-infected patients as it was for HCV genotype 1 mono-infected patients. There do not appear to be any unexpected interactions of the second generation DAAs with anti-retroviral medications. The numbers in each trial are small, particularly when examining the subgroups defined by prior treatment and cirrhosis. Large observational studies will be helpful to more firmly establish the efficacy of each of these drug combinations. It is worth noting that the combinations without interferon appear to have lower discontinuation rates than those with interferon.

Pre- or post-transplant

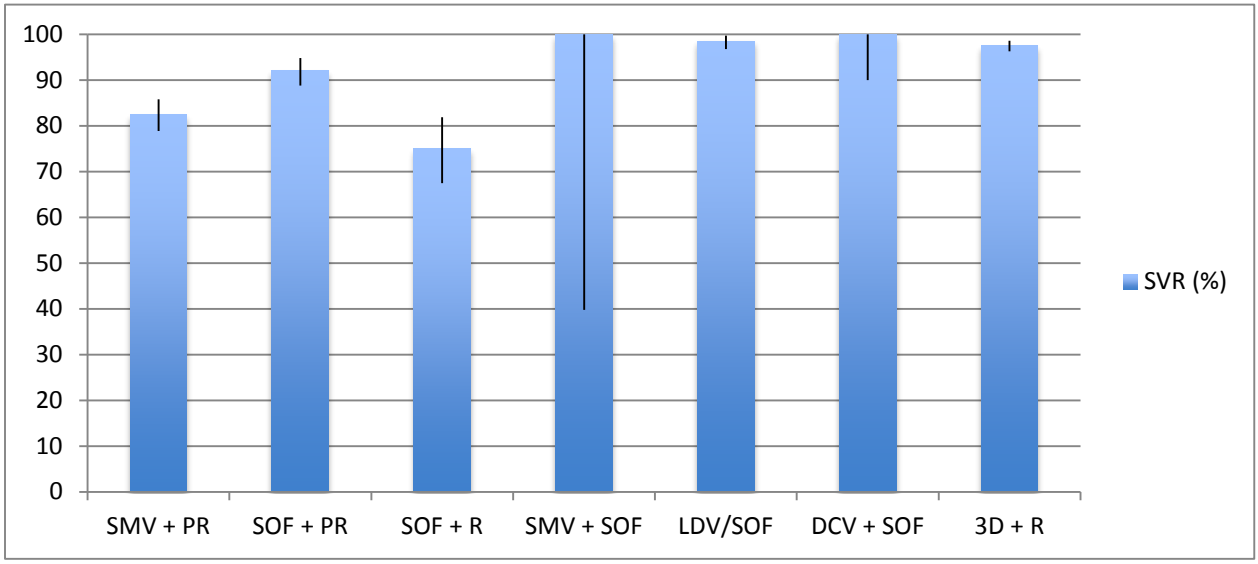
Similarly, data on the outcomes of treatments for patients on the liver transplant waiting list or post-transplant are rapidly emerging. There are four published trials: one in patients awaiting transplant and three in patients with recurrent infections after liver transplant (see Appendix Tables C19 and C20). The initial results are encouraging, but the discontinuation rates are high, reflecting the illness burden of the near- and post-transplant population. Interactions with immunosuppressive drugs did not interfere with therapy. Data from the pre-transplant population suggest that the earlier SVR is achieved prior to transplant, the more likely for a durable cure after transplant.

6.2 SVR Outcomes of Treatment of HCV Genotype 1 in Treatment-naïve, Non-cirrhotic Patients

Figure 2 below presents the results of our fixed-effects meta-analysis of the proportion of treatment-naïve, non-cirrhotic patients achieving SVR in the available prospective cohorts for the seven primary treatment combinations reviewed in this report. The height of each blue bar represents the best estimate of patients achieving SVR, and the vertical black line running through each bar represents the 95 percent confidence interval (95% CI) for the results of each treatment. As noted earlier, there were insufficient placebo-controlled and comparative trials to allow for a network meta-analysis. The first three bars represent treatment with a single DAA plus PR or R alone. The following four bars represent combinations of two or more DAAs without interferon.

The SVR estimates for simeprevir + PR, sofosbuvir + PR, and sofosbuvir + R differ from those in our March 2014 CTAF assessment because of the change in methods used for the meta-analyses and because we did not separate out patients with cirrhosis from those without cirrhosis in the prior assessment. For example, in the prior analysis, our summary estimate from the network meta-analysis for the SVR12 of sofosbuvir + PR in treatment-naïve patients with genotype 1 was 83%. In our updated analysis, our summary estimate for the SVR12 of sofosbuvir + PR in treatment-naïve patients with genotype 1 is 92% in patients without cirrhosis and 81% in those with cirrhosis.

Figure 2: SVR and 95% Confidence Intervals for the Primary DAA Regimens in Treatment-naïve, Non-cirrhotic Patients



It is worth noting that some of the estimates have wide confidence intervals. For example, in Figure 2, the combination of simeprevir + sofosbuvir for 12 weeks was only studied in four patients, and the 95% CI for the SVR ranges from 39.8% to 100%.

Additional information, including the number of patients studied for each drug combination as well as the treatment duration and discontinuation rates are summarized in Table 5 below. As noted above, the discontinuation rate includes patients who withdrew consent or were lost to follow-up in addition to those who stopped treatment due to adverse events. Table 5 also includes data for combination therapy used for shorter or longer durations than the FDA indication or for multiple durations when there is not yet an indication for a particular drug combination. We also included the data for 3D without ribavirin, although we did not include it in Figure 2 because it has been less studied and appears to have a lower SVR than the combination of 3D + R. For Figure 2, we chose to represent the most commonly recommended length of treatment for this population of patients (genotype 1, treatment-naïve, non-cirrhotic).

Table 5: Summary Estimates of SVR and Discontinuation Rates for Treatment-naïve Patients without Cirrhosis

Therapy	N	Tx Duration	SVR (95% CI)	DR (95% CI)
SMV + PR	473	SMV 12 weeks PR 24-48	.825 (.789-.858)	.062 (.042-.086)
SOF + PR	348	12 weeks	.920 (.888-.948)	.103 (.072-.139)
SOF + R	157	24 weeks	.750 (.675-.819)	.078 (.036-.131)
SMV + SOF	4	12 weeks	1.00 (.398-1.00)	.000 (.000-.602)
SMV + SOF	2	24 weeks	1.00 (.158-1.00)	.000 (.000-.842)
DCV + SOF	41	12 weeks	1.00 (.914-1.00)	.000 (.000-.086)
DCV + SOF	14	24 weeks	1.00 (.768-1.00)	.071 (.002-.339)
LDV/SOF	235	8 weeks	.948 (.913-.976)	.002 (.000-.018)
LDV/SOF	482	12 weeks	.985 (.968-.997)	.013 (.002-.029)
LDV/SOF	184	24 weeks	.984 (.953-.997)	.038 (.015-.077)
3D	493	12 weeks	.949 (.927-.967)	.029 (.015-.046)
3D + R	823	12 weeks	.976 (.963-.986)	.010 (.003-.019)
3D + R	40	24 weeks	.900 (.763-.972)	.075 (.016-.024)

Tx Treatment
SVR Sustained virologic response
DR Discontinuation rate

PR Pegylated interferon + ribavirin
R Ribavirin
SMV Simeprevir
SOF Sofosbuvir
LDV Ledipasvir
DCV Daclatasvir
3D AbbVie combination therapy

None of the treatment combinations has been directly compared to any of the others in clinical trials. Thus, the differences in the heights of each bar may in part reflect differences in the populations studied and not true differences in the effectiveness of the respective treatment combinations. Several trends do appear. First, the DAA combinations appear to have higher SVRs than the single DAAs + PR or R with the exception of sofosbuvir + R. Second, the SVRs for these same four combinations do not appear to differ from one another, although there is considerable uncertainty in the estimates for both simeprevir + sofosbuvir and daclatasvir + sofosbuvir. Third, the discontinuation rates during therapy are lower in the new combination therapies with the exception of the 24 week 3D therapy that includes ribavirin.

6.3 SVR Outcomes of Treatment of HCV Genotype 1 in Treatment-naïve, Cirrhotic Patients

A similar picture emerges for treatment-naïve patients with cirrhosis, although there is much greater uncertainty for each of the individual treatments (see Figure 3 below). The new, multiple DAA combinations have higher SVRs than the earlier single DAA treatments. It is worth noting in Table 6 on the next page that the SVR12 for 12 weeks of simeprevir + sofosbuvir was only 67%. However, as described in section 6.5 below, the same combination of simeprevir + sofosbuvir for 12 weeks has a 100% SVR when studied in a sample of treatment-experienced cirrhotic patients who should be more difficult to treat. It is likely that the SVR of simeprevir + sofosbuvir in a larger sample of treatment-naïve, cirrhotic patients will be higher than the 67% reported in the COSMOS trial. This example highlights the imprecision in the estimates derived from the small number of patients studied for each combination in important patient subgroups.

Figure 3: SVR and 95% Confidence Intervals for the Primary DAA Regimens in Treatment-naïve, Cirrhotic Patients

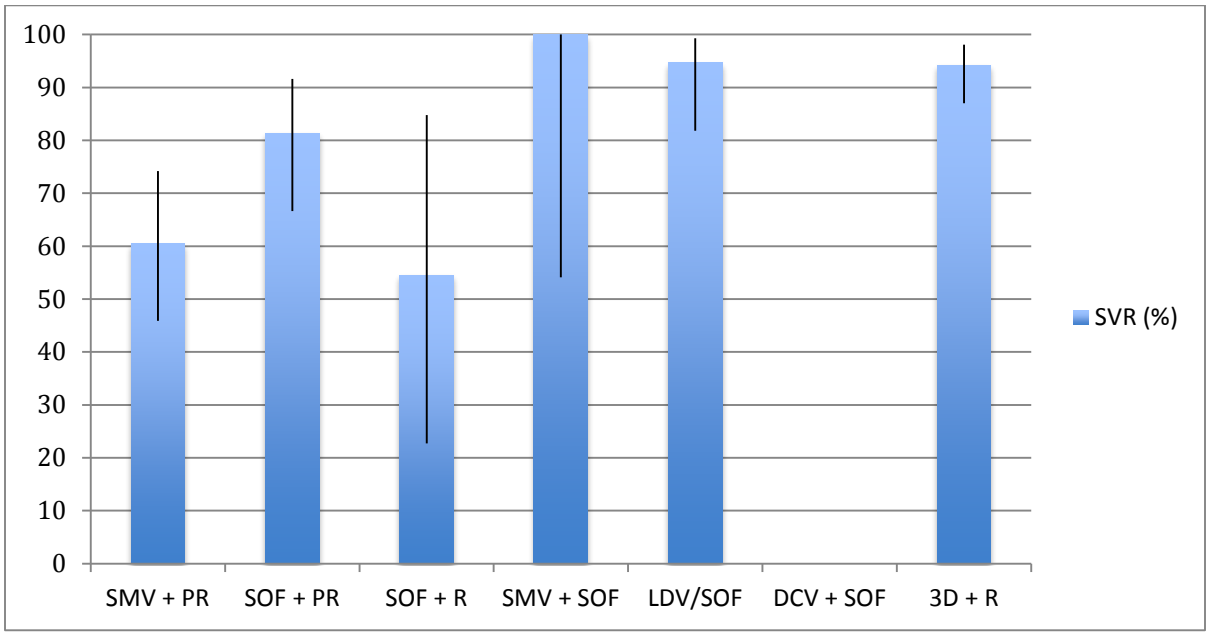


Table 6 gives more detail on each combination therapy as well as additional treatment combinations, primarily varying by length of treatment. The discontinuation rates are generally lower for the new combination therapies, but the confidence intervals are very wide, reflecting the small number of patients with cirrhosis enrolled in these trials.

Table 6: Summary Estimates of SVR and Discontinuation Rates for Treatment-naïve Patients with Cirrhosis

Therapy	N	Tx Duration	SVR (95% CI)	DR (95% CI)
SMV + PR	48	SMV 12 weeks PR 24-48	.605 (.459-.742)	.061 (.005-.155)
SOF + PR	43	12 weeks	.814 (.666-.916)	.116 (.039-.251)
SOF + R	11	24 weeks	.545 (.227-.848)	.000 (.000-.013)
SMV + SOF	3	12 weeks	.667 (.094-.992)	.333 (.008-.906)
SMV + SOF	6	24 weeks	1.00 (.541-1.00)	.167 (.004-.641)
DCV + SOF	-	12 weeks	-	-
DCV + SOF	-	24 weeks	-	-
LDV/SOF	-	8 weeks	-	-
LDV/SOF	37	12 weeks	.946 (.818-.993)	.027 (.001-.142)
LDV/SOF	33	24 weeks	.939 (.798-.993)	.061 (.007-.202)
3D	-	-	-	-
3D + R	86	12 weeks	.942 (.870-.981)	.023 (.003-.081)
3D + R	74	24 weeks	.946 (.867-.985)	.054 (.015-.133)

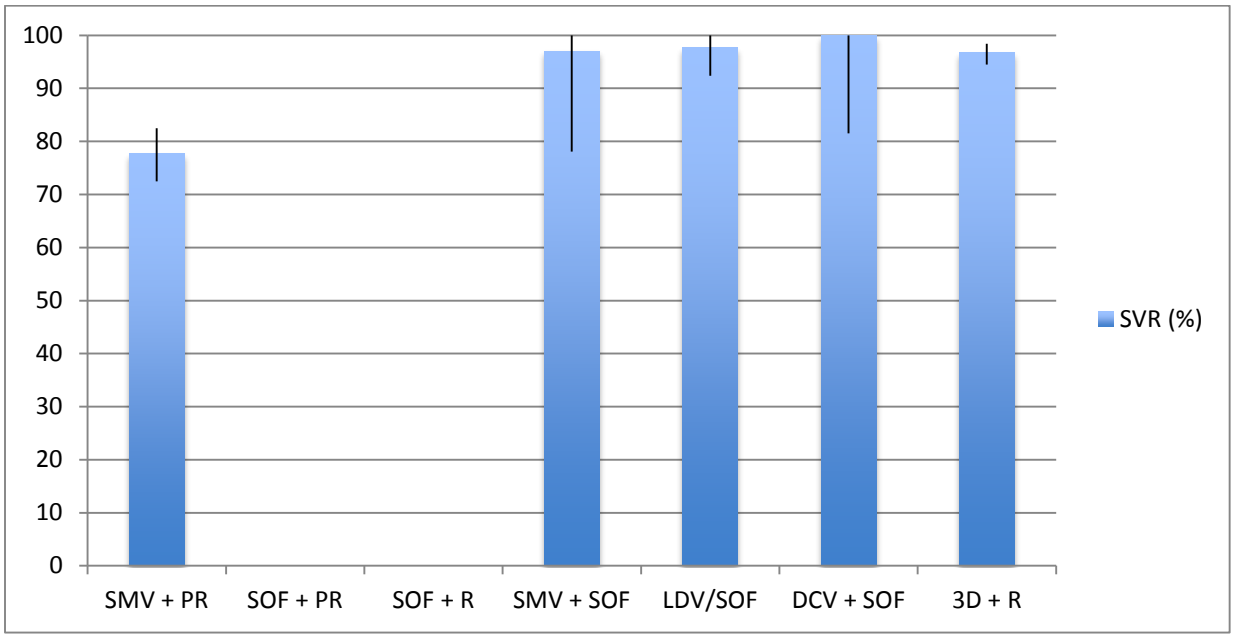
Tx Treatment
SVR Sustained virologic response
- No data
DR Discontinuation rate

PR Pegylated interferon + ribavirin
R Ribavirin
SMV Simeprevir
SOF Sofosbuvir
LDV Ledipasvir
DCV Daclatasvir
3D AbbVie combination therapy

6.4 SVR Outcomes of Treatment of HCV Genotype 1 in Treatment-experienced, Non-cirrhotic Patients

There were no studies of sofosbuvir + PR or sofosbuvir + R in treatment-experienced patients with genotype 1 infection (see Figure 4 on the following page). The multiple DAA combinations have similar SVR rates that are consistently higher than simeprevir + PR, although there is greater uncertainty in the estimates for simeprevir + sofosbuvir and daclatasvir + sofosbuvir.

Figure 4: SVR and 95% Confidence Intervals for the Primary DAA Regimens in Treatment-experienced, Non-cirrhotic Patients



The discontinuation rates were remarkably low for these treatment-experienced patients (see Table 7 below), perhaps reflecting the tenacity of patients who elect for retreatment.

Table 7: Summary Estimates of SVR and Discontinuation Rates for Treatment-experienced Patients without Cirrhosis

Therapy	N	Tx Duration	SVR (95% CI)	DR (95% CI)
SMV + PR	274	SMV 12 weeks PR 24-48	.777 (.725-.825)	.015 (.002-.035)
SOF + PR	-	12 weeks	-	-
SOF + R	-	24 weeks	-	-
SMV + SOF	17	12 weeks	.970 (.781-1.00)	.000 (.000-.083)
SMV + SOF	19	24 weeks	.922 (.724-1.00)	.078 (.000-.276)
DCV + SOF	-	12 weeks	-	-
DCV + SOF	21	24 weeks	1.00 (.839-1.00)	.000 (.000-.161)
LDV/SOF	-	8 weeks	-	-
LDV/SOF	95	12 weeks	.977 (.924-1.00)	.000 (.000-.004)
LDV/SOF	87	24 weeks	.989 (.938-1.00)	.023 (.003-.081)
3D	91	12 weeks	.934 (.862-.975)	.066 (.025-.138)
3D + R	414	12 weeks	.967 (.945-.984)	.015 (.004-.031)
3D + R	20	24 weeks	1.00 (.832-1.00)	.000 (.000-.168)

Tx Treatment
SVR Sustained virologic response
- No data
DR Discontinuation rate

PR Pegylated interferon + ribavirin
R Ribavirin
SMV Simeprevir
SOF Sofosbuvir
LDV Ledipasvir
DCV Daclatasvir
3D AbbVie combination therapy

6.5 SVR Outcomes of Treatment of HCV Genotype 1 in Treatment-experienced, Cirrhotic Patients

The final patient population considered is patients infected with genotype 1 who are both treatment-experienced and cirrhotic (see Figure 5 below). The study sizes are generally small: 52 patients treated with SMV + PR, 76 patients treated with the three dual DAA regimens combined, and 220 patients treated with 3D + R (see Table 8 on the following page). The point estimate is for nearly 100% SVR rates for the interferon-free therapies compared to 73% for SMV + PR. Furthermore, none of the patients treated with the interferon-free combinations discontinued therapy. If these results are reproduced in larger studies, then we will have confidence that even the most difficult-to-treat patients have an excellent chance to achieve lasting SVR. A study published too recently to be included in the meta-analysis offers additional evidence that this may be the future. Osinusi and colleagues studied 14 patients with HCV genotype 1 who had relapsed after 24 weeks of treatment with sofosbuvir + R in the NIH SPARE trial.[73,79] Half of the patients had advanced liver disease by the Knodell Histology Activity Index. All 14 patients achieved SVR12 (100%) following 12 weeks of therapy with ledipasvir/sofosbuvir.[79]

Figure 5: SVR and 95% Confidence Intervals for the Primary DAA Regimens in Treatment-experienced, Cirrhotic Patients

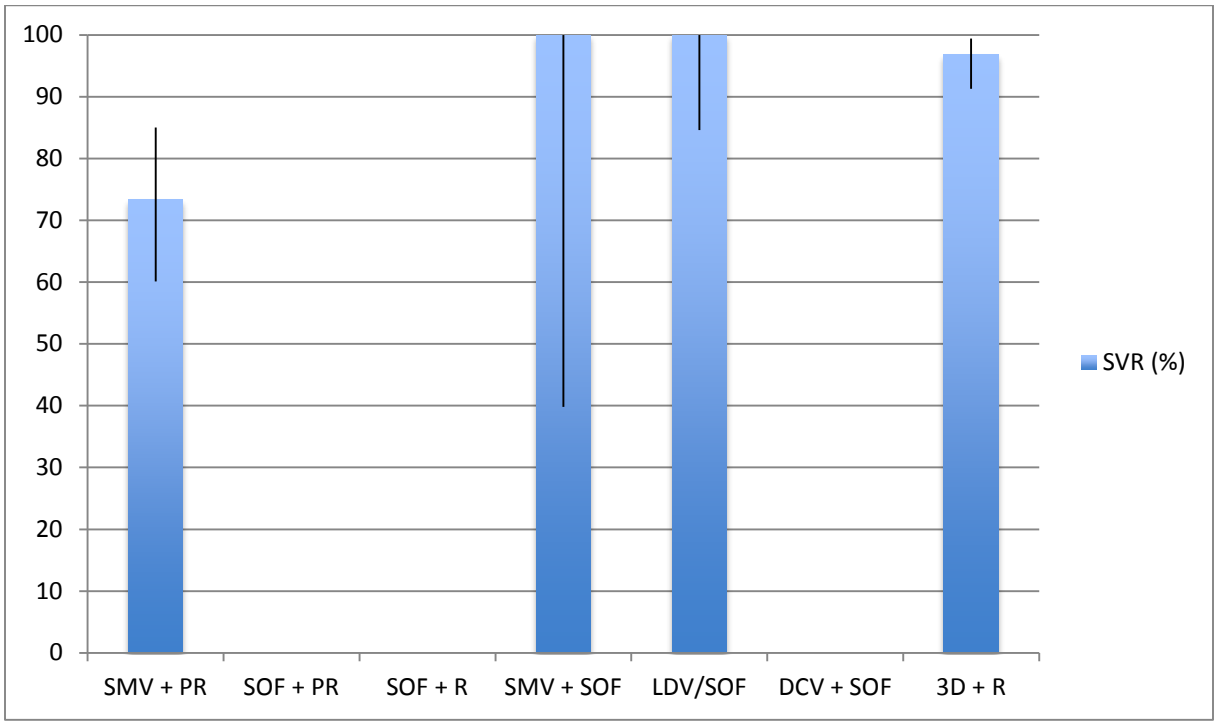


Table 8: Summary Estimates of SVR and Discontinuation Rates for Treatment-experienced Patients with Cirrhosis

Therapy	N studied	Tx Duration	SVR (95% CI)	DR (95% CI)
SMV + PR	52	SMV 12 weeks PR 24-48	.734 (.601-.850)	.166 (.071-.286)
SOF + PR	-	12 weeks	-	-
SOF + R	-	24 weeks	-	-
SMV + SOF	4	12 weeks	1.00 (.398-1.00)	.000 (.000-.602)
SMV + SOF	4	24 weeks	1.00 (.398-1.00)	.000 (.000-.602)
DCV + SOF	-	12 weeks	-	-
DCV + SOF	-	24 weeks	-	-
LDV/SOF	-	8 weeks	-	-
LDV/SOF	43	12 weeks	.846 (.712-.948)	.000 (.000-.044)
LDV/SOF	22	24 weeks	1.00 (.846-1.00)	.000 (.000-.154)
3D	-	12 weeks	-	-
3D + R	122	12 weeks	.902 (.834-.948)	.016 (.002-.058)
3D + R	98	24 weeks	.969 (.913-.994)	.000 (.000-.168)

Tx Treatment
SVR Sustained virologic response
- No data
DR Discontinuation rate

PR Pegylated interferon + ribavirin
R Ribavirin
SMV Simeprevir
SOF Sofosbuvir
LDV Ledipasvir
DCV Daclatasvir
3D AbbVie combination therapy

6.6 Harms of Treatment

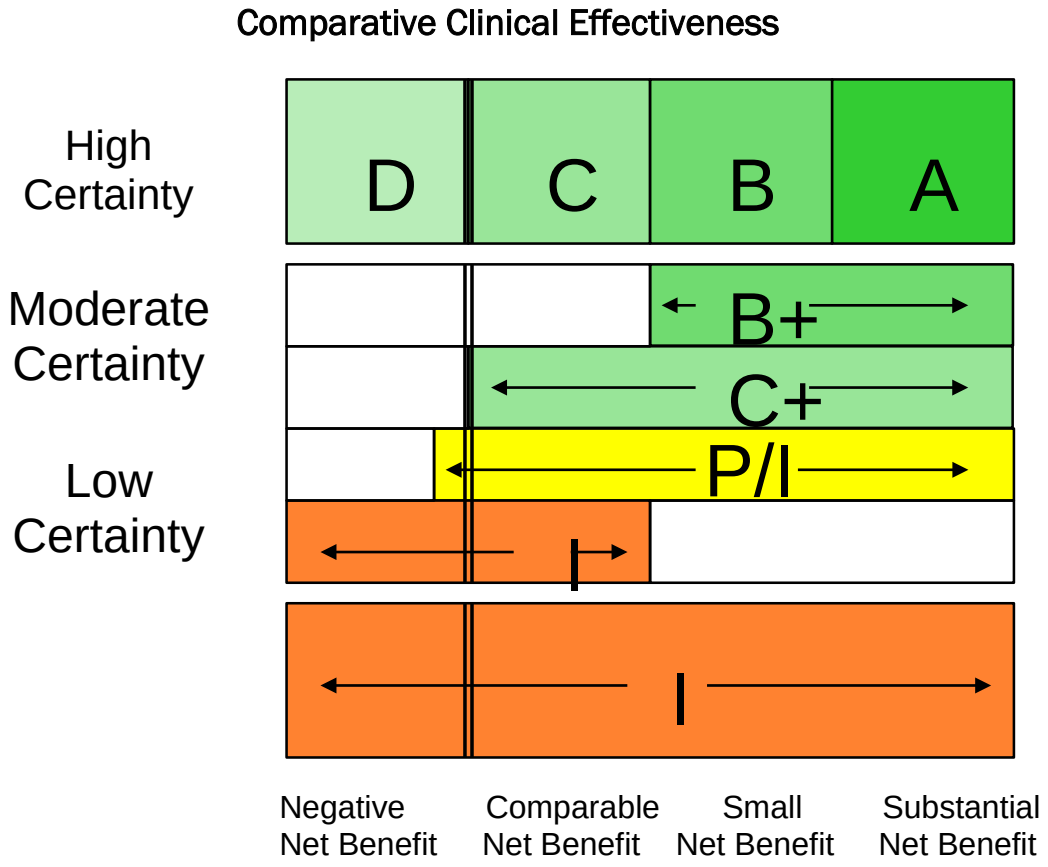
The adverse events reported in the clinical trials are summarized in Table 9 on the next page. The combinations that include ribavirin have an increased incidence of anemia, particularly when taken for 24 weeks or when combined with interferon. The combinations that include simeprevir are associated with a greater incidence of rashes. However, it is evident in Table 9 that the elimination of interferon from the treatment regimen markedly decreases the risk for several adverse events including fatigue, headache, flu-like illness, anemia, pruritus, nausea, and rashes. There were also significantly fewer grade 3 or 4 adverse events, when those were reported.

Table 9: Adverse Events in the Clinical Trials of New Drug Combinations for Hepatitis C

	SMV12 + PR24/48	SOF12 + PR12	SOF24 + R24	SMV + SOF12	SMV + SOF24	LDV/SOF8	LDV/SOF12	LDV/SOF24	DCV + SOF12	DCV + SOF24	DCV + ASV	3D + R12	3D + R24
	N = 781	N = 327	N = 566	N = 28	N = 31	N = 215	N = 539	N = 326	N = 41	N = 80	N = 645	N = 1379	N = 172
Any Adverse Event	95%	95%	88%	71%	94%	76%	69%	81%	93%	84%	85%	85%	91%
Significant Adverse Events	2%	1%	4%	0%	3%	2%	2%	6%	2%	8%	6%	3%	5%
Grade 3 or 4 AE	23%	15%	7%	7%	13%	NR	NR	NR	2%	2%	NR	NR	NR
Therapy stopped due to AE	3%	2%	1%	0%	7%	0%	1%	0%	0%	1%	2%	1%	2%
Common AEs													
Fatigue	36%	59%	40%	25%	25%	21%	22%	24%	39%	36%	22%	33%	46%
Headache	33%	36%	23%	21%	21%	14%	21%	24%	34%	25%	24%	30%	31%
Flu-like illness	26%	16%	3%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Insomnia	17%	25%	16%	14%	14%	5%	8%	9%	10%	5%	2%	14%	18%
Anemia (hemoglobin < 10 g/dL)	12%	23%	9%	0%	3%	0%	0%	0%	0%	0%	NR	3%	10%
Pruritus	22%	17%	9%	11%	11%	1%	4%	3%	2%	4%	7%	15%	19%
Nausea	22%	34%	20%	21%	21%	7%	11%	11%	20%	28%	12%	20%	20%
Rash	28%	18%	8%	11%	16%	1%	4%	6%	5%	4%	NR	11%	14%
Photosensitivity	3%	NR	NR	7%	7%	NR	NR	NR	NR	NR	NR	NR	NR
Diarrhea	NR	NR	NR	NR	16%	7%	7%	10%	5%	10%	NR	12%	17%

6.7 ICER Staff Evidence Rating

The ICER clinical effectiveness rating arises from a joint judgment of the level of certainty provided by the body of evidence and the magnitude of the net health benefit -- the overall balance between benefits and harms. This method for rating the clinical effectiveness is modeled on the "Evidence-Based Medicine (EBM) matrix" developed by a multi-stakeholder group convened by America's Health Insurance Plans. This matrix is depicted below:



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable" - High certainty of a comparable net health benefit
D="Negative" - High certainty of an inferior net health benefit
B+="Incremental or Better" – Moderate certainty of a small net health benefit, with high certainty of at least incremental net health benefit
C+="Comparable or Better" - Moderate certainty of a comparable net health benefit, with high certainty of at least comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" – Either moderate certainty that the best point estimate of comparative net health benefit is comparable or inferior; or any situation in which the level of certainty in the evidence is low

When the four multiple DAA therapies are compared to the three older SMV or SOF + PR or R regimens, there is moderate certainty of substantial net benefit with high certainty of at least a small benefit. **Rating: B+.**

Rationale: The net benefit reflects the clinically important increase in SVR12 with the multiple DAA-containing therapies and fewer side effects, shorter duration of therapy, and less burdensome treatment (fewer pills, no injections, no interferon); the limitations are the small study sizes with no relevant comparators and SVR12 being only a moderately validated intermediate outcome.

When the four multiple DAA therapies are compared to each other, there is low certainty about the superiority of any one therapy. **Rating: I**
Rationale: There are no studies directly comparing two or more of the therapies. In addition, the number of patients in the existing studies is often small, so the estimates of benefits and harms have wide confidence intervals. In addition, the four therapies had roughly comparable net benefits in each of the four subgroups studied**.**

6.8 Summary

Treatment for chronic hepatitis C infection has come a long way from 2010, when interferon combined with ribavirin was the sole therapy. This early drug combination, while providing the first effective treatment for chronic hepatitis C, caused fever and flu-like symptoms in almost half of patients, required a year of injections, and led to viral clearance in fewer than half of patients with the most common form of infection, genotype 1. The combination of PR with first-generation DAAs telaprevir or boceprevir increased the rate of viral clearance above 50% but caused severe anemia in up to half of patients, along with significant nausea, and many drug interactions in addition to the side effects of interferon and ribavirin. The clinical trial data on simeprevir and sofosbuvir demonstrated further increases in the rate of viral clearance, shortened length of therapy, and decreased side effects but still required interferon for patients with genotype 1. Treatments that combine two or more DAAs are simpler, shorter, and cause very few side effects while producing extremely high rates of viral clearance in clinical trials.

The evidence on the clinical effectiveness of the all-oral DAA combination treatment regimens compared to second generation single DAA regimens appears consistent in all four major treatment subgroups. Among treatment-naïve patients without cirrhosis, the SVR12 for simeprevir or sofosbuvir combined with interferon and/or ribavirin is between 75% and 92%, whereas the SVR12 for DAA combination therapy (simeprevir + sofosbuvir, ledipasvir/sofosbuvir, daclatasvir + sofosbuvir, 3D) is higher, ranging from 95% to 100%. Among treatment-naïve patients with cirrhosis, the SVR12 for single DAA therapy ranges from 55% to 81% compared to 67% to 95% for DAA combination therapy. For treatment-experienced patients, the SVR12 for older therapy is about 75% for both cirrhotic and non-cirrhotic patients compared with 95% to 100% for DAA combination therapy.

Due to the very similar high levels of SVR12 achieved by all DAA combination therapies, and the lack of head-to-head trials, there is inadequate evidence to distinguish the overall effectiveness of the

various DAA combination therapies. At the time of the initial assessment, only two combinations had FDA approval (SMV + SOF, LDV/SOF). Two of the combinations (SMV + SOF, DCV + SOF) have been studied among very few patients, and the confidence intervals around the estimates for their SVRs are wide. For the patient population with cirrhosis, the confidence intervals are wide for all four of the new DAA combinations. Furthermore, since these data come from single arm studies, in which everyone enrolled in a trial receives the experimental therapy, selection bias may explain some of the observed differences among the SVR point estimates.

Adverse effects are an important part of comparative clinical effectiveness, but there were very few discontinuations from therapy in any of the studies due to adverse events, and the rate of serious adverse events was similarly low. When patient characteristics require longer therapy with ribavirin-based therapy (sofosbuvir + R for 24 weeks, 3D + R for 24 weeks), the adverse event rates are higher (e.g., the rate of significant anemia is higher, simeprevir also causes photosensitivity and more rashes).

Pragmatic randomized trials or high-quality observational studies from real world settings will be essential for evaluating the comparative effectiveness of the combination DAA therapies. It is unlikely that there will be head-to-head randomized trials of the current therapies, and many more new drug combinations are being tested in clinical trials today. The SVR12 rates of the studied combination therapies will undoubtedly be lower in observational studies than those reported in the clinical trials, as has been seen with earlier DAAs. Patients who qualify to be in clinical trials are generally more motivated, adherent, and have fewer comorbidities than the larger population of patients with chronic HCV infection who need to be treated. Studies including larger numbers of patients treated with each of the drug combinations will help to identify rare adverse events that have not yet been anticipated and should help to clarify specific patient populations that benefit more from one combination therapy than another. It is incumbent upon researchers working closely with the clinical community to continue to collect high quality observational data to help answer the many remaining questions.

7. Model of Clinical and Economic Outcomes of Treatment Strategies for Hepatitis C

As noted in this review, new medications for hepatitis C have the potential to change clinical expectations for achieving sustained virologic response in many more patients than previously thought possible. However, these medications also have the potential to substantially increase health-system costs. We developed simulation models of these new regimens for the express purpose of assessing their potential value along two important constructs:

- ***Care Value:***
    1. Comparative clinical effectiveness of each regimen vs. alternatives (considering both clinical benefits and harm)
    2. Any additional "non-clinical" benefits (e.g., reduced caregiver burden)
    3. Contextual considerations (no other acceptable treatment, vulnerable populations)
    4. Cost-effectiveness (incremental cost to achieve important patient outcomes vs. alternatives)

- ***Health System Value:***
    1. Care value of the regimen of interest (as above): *and*
    2. Potential effects of short-term budgetary impact from each regimen on other patients in the health care system

Discussion of the methods and results of our modeling efforts can be found starting in Section 7.2. For comparison purposes, we also identified published studies of the cost-effectiveness of both existing and proposed treatment options for hepatitis C, which are summarized in Section 7.1 below. We limited our summary to those studies focusing on the agents of interest in this review and also included studies that focused on hypothetical all-oral regimens.

7.1 Prior Published Evidence on Costs and Cost-effectiveness

We identified a total of seven studies evaluating the cost-effectiveness of sofosbuvir-based regimens, including two that also assessed the use of simeprevir. We found no published studies that have as of yet assessed the cost-effectiveness of ledipasvir/sofosbuvir (LDV/SOF). However, we did identify three studies that focused on the potential cost-effectiveness of hypothetical all-oral regimens for hepatitis C. Populations analyzed, regimens evaluated, and primary findings are summarized in the sections that follow; not surprisingly, most of these analyses found that results were highly sensitive to the assumed costs of treatment and SVR rates.

Sofosbuvir vs. Simeprevir

Hagan and colleagues developed a Markov state-transition model to assess the lifetime cost-effectiveness of SMV + SOF (12 weeks) vs. SOF + R (24 weeks) in a 50-year old cohort of genotype 1 patients ineligible or intolerant to interferon.[167] A SMV + SOF strategy was found to produce three months of additional quality-adjusted life expectancy relative to SOF + R and was cost-saving, reducing overall costs by nearly $80,000 per patient on a lifetime basis.

Another recent Markov model evaluated the lifetime economic impact of PR therapy alone as well as in combination with sofosbuvir, simeprevir, telaprevir, or boceprevir in a cohort of genotype 1 patients aged 52 years.[168] Outcomes and costs were evaluated separately for treatment-naïve, treatment-experienced, and HIV-coinfected patients. SOF + PR was less costly and more effective than any other triple therapy in all three cohorts of interest and yielded cost-effectiveness estimates of <$10,000 per QALY gained vs. no treatment as well as <$30,000 per QALY gained vs. PR alone.

Sofosbuvir vs. Older Regimens

Two studies compared the cost-effectiveness of sofosbuvir to older regimens among patients with genotype 1 infection.[169, 170] One was a lifetime simulation model conducted from the perspective of the Italian National Health Service, and it involved separate comparisons of triple therapy with sofosbuvir vs. boceprevir and telaprevir in genotype 1 patients who were naïve to treatment and age 50 years.[169] Strategies with an incremental cost per life-year gained less than €25,000 ($35,000) were considered to be cost-effective. Sofosbuvir triple therapy was estimated to increase life expectancy by approximately eight months relative to boceprevir and three months vs. telaprevir. Sofosbuvir was considered to be cost-effective in comparison to either of the competing strategies but not universally so across all subgroups. For example, sofosbuvir was considered to be cost-effective among cirrhotic patients and those with the IL28b CC allele but not in patients with lower levels of fibrosis or in patients with the genotype 1b subtype.

The other study assessed the lifetime cost-effectiveness of sofosbuvir to older regimens among incarcerated individuals in the US serving either short (<1.5 years) or long (≥1.5 years) prison terms.[170] Among those serving short sentences (with no treatment as the only alternative), SOF + PR produced three- to four-fold reductions in the incidence of severe liver-related complications, generated over two additional years of quality-adjusted life expectancy, and resulted in a cost-effectiveness estimate of ~$26,000 per QALY gained. Findings were similar for those incarcerated long-term, and sofosbuvir triple therapy had more favorable cost-effectiveness ratios than boceprevir triple therapy or PR alone. This study also addressed the affordability question, estimating that sofosbuvir would increase treatment costs for 500,000 prisoners by $27-$30 billion, and cost offsets from reductions in liver-related complications ($2-$5 billion) would likely be realized outside the prison system.

An additional two analyses assessed the cost-effectiveness of sofosbuvir-based regimens across genotypes 1, 2, and 3 vs. the previous standard of care from the perspectives of the French and Spanish national health systems respectively.[171, 172] For genotype 1, the comparison was to triple therapy with telaprevir or boceprevir as well as to PR alone. Both studies considered a benchmark of €40,000 ($50,000) per QALY gained to represent a cost-effective use of resources. The French evaluation found that, across all genotypes, sofosbuvir-based regimens increased quality-adjusted life expectancy by an average of two years and resulted in an incremental cost-effectiveness ratio of approximately €16,000 ($20,000) per QALY gained.[171] Cost-effectiveness improved with increasing fibrosis stage, but treatment met the cost-effectiveness threshold at all stages. In contrast, the Spanish evaluation found that sofosbuvir-based regimens were below the cost-effectiveness benchmark only for genotypes 1 and 3; genotype 2 regimens exceeded this threshold, as did SOF + R for 24 weeks when used in any of the three genotypes.[172]

Cost-Effectiveness of All-Oral Hepatitis C Regimens

As mentioned previously, we found no published assessments of the economic impact of LDV/SOF. However, three simulation models have assessed the potential cost-effectiveness of hypothetical combinations of all-oral drugs.[173, 174, 175] In an NIH-funded analysis, Hagan and colleagues assessed the cost-effectiveness of a hypothetical 2-drug regimen over a lifetime vs. standard care (i.e., triple therapy with older DAAs or PR) across all genotypes in a 50 year-old treatment-naïve cohort using a societal perspective.[173] Based on SVR and drug cost estimates of 90% and $70,000 respectively, all-oral therapy resulted in an overall gain of five months of quality-adjusted life expectancy while generating approximately $20,000 more in costs. The resulting cost-effectiveness ratio was $45,000 per quality-adjusted life year (QALY) gained. However, all-oral therapy was no longer considered cost-effective in this model (at a $50,000 per QALY threshold) at prices exceeding $75,000. An industry-funded analysis involving the same comparators produced a lower cost-effectiveness ratio ($15,709 per QALY gained), which appears to be closely tied to the assumptions that (a) all-oral drug costs would be equivalent to those of existing triple therapy with telaprevir; and (b) SVR rates with all-oral therapy would be 99%, with no discontinuation.[174]

The third evaluation involved a comparison of hypothetical all-oral treatment to both older triple therapy with telaprevir and boceprevir as well as to SOF + PR in treatment-naïve genotype 1 patients.[175] SVR rates were assumed to be 89% for SOF + PR and 85-95% for all-oral treatment, depending on fibrosis stage. Costs of SOF+PR were estimated to be approximately €5,100 ($6,375) per week based on the French early access price; costs of all-oral therapy were assumed to be double this amount. Treatment with SOF + PR was cost effective relative to older triple therapy (~$47,000 per QALY gained), but only for patients treated at F2 and above. All-oral regimens were not cost-effective at assumed prices (ICERs of $170,000-$400,000 per QALY gained, depending on fibrosis stage) but would be considered cost-effective at weekly prices similar to those of SOF + PR.

7.2 Model of Care Value: Overview and Methods

Overview

We constructed a decision-analytic multistate Markov model[125] to determine the cost-effectiveness of six treatment regimens for HCV genotype 1 marketed in the US marketed in the US as of the December 18, 2014 CTAF public meeting date, as shown in Table 10 below. Note that there are two rows for LDV/SOF; we alternatively assumed that 1) a percentage of treatment-naïve non-cirrhotic patients would be candidates for eight weeks of therapy (LDV/SOF 8/12) and 2) all treatment-naïve patients would receive 12 weeks of therapy (LDV/SOF 12). The percentage of patients eligible for eight weeks of therapy in the LDV/SOF 8/12 strategy was assumed to be 67% based on the proportion of clinical trial subjects with viral loads <6 million IU/ml; this percentage was varied from 30% to 90% in sensitivity analyses.

Table 10. Modeled Therapies: Interferon-based and Interferon-free Treatments

		Duration of therapy (weeks)	
		Treatment-naïve	Treatment-experienced
Interferon-based therapies			
1	Peg-Interferon + ribavirin (PR)	48	48
2	Sofosbuvir + PR (SOF + PR)	12	12
Interferon-free therapies			
3	Sofosbuvir + R (SOF + R)	24	--
4	Simeprevir + sofosbuvir (SMV + SOF)	12	12
5	Ledipasvir/sofosbuvir (LDV/SOF 8/12)	8/12*	--
6	Ledipasvir/sofosbuvir (LDV/SOF 12)	12	12/24†

* – F0-F3 – treatment duration for 67% of patients is 8 weeks, duration for 33% is 12 weeks; F4 – treatment duration is 12 weeks

† – F0-F3 – treatment duration is 12 weeks, F4 – treatment duration is 24 weeks.

The FDA-recommended dosing used in this model is daily 400mg of sofosbuvir, daily 1200mg of ribavirin, and weekly 180mcg subcutaneous injection of peg-interferon alfa-2a.[136]

We limited our inclusion of simeprevir to its recently-approved use with sofosbuvir, as utilization data indicate that simeprevir + PR, while FDA-approved for genotype 1, is rarely used.[46] We also did not consider the first-generation DAAs (boceprevir and telaprevir), as their use has either formally or essentially been discontinued in the US. Finally, we excluded daclatasvir and the 3D regimen from these analyses, as these agents were not yet FDA-approved by the CTAF meeting date and no estimates were available on their projected cost. As another referent category, we also calculated outcomes and costs among patients receiving *no* antiviral therapy (i.e., "no treatment").

The model is designed to calculate the net costs, health benefits, and incremental cost-effectiveness ratios (ICERs) of these therapies. It was also designed to determine how these ICERs change if treatment is delayed to a more advanced stage of disease as compared with treating

people at all disease stages. We thus aimed to address two key policy or program questions with regard to HCV therapy:

- Comparing *regimens.* Which regimens are most cost-effective? Specifically, what is the incremental cost-effectiveness of more expensive and effective regimens?

- Comparing population treatment *strategies.* What is the cost-effectiveness of treating all individuals, as compared with waiting to treat at more advanced disease stages?

To address these issues, the model portrays HCV natural history: the lifetime progression of a prevalent cohort based on the fibrosis stage (i.e., METAVIR F0-F4) of individuals who are aware of their HCV status. The model also portrays *regression* of liver damage after successful treatment.[125] Costs include those of treatment, other medical care outside of and after treatment, and costs of treating serious HCV-related complications such as decompensated cirrhosis and hepatocellular carcinoma. Effectiveness is measured primarily in terms of quality-adjusted life years; however, the incidence of serious HCV-related complications also is assessed.

All results are portrayed for the individual's lifetime and discounted to the present. Separate analyses were conducted for treatment-naïve and treatment-experienced patients. While regimens also differ in terms of whether patients have cirrhosis, this was incorporated into our calculations based on disease progression and regression; for example, LDV/SOF patients treated at METAVIR stage F4 (cirrhosis) received a longer duration of treatment and had different rates of viral clearance. For each of these two groups, we also present results for the two treatment strategies, "treat all" and "wait until more advanced disease." Finally, we present results for a mixed cohort of treatment-naïve and treatment-experienced patients.

Health benefits, including rates of sustained virologic response (SVR), were adjusted for rates of discontinuation as reported in clinical trials (see Appendix Tables D3 and D4). For each treatment regimen both the costs of managing treatment-associated adverse events and the accompanying "disutility" (reduction in well-being) were estimated and incorporated. Consistent with standard methods for health-economic evaluations, future benefits and costs were discounted by 3%,[126] and all cost inputs were adjusted to 2014 dollars by the medical component of the US Consumer Price Index (CPI) (http://www.bls.gov/cpi/cpid1408.pdf).

The model was constructed in TreeAge® Pro 2014, with additional analyses in Microsoft Excel®.

Perspective

In keeping with CTAF standards, analyses were conducted from the health care payer perspective such as a state Medicaid agency or a managed care organization. Cost estimates were thus limited to direct medical costs only (i.e., costs of drug treatment, HCV management, and treatment of HCV

complications). Direct costs to patients (e.g., transportation) and time costs (i.e., productivity losses associated with getting treated) were not included. Potential increases in future lifetime productivity resulting from successful treatment were also not quantified.

There are no universally accepted criteria for what constitutes an acceptable cost-effectiveness threshold for medical care interventions in the United States. Historically, an ICER under $50,000 per QALY has been used as one threshold, whereas more recent investigators and policy makers have suggested that ICERs under $150,000 per QALY may be a reasonable threshold for an intervention to be deemed "cost-effective."[129, 130] Recently, the World Health Organization has promulgated suggested cost-effectiveness thresholds linked to national Gross Domestic Product (GDP).[131, 132] According to the WHO, an intervention with a cost per QALY less than 1 x GDP per capita can be considered "highly" cost-effective, whereas a cost per QALY higher than 3 x GDP is considered not cost-effective. Current GDP for the US is approximately $50,000 per capita, and therefore thresholds of $50,000 per QALY and $150,000 per QALY are considered in this report as important benchmarks.

Patient Population

Patients for this model were assumed to weigh 75kg and be 60-years of age, selected on the basis of a 2010 analysis of National Health and Nutrition Examination Survey (NHANES) data, indicating that the highest HCV prevalence, (3.5%), is found among individuals born between 1945 and 1965 (i.e., ages 45-65).[133] Since 2010, the age distribution has likely shifted, suggesting that an average age of 60 for a prevalent population is appropriate for estimating the impact of HCV therapy. The distribution of patients across fibrosis stages F0-F4 in our modeled cohort is 0.17, 0.35, 0.22, 0.14, and 0.12, respectively (see Appendix Table D1 for details).[137] This distribution is based on empirical assessments of individuals with known HCV infection.[134] The model does not distinguish patients by viral concentrations, sex, or race, although these factors may affect treatment outcomes and disease progression.[135]

Natural History of Progression and Treatment Effects

The natural history of HCV progression and the related disease-state transition probabilities are based on a review of published literature (see Table 11 on the following page). The SVR rates for all treatments except PR were derived from the meta-analyses described in Section 6 of this report. More details on the design of the natural history model including graphical depictions are available in Appendix E.

Table 11: Key model Inputs: Chronic Hepatitis C Annual Transition Probabilities, Background Mortality, Weekly Cost of Drugs, Cost of Treatment-related Medical Care, and Annual Cost of CHC-related Health Care. Note: All costs are in 2014 dollars.

Natural History					
Source State	**Target State**	**Base case**	**Lower limit**	**Upper limit**	**Referenc**
F0	No progression (proportion)*	0.24	0.10	0.40	138
	F1	0.077	0.067	0.088	137
	Spontaneous Resolution	0.002	0	0.005	139
F1	F2	0.074	0.064	0.086	137
F2	F3	0.089	0.077	0.103	137
F3	F4 (Compensated Cirrhosis)	0.088	0.075	0.104	137
	Decompensated Cirrhosis	0.012	0.01	0.014	140
	Hepatocellular Carcinoma*	0.00725	0	0.02669	141
F4	Decompensated Cirrhosis	0.039	0.03	0.048	141
	Hepatocellular Carcinoma	0.019	0.017	0.055	141
Decompensated Cirrhosis	Hepatocellular Carcinoma	0.014	0.011	0.017	140
	Liver Transplant	0.017	0.0169	0.045	142
	Death	0.129	0.1032	0.1548	141
Hepatocellular Carcinoma	Liver Transplant	0.017	0.0169	0.045	142
	Death	0.4270	0.3416	0.5124	141
Liver Transplant	Death (Year 1)	0.107	0.09	0.13	142
	Death (Year 2+)	0.0485	0.0385	0.0585	142
Background Mortality					
Source State	**Target State**	**Base case**	**Lower limit**	**Upper limit**	**Referenc**
CHC all-cause mortality ratio	Compared to no CHC (General population)	2.37*	1.28	4.38	143
All-cause mortality ratio after SVR	Compared to no CHC (General population)	1.4*	1.0	2.5	144
Background mortality	Death	Age-specific mortality from US 2009 Life Tables			145
Weekly cost of drugs†					
Drug		**Base**	**Min‡**	**Max‡**	**Referenc**
P 180mcg subcutaneous injection weekly		825	413	1238	146
R 1200mg daily		48	24	72	146
Simeprevir 150mg daily		5,530	2765	8295	146
Sofosbuvir 400mg daily		7,000	3500	10500	146
Ledipasvir 90mg + Sofosbuvir 400mg (daily, fixed-dose combination)		7,875	3938	11813	146
Treatment-related medical care costs (excluding drugs) §					
Service type		**Base**	**Min**	**Max**	**Referenc**
Anti-HCV (antibody) test		26	13	39	147

HCV RNA quantification	79	39	118	[147]
Genotype assay	475	237	712	[147]
CBC w/Differential	14	7	22	[147]
Hepatic function panel	15	8	23	[147]
Office visit (outpatient)	97	49	146	[148]
Fibrosis assessment	262	131	393	[149]
Annual cost of CHC-related health care by disease state				
Health State	**Base**	**Min**	**Max**	**Referenc**
F0 – No fibrosis#	810	405	3,240	[150, 151]
F1 – Portal Fibrosis without septa#	810	405	3,240	[150, 151]
F2 – Portal fibrosis with rare septa#	810	405	3,240	[150, 151]
F3 – Numerous septa without cirrhosis#	2,150	1,075	8,600	[150, 151]
F4 – Compensated cirrhosis	2,516	1,258	10,064	[150, 151]
Decompensated cirrhosis	29,795	27,962	31,627	[142, 152]
Hepatocellular carcinoma	47,525	46,653	52,392	[142]
Liver transplant, year 1	188,671	173,986	203,351	[142]
Liver transplant, year 2+	41,090	33,576	48,606	[142]
Post-SVR costs for F0-F3	50% of no SVR			[150,151]
Post-SVR costs for compensated cirrhosis	50% of no SVR			[150, 151]

* — Increased by a factor of 2.37 or 1.4 for patients in F3, F4 fibrosis stages with CHC and after SVR, respectively (patients in F0-F2 stages experience the same baseline mortality as no-CHC population based on 2009 US life tables)
† — Wholesale Acquisition Cost, WAC – from Red Book Online.
‡ — The lower and upper bounds for sensitivity analyses are set at 50%-150% of base case.
§ — Cost per unit. For frequency of tests and office visits and the number of each, see Appendix Table D5.
# — F0 to F3 costs based on $900 weighted average. The cost gradient from F0 to F3 leading into F4 costs was established using fibrosis stage prevalence shown in Appendix Table D1.

In response to treatment, the risk of progressing to worsening stages of disease is reduced.[140,141] It is also possible for the liver damage caused by HCV to be at least partially reversed in some patients following successful therapy (see Appendix Table D2).[140, 153-157] Therefore, the model assumes a proportion of patients regress to an improved fibrotic state as indicated by the proportions listed under the heading "Fibrosis Regression Post-SVR (Proportions)" in Appendix Table D2. In stages F3 and F4, patients are subject to an all-cause mortality rate that is 2.37 times the background population rate for their ages. This is reduced to 1.4 in patients achieving SVR.

Costs

Cost of drugs (intervention): The weekly costs of sofosbuvir, simeprevir, and ledipasvir/sofosbuvir, peg-interferon, and ribavirin were determined using wholesale acquisition price (WAC) from Red Book Online in October 2014 (see Table 11 on the previous page).[146]

Treatment-related health care costs: The non-drug treatment-related costs shown in Table 11 are applied only for the duration of the treatment. They include HCV testing, genotyping, fibrosis staging, and therapy monitoring, including clinic visits, blood and hepatic tests, and HCV RNA quantification. See Appendix Table D5 for the frequency of these costs.

Health care costs: The annual medical care costs associated with the chronic hepatitis C (CHC) health states were determined from previously published research.[138,140] These costs were determined using Medicare reimbursement schedule and published literature.[147-149] Due to substantial uncertainty, we conducted wide sensitivity analyses.

Adverse event costs: There is limited experience with the cost of side-effect management with newer therapies. Costs were estimated by combining published cost estimates for similar events with frequencies of serious and common side-effects from clinical trials (see Table 12 below).

Table 12: Total Treatment Costs of Associated Adverse Events, 2014 (USD)

	Base*	**Min†**	**Max†**	
PR (48 weeks)	2073	1037	3110	Calculated
Sofosbuvir + PR (12 weeks)	1711	856	2567	Calculated
Sofosbuvir + R (24 weeks)	928	464	1392	Calculated
Ledipasvir/sofosbuvir (8 weeks)	868	434	1302	Calculated
Ledipasvir/sofosbuvir (12 weeks)	775	388	1163	Calculated
Simeprevir + sofosbuvir (12 weeks)	751	376	1127	Calculated

* — Based on cost of serious adverse events of $2,706 and cost of common adverse events of $516. Costs are weighted by frequency of serious and common adverse events and summed to calculate the costs in the table

† — The lower and upper bounds for SA are set at 50%-150% of base case.

Adjusting costs for early discontinuation: For patients who discontinue therapy, we assumed discontinuation mid-way through the treatment and thus both the treatment costs and the costs of managing adverse events were decreased by 50%.

Quality-of-life / Health State Utilities

Pre- and post-SVR health state utilities: CHC, independent of its progression to liver disease, can adversely impact patients' lives at all stages. The model uses health state utilities associated with each stage of CHC, including utilities post-SVR, and temporary loss of quality of life during treatment. These utilities represent individuals' preferences for a specific health care state associated with CHC and range from 0 (death) to 1 (normal health).[158] Significant decrements in quality of life accelerate as patients move from F2 to F3. The utility values are determined based on a literature review as shown in Table 13 on the next page.

Table 13: Health State Utilities in CHC Pre-SVR and Post-SVR

State	Base case	Lower limit	Upper limit	Reference
Utilities for HCV states				
F0	0.98	0.92	1	138, 159
F1	0.98	0.92	1	138, 159
F2	0.92	0.72	1	159
F3	0.79	0.77	0.81	160
F4 (Compensated Cirrhosis)	0.76	0.70	0.79	160
Decompensated Cirrhosis	0.69	0.44	0.69	160
Hepatocellular Carcinoma	0.67	0.60	0.72	160
Liver Transplant, Year 1	0.5	0.40	0.69	160
Liver Transplant, Year 2+	0.77	0.57	0.77	160
Death	0	0	0	
Utilities after SVR per Markov cycle				
SVR F0	1	0.98	1	138
SVR F1	1	0.98	1	138
SVR F2	0.933	0.92	1	138
SVR F3	0.86	0.82	0.90	140
SVR Compensated Cirrhosis	0.83	0.79	0.87	140

Utility loss with treatment: Treatment-related side-effects contribute to transient loss of quality of life. A utility penalty (or loss) due to treatment was therefore also modeled. The utility loss is calculated using utility weights of serious and common AEs weighted by the frequency of AEs reported in clinical trials and adjusted for duration of therapy.[161-164] The base case values of these disutilities range from -0.1782 for PR (48 weeks) to -0.0116 for LDV/SOF (8 weeks) (see Appendix Table D6).

Calculating Results

The model produced lifetime discounted QALYs and costs to calculate incremental cost-effectiveness ratios (ICERs). Costs, QALYs gained, incremental costs, and incremental QALYs were calculated for each regimen in comparison with the next least costly regimen. ICERs by definition compare the additional costs and clinical outcomes for regimens ordered sequentially from least to most costly. This method is usually the most policy-relevant way to portray the cost-effectiveness of a set of options, provided that all of them are feasible. However, for completeness, we also included cost-effectiveness ratios in which each treatment option is compared alternatively with no treatment, as well as with PR as a universal historical control. We did this because some differences between regimen costs and efficacy are small and subject to uncertainty, making direct comparisons less definitive than comparisons to no intervention or PR. These results are displayed in tables 14 - 20 in this section of the report. The ICER for each regimen's "treat all" strategy also was calculated against "treat at F3, F4" in order to assess the cost-effectiveness of a universal treatment approach versus a prioritized one.

Scenario and Sensitivity Analyses

We portrayed scenarios in which alternative treatment discontinuation rates, the distribution of the patient cohort by fibrosis stage, the cost of care gradient from F0 to F3, and the cohort's age were altered. We documented the effect that these different, plausible values have on results. We also conducted sensitivity analyses on each of the key model inputs one at a time, to determine the model's sensitivity to the level of uncertainty with each input. The range of each variable was based on confidence intervals from published articles when these are available, as they are for example, on the probabilities of disease progression.

The confidence intervals for the SVR rates were provided by the meta-analysis described in Section 6 of this report. When formal confidence intervals were not available, as in the case of drug costs, for example, we varied each input from 50% to 150% of its base case value. To reflect the greater uncertainty in health state utility values, we adopted a wider range of 50% - 300% for those variables. To quantify the uncertainty in all inputs considered simultaneously, we carried out Monte Carlo probabilistic sensitivity analysis, using uniform distributions for all variables and 10,000 iterations. Results of the probabilistic multi-way sensitivity analyses were displayed as cost-effectiveness acceptability curves. In these figures, the X axis shows various costs per QALY gained that might be acceptable to a payer, sometimes called a "willingness-to-pay" (WTP). The Y axis shows the likelihood of any particular WTP being achieved given the range of results observed in the iterations.

7.3 Model of Care Value: Results

The cost-effectiveness results are presented in three parts:

1. *Results for the base-case*. "Base-case" refers to results associated with the values of input for the model that we believe are most likely to be accurate and relevant. This is further divided into sub-sections according to whether the modeled cohort was treatment-naïve; treatment-experienced; or a mixed naïve and experienced cohort; and according to whether the population strategy is "treat all" or "treat at F3, F4." The base-case analysis also reports the results of a comparison with PR (48 weeks) only, and a comparison for each treatment regimen considered separately of "treat all" versus "treat at F3, F4".
2. *"Scenario analyses".* This section presents results for different but plausible alternative values for four key inputs, in order to document how robust the base-case results are to different characteristics of the patient cohort.
3. "*Sensitivity analyses*". In this section, the values of all key inputs are altered across a wide range in order to assess the effect of uncertainty on model results.

7.3.1 Base-case Results

Treatment-naïve cohort and "treat all" strategy

In a prevalent, treatment-naïve cohort, PR had an ICER of $11,385 compared with no treatment. LDV/SOF (8/12 weeks) added 1.41 QALYs compared with PR, yielding an ICER of $20,132, well under the $50,000 per QALY threshold to be considered highly cost-effective. All other sofosbuvir-based regimens were found to be "dominated", meaning that the regimen both costs more and is less effective and is therefore excluded from consideration, with the exception of LDV/SOF for 12 weeks in all patients. This regimen was only slightly more effective than the 8/12 strategy (approximately three additional weeks of quality-adjusted life expectancy), but much more expensive, yielding an ICER of nearly $300,000 per QALY gained (see Table 14 below).

Table 14. Cost-effectiveness of Alternative Treatment Regimens for Hepatitis C, for Treatment-naive Patients and a "Treat All" Strategy

	Incremental comparison of regimens					
Strategy	**Net cost**	**Incr Net cost**	**Eff**	**Incr Eff**	**ICER**	**Comment**
Tx naïve, treat all						
No Treatment	$ 45,313	$ -	11.82	0.00	$ -	undominated
PR (48 weeks)	$ 62,540	$ 17,227	13.34	1.51	$ 11,385	undominated
LDV/SOF (8/12 weeks)	$ 90,991	$ 28,451	14.75	1.41	$ 20,132	undominated
SOF + PR (12 weeks)	$ 107,942	$ 16,951	14.52	-0.23	$ (73,572)	abs. dominated
LDV/SOF (12 weeks)	$ 108,619	$ 17,628	14.81	0.06	$ 283,927	undominated
SMV + SOF (12 weeks)	$ 163,336	$ 54,717	14.74	-0.08	$ (719,351)	abs. dominated
SOF + R (24 weeks)	$ 186,513	$ 77,894	13.99	-0.82	$ (95,006)	abs. dominated

Incr Net Cost — Incremental Net Cost; Eff — Effectiveness; Incr Eff — Incremental Effectiveness; abs. — absolutely

Treatment-naïve cohort and "treat F3, F4" strategy

As shown in Table 15 on the next page, with ICERs of $2,727 and $15,940 respectively, PR and LDV/SOF 8/12, are somewhat more cost-effective if treatment is delayed until stages F3 or F4. Other regimens either have unfavorable ICERs (e.g., LDV/SOF 12 weeks) or are more costly and less effective (i.e., dominated).

Table 15. Cost-effectiveness of Alternative Treatment Regimens for Hepatitis C, for Treatment-naive Patients and a "Treat at F3, F4" Strategy

Strategy	Incremental comparison of regimens					
	Net cost	Incr Net cost	Eff	Incr Eff	ICER	Comment
Tx Naive, treat at F3, F4						
No Treatment	$ 45,313	$ -	11.82	0.00	$ -	undominated
PR (48 weeks)	$ 48,435	$ 3,121	12.97	1.14	$ 2,727	undominated
LDV/SOF (8/12 weeks)	$ 65,287	$ 16,853	14.02	1.06	$ 15,940	undominated
SOF + PR (12 weeks)	$ 70,701	$ 5,414	13.85	-0.17	$ (31,593)	abs. dominated
LDV/SOF (12 weeks)	$ 80,653	$ 15,365	14.07	0.04	$ 349,851	undominated
SMV + SOF (12 weeks)	$ 99,733	$ 19,080	13.98	-0.09	$ (223,631)	abs. dominated
SOF + R (24 weeks)	$ 115,070	$ 34,417	13.42	-0.65	$ (53,256)	abs. dominated

Incr Net Cost — Incremental Net Cost; Eff — Effectiveness; Incr Eff — Incremental Effectiveness; abs. — absolutely

Treatment-experienced cohort and "treat all" strategy

Net costs are somewhat higher in treatment-experienced patients compared with treatment-naïve patients in large part due to the longer regimens these patients require, while effectiveness is somewhat lower. LDV/SOF (12/24 weeks) has a very favorable ICER of $10,200. This regimen costs more than SOF + PR (12 weeks) but added enough QALYs to have a better ICER; hence, extended dominance – while both regimens are more effective than PR alone, LDV/SOF (12/24 weeks) has a better cost-effectiveness ratio than SOF + PR (12 weeks) (see Table 16 below). Note that SOF + R is not considered an option for treatment-experienced patients.

Table 16. Cost-effectiveness of Alternative Treatment Regimens for Hepatitis C, for Treatment-experienced Patients and a "Treat All" Strategy

Strategy	Incremental comparison of regimens					
	Net cost	Incr Net cost	Eff	Incr Eff	ICER	Comment
Tx exp, treat all						
No Treatment	$ 45,313		11.82		$ -	
PR (48 weeks)	$ 72,305	$ 26,992	12.13	0.31	$ 88,022	undominated
SOF + PR (12 weeks)	$ 112,226	$ 39,922	14.11	1.98	$ 20,130	ext. dominated
LDV/SOF (12/24 weeks)	$ 119,603	$ 7,376	14.84	0.72	$ 10,200	undominated
SMV + SOF (12 weeks)	$ 165,800	$ 46,197	14.70	-0.14	$ (341,582)	dominated

Incr Net Cost — Incremental Net Cost; Eff — Effectiveness; Incr Eff — Incremental Effectiveness; ext. — extended

Treatment-experienced cohort and "Treat F3, F4" strategy

As shown in Table 17 on the next page, the ICER for PR is $186,159 relative to no treatment, followed by a far more favorable ICER for LDV/SOF (12/24 weeks) of $8,585. As in the "treat all" strategy, SOF + PR was cost-effective relative to PR alone ($9,734 per QALY gained), but the ICER for LDV/SOF 12/24 was better (i.e., extended dominance). SMV + SOF was both more expensive and less effective than LDV/SOF 12/24 (i.e., dominated).

Table 17. Cost-effectiveness of Alternative Treatment Regimens for Hepatitis C, for Treatment-experienced Patients and a "Treat at F3, F4" Strategy

Strategy	Incremental comparison of regimens					
	Net cost	Incr Net cost	Eff	Incr Eff	ICER	Comment
Tx exp, treat at F3, F4						
No Treatment	$ 45,313		11.82		$ -	
PR (48 weeks)	$ 59,873	$ 14,560	11.90	0.08	$ 186,159	undominated
SOF + PR (12 weeks)	$ 75,121	$ 15,248	13.47	1.57	$ 9,734	ext. dominated
LDV/SOF (12/24 weeks)	$ 80,382	$ 5,261	14.08	0.61	$ 8,585	undominated
SMV + SOF (12 weeks)	$ 101,840	$ 21,458	14.00	-0.08	$ (276,952)	dominated

Incr Net Cost — Incremental Net Cost; Eff — Effectiveness; Incr Eff — Incremental Effectiveness; ext. — extended

Comparisons with PR only

Table 18 on the following page presents the base case results for both treatment-naïve and experienced patients and for both the "treat all" and "treat at F3, F4" strategies. However, rather than presenting incremental results for each successively more costly intervention, each regimen is compared directly with PR. For a treatment-naïve cohort, the ICERs are under $50,000 when all patients are treated, with the exception of SMV + SOF (12 weeks), which has an ICER of $72,038, and SOF + R (24 weeks) with an ICER of $189,160. In the treatment-naïve and "treat at F3, F4" strategy, all ICERs were under $50,000 except SOF + R (24 weeks) with an ICER of $146,472.

For treatment-experienced cohorts, *all* sofosbuvir-containing regimens had highly favorable ICERs of under $36,000 in the "treat all" strategy and under $20,000 in the "treat at F3, F4" strategy when compared to PR alone. For both treatment-naïve and experienced patients, lower (more favorable) ICERs resulted from the "treat at F3, F4" strategy than from the "treat all" strategy.

Table 18: Cost-effectiveness of Alternative Treatment Regimens for Hepatitis C, Compared to PR Alone

	Vs. PR		
Strategy	**Net cost**	**Eff**	**ICER**
Tx naïve, treat all			
No Treatment	$ (17,227.08)	-1.513	$ 11,385
PR (48 weeks)			
LDV/SOF (8/12 weeks)	$ 28,450.78	1.413	$ 20,132
SOF + PR (12 weeks)	$ 45,401.89	1.183	$ 38,386
LDV/SOF (12 weeks)	$ 46,078.83	1.475	$ 31,234
SMV + SOF (12 weeks)	$ 100,795.53	1.399	$ 72,038
SOF + R (24 weeks)	$ 123,972.50	0.655	$ 189,160
	Vs. PR		
Strategy	**Net cost**	**Eff**	**ICER**
Tx Naive, treat at F3, F4			
No Treatment	$ (3,121.47)	-1.145	$ 2,727
PR (48 weeks)			
LDV/SOF (8/12 weeks)	$ 16,852.92	1.057	$ 15,940
SOF + PR (12 weeks)	$ 22,266.46	0.886	$ 25,134
LDV/SOF (12 weeks)	$ 32,218.13	1.101	$ 29,257
SMV + SOF (12 weeks)	$ 51,298.18	1.016	$ 50,497
SOF + R (24 weeks)	$ 66,635.17	0.455	$ 146,472
	Vs. PR		
Strategy	**Net cost**	**Eff**	**ICER**
Tx exp, treat all			
No Treatment	$ (26,991.61)	-0.307	$ 88,022
PR (48 weeks)			
SOF + PR (12 weeks)	$ 39,921.83	1.983	$ 20,130
LDV/SOF (12/24 weeks)	$ 47,297.98	2.706	$ 17,477
SMV + SOF (12 weeks)	$ 93,495.25	2.571	$ 36,364
	Vs. PR		
Strategy	**Net cost**	**Eff**	**ICER**
Tx exp, treat at F3, F4			
No Treatment	$ (14,560.10)	-0.078	$ 186,159
PR (48 weeks)			
SOF + PR (12 weeks)	$ 15,247.96	1.566	$ 9,734
LDV/SOF (12/24 weeks)	$ 20,508.59	2.179	$ 9,411
SMV + SOF (12 weeks)	$ 41,967.02	2.102	$ 19,968

Eff —Effectiveness

"Treat all" versus "treat at F3, F4" within regimens

For both treatment-naïve and treatment-experienced patients, we made within-regimen comparisons of the "treat all" versus "treat at F3, F4" strategies (see Table 19 below). For each regimen, treating at all fibrosis stages was a more costly approach than treating only at F3, F4, but also yielded substantial health benefit (one-half to three-quarters of a year of quality-adjusted life expectancy for sofosbuvir-based regimens). For example, treating all naïve patients with LDV/SOF (8/12 weeks) added ~$26,000 in lifetime costs versus a "treat F3, F4" strategy, but also >0.7 QALYs, for an ICER of ~$35,000 per QALY gained. Incremental costs for LDV/SOF were higher among treatment-experienced patients (where duration is 12 weeks of treatment for non-cirrhotic patients and 24 weeks for cirrhotic patients), but incremental cost-effectiveness is still approximately $50,000 per QALY gained.

Table 19: Cost-effectiveness of Alternative Treatment Regimens for Hepatitis C, Comparing a "Treat-All" Strategy with "Treat at F3, F4 Only"

Treat All vs. Treat at F3, F4			
Strategy	**Net cost**	**Eff**	**ICER**
Tx naïve, treat all			
No Treatment			
PR (48 weeks)	$14,106	0.368	$ 38,282
LDV/SOF (8/12 weeks)	$25,703	0.724	$ 35,484
SOF + PR (12 weeks)	$37,241	0.665	$ 55,975
LDV/SOF (12 weeks)	$27,966	0.743	$ 37,663
SMV + SOF (12 weeks)	$63,603	0.752	$ 84,602
SOF + R (24 weeks)	$71,443	0.569	$ 125,577
Treat All vs. Treat at F3, F4			
Strategy	**Net cost**	**Eff**	**ICER**
Tx exp, treat all			
No Treatment			
PR (48 weeks)	$12,432	0.228	$ 54,421
SOF + PR (12 weeks)	$37,105	0.645	$ 57,510
LDV/SOF (12/24 weeks)	$39,221	0.756	$ 51,911
SMV + SOF (12 weeks)	$63,960	0.698	$ 91,662

Eff — Effectiveness

The added QALYs associated with the "treat all" strategy arise from both quality of life improvements and from reductions in mortality. First, SVR improves the quality of life for patients in fibrosis stages F0-F2. This is due both to slightly higher utility in the same fibrosis stages and to substantially higher utility in the earlier stages to which individuals often regress following SVR. In addition, SVR is not a cure for all patients. A significant minority continue to progress even after

achieving SVR in stage F3. That risk is reduced by preventing patients from reaching F3. This slowing is important because F3 carries three types of added risk of disutility and death despite immediate antiviral treatment and high SVR at F3: 1) F3 has lower utility post-SVR than post-SVR utility in F0-F2; 2) in F3, there is a higher risk of death than in the general population even with SVR, and this excess risk is assumed not to be present in F0-F2; and 3) there is an ongoing risk of progression to HCC and liver failure/transplantation, with high associated risks of death. Depending on the regimen evaluated, the majority (55-74%) of the QALY benefit of early treatment is from quality-of-life improvements, while the remaining 26-45% comes from reduced mortality.

Combined treatment-experienced and treatment-naive cohort

In this comparison, we present cost-effectiveness results for a cohort containing a mix of treatment-naïve (79%) and treatment-experienced patients (21%). This is the mix reported in a recent study that examined the natural history of HCV in clinical practice, which we adjusted for those who achieved SVR.[165] We present only the results for the comparison of LDV/SOF to PR, given that it is the regimen with the most favorable cost-effectiveness findings in base-case analyses. Table 20 below shows that the ICERs for LDV/SOF relative to PR (48 weeks) are highly favorable, under $20,000 per QALY gained for both the "treat all" and the "treat at F3, F4" strategies ($19,229 and $13,611, respectively). "Treat at F3, F4" is somewhat more cost-effective due to the lower total net treatment cost from delaying therapy in most individuals.

Table 20: Cost-effectiveness of LDV/SOF vs. PR Alone in a Mixed Cohort of Treatment-naïve and Treatment-experienced Patients with Hepatitis C*

	Vs. PR		
Strategy	**Net cost**	**Incr Eff**	**ICER**
Treat all			
LDV/SOF (8/12 weeks)† - LDV/SOF (12/24 weeks)‡	$ 32,446	1.687	$ 19,229
Treat at F3, F4			
LDV/SOF (8/12 weeks)† - LDV/SOF (12/24 weeks)‡	$ 17,628	1.295	$ 13,611

* — 79.5% of patients are treatment-naive; 20.5% treatment-experienced.

† — Regimen for treatment-naïve patients

‡ — Regimen for treatment-experienced patients

Incr Eff — Incremental Effectiveness

7.3.2 Scenario Analyses

In this section, we present the results associated with varying four key assumptions underpinning the model. These are (1) a higher prevalence of patients in stage F4; (2) the costs of annual medical

care increase as patients progress from stages F0 – F3; (3) an increase in discontinuation rates to reflect "real world" experience; and (4) variation in the average age of the cohort. Results are presented here based on the "treat all" strategy for treatment-naïve patients. Results of these scenario analyses, including results for treatment-experienced patients as well as the "treat at F3, F4" strategy for all patients, are presented in Appendix Tables F1-F4.

Distribution among fibrosis stages

In the base case, the distribution of patients across F0-F4 is 17%, 35%, 22%, 14%, and 12%, respectively. In this revised scenario, the prevalence of F4 is increased from 12% to 20% by reducing prevalence in each of the other stages by two percentage points. PR (48 weeks), LDV/SOF (8/12 weeks) and LDV/SOF (12 weeks) are the only options that are not both more costly and less effective than their comparators. Results are very similar to the base-case analysis, both in terms of comparisons of these regimens to each other as well as to the within-regimen comparisons of "treat all" vs. "treat at F3, F4". There are a number of reasons for this relatively small change in results. First, only 8% of individuals were reclassified to F4, leaving 92% in the same fibrosis stages. Second, the differences in the regimens are generally stable across fibrosis stages, so that their comparison is not materially affected by the modest shift in fibrosis stage distribution. Finally, the added costs and benefits of treating early continue to apply to the individuals who are still in the pre-F3 stages.

Equal costs for medical care for patients in stage F0-F3

In the base case, we assumed equal annual medical care costs for patients in stages F0 through F2 of $810, followed by increases to $2,150 and $2,516 in stages F3 and F4, respectively. In this scenario, we assume equal costs for each stage of $1,023 per year for F0 – F3, followed by the same increase to $2,516 in F4. As with the scenario analysis above, findings were essentially identical to the base-case. This is not surprising, since annual medical care costs make up a relatively small proportion of total costs in relation to the costs of drug treatment and downstream complications.

Discontinuation rates

Discontinuation rates were increased by 50% for Interferon-based treatment in the treatment-experienced cohort and doubled for all other treatments (in both treatment-naïve and -experienced cohorts). Note that, in some instances, the meta-analysis from which the SVRs were derived resulted in a base case discontinuation rate of "0." In such cases, for this scenario analysis, we selected the lowest non-zero value from a comparable therapy.

In this scenario, PR (48 weeks), LDV/SOF (8/12 weeks), and LDV/SOF (12 weeks) had ICERs of $20,160, $15,736 and $411,658 respectively, versus $11,385, $20,132, and $283,927 respectively in the base case. The relatively large change in the LDV/SOF 12-week ratio is likely due to a greater absolute difference in discontinuation rates after doubling (2.6% for the 12-week regimen vs. 0.4% for 8 weeks).

Age of cohort is 50 years

A younger cohort will have a longer average life expectancy, and thus potentially more QALYs of benefit from treatment, but also potentially higher lifetime medical care costs as more individuals live long enough to progress to more advanced disease. In this scenario, we assumed that the patients were 10 years younger than those in our base case analysis and had accordingly higher rates of disease progression.[166] PR (48 weeks), LDV/SOF (8/12 weeks), and LDV/SOF (12 weeks) had ICERs of $5,141, $12,562, and $201,418, respectively. Cost-effectiveness of the "treat all" vs. "treat at F3, F4" was somewhat improved, however, as a result of greater slowing of disease progression with effective treatment.

7.3.3 Sensitivity Analyses

Both one-way and multi-way sensitivity results are presented for treatment–naïve patients in this section; we did not conduct similar analyses for treatment-experienced patients given the similarity in base-case results. Under each of these headings, results for the "treat all" approach are presented first, followed by results when treatment is initiated only at stages F3 and F4. In the "Tornado diagrams", we present only those variables that significantly affected results.

One-way sensitivity analyses

We present the results of one-way sensitivity analyses by means of tornado diagrams. These diagrams show the low to high range of ICER values for uncertainty in each variable, over the range displayed in the legend. The longer the bar associated with each variable, the greater its influence on the ICER. Only the 12 most influential input variables are displayed.

Importantly, none of the variations in parameter estimates we tested resulted in an incremental cost-effectiveness ratio above $50,000 per QALY gained. For example, for the treatment-naïve, "treat all" strategy, the ICER of LDV/SOF (8/12 weeks) versus PR (48 weeks) varied from "cost saving" (i.e., more effective, less expensive) to approximately $48,000 per QALY gained as the weekly drug cost varied from $3,937 to $11,812. The weekly cost of drugs for PR (48 weeks) had the second-largest effect on the ICER. Other inputs had much smaller effects (see Figure 6 on the following page); for example, varying the percentage of patients eligible for the 8-week LDV/SOF regimen from 30% to 90% caused the ICER to range from $15,000 to $26,000 per QALY gained relative to PR alone.

Comparing the same regimens of LDV/SOF (8/12 weeks) versus PR (48 weeks) but assuming a "treat at F3, F4" strategy, the weekly cost of drugs remained the most important variables in determining cost-effectiveness (see Figure 7 on page 63).

Figure 6: One-way Sensitivity Analyses for Treatment-naïve Patients and "Treat All" Strategy

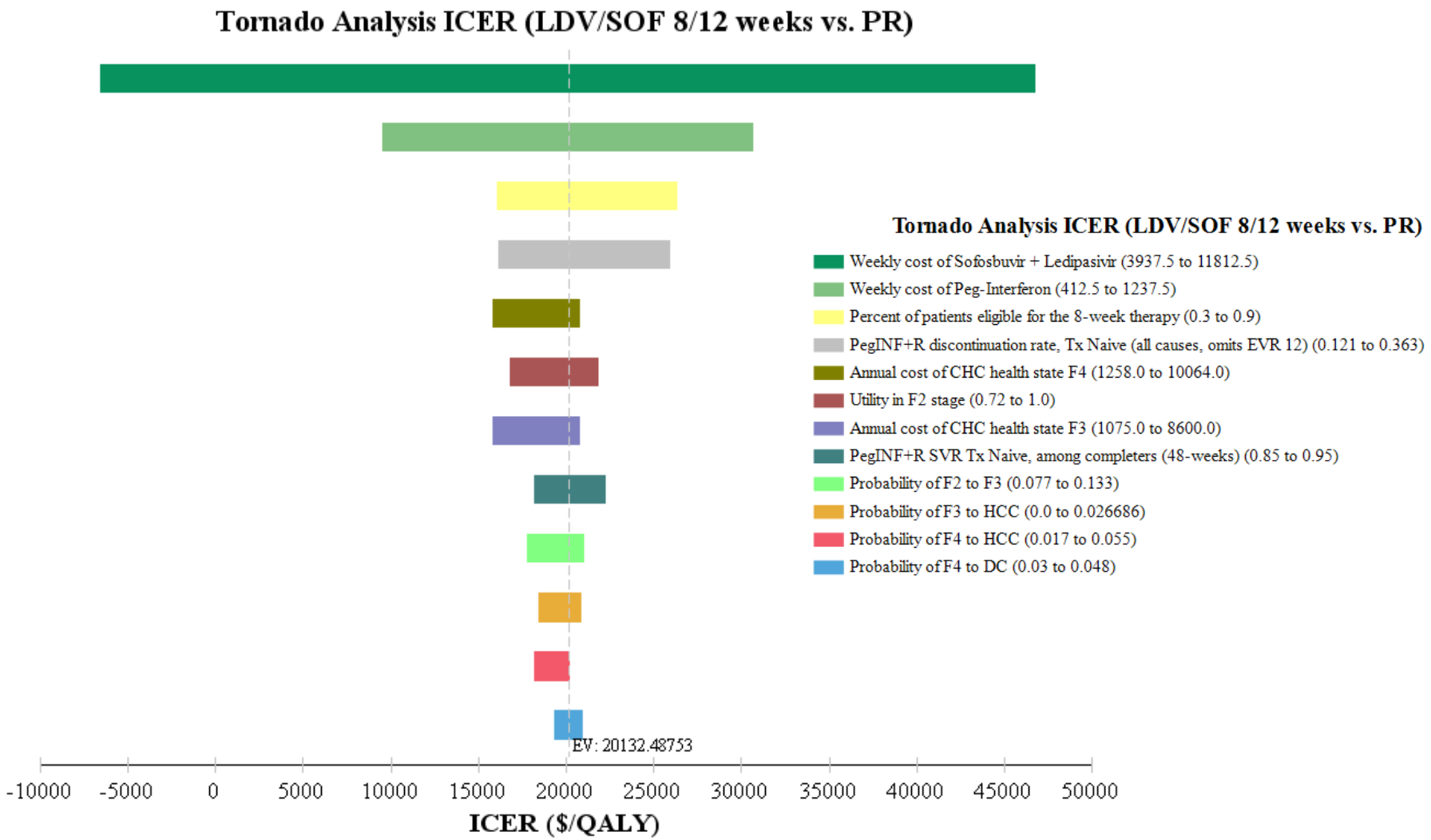
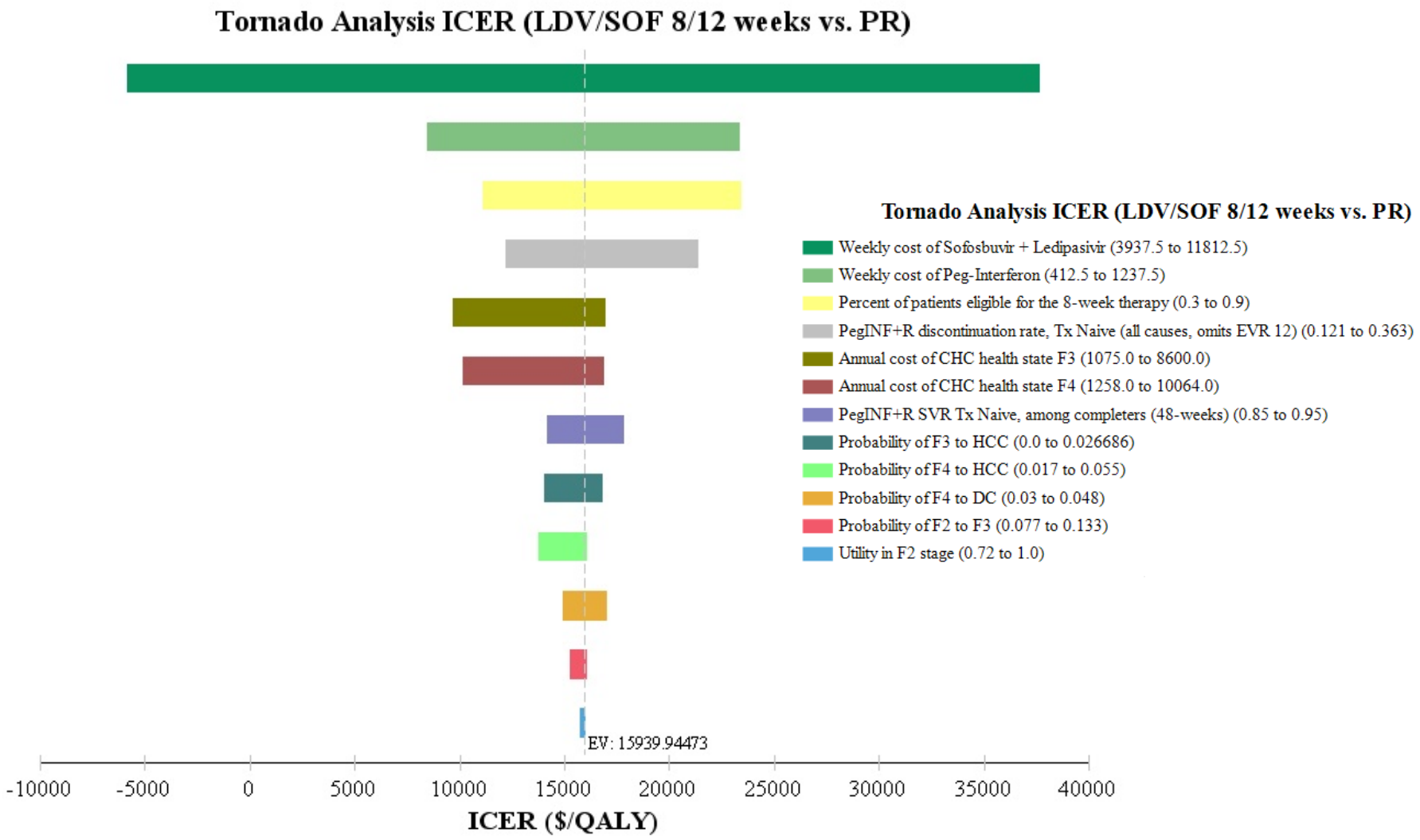


Figure 7: One-way Sensitivity Analyses for Treatment-naïve Patients and "Treat at F3, F4" Strategy



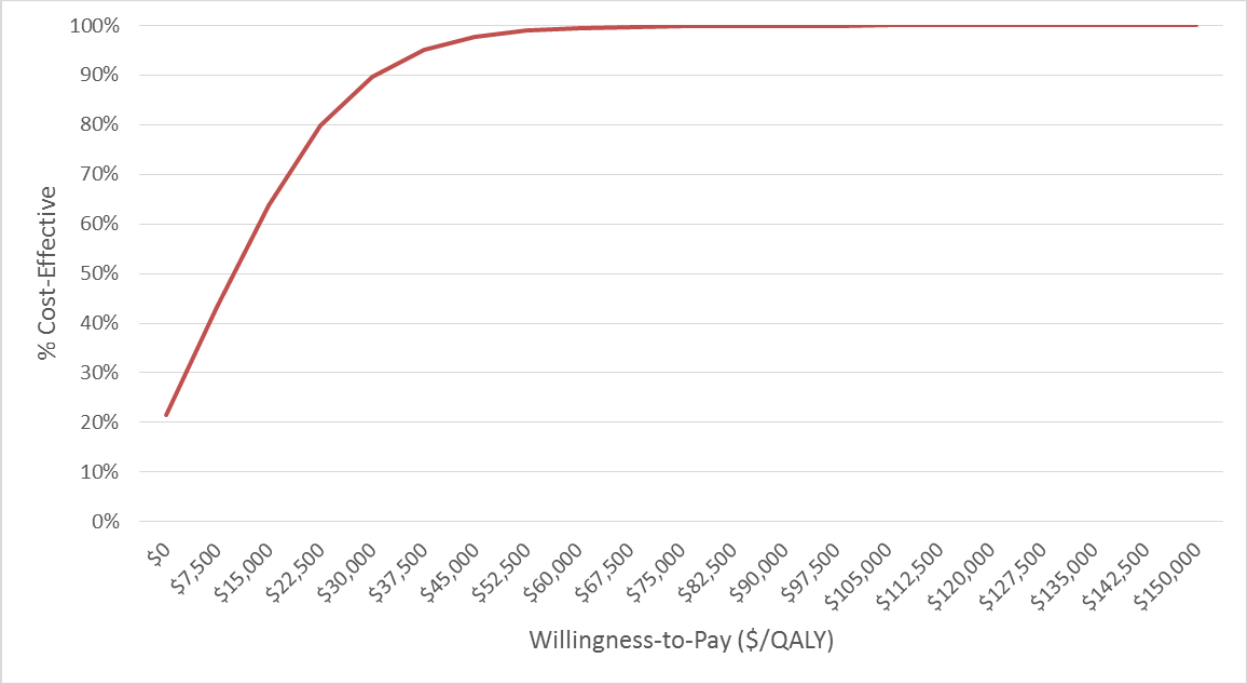
Multi-way probabilistic sensitivity analyses

Multi-way sensitivity analyses are presented by means of cost-effectiveness acceptability curves. We show the distribution of ICERs across 10,000 model runs for LDV/SOF (8/12 weeks) versus PR (48 weeks), varying the base case assumptions for all variables in the model. We used the same range of the input variables employed in the one-way sensitivity analyses (i.e., either published confidence intervals, or 50% - 150% of the base case value if confidence intervals were unavailable). In Figure 8 below and Figure 9 on page 65, the horizontal axis represents the ICERs for LDV/SOF vs. PR, which can be taken to represent possible levels at which a health care system is "willing to pay" for the additional health gain of a QALY. The vertical axis is the percent of the model runs that produced an ICER at or below that particular level, indicating the percent likelihood that LDV/SOF would be considered "cost-effective" at that particular willingness to pay level.

Treat all

Under this strategy, approximately 98% of the simulations yielded an acceptable cost-effectiveness ratio at a willingness to pay threshold of $50,000 per QALY gained, suggesting that the finding that LDV/SOF is cost-effective at that threshold is robust. At $150,000 per QALY gained, effectively 100% of the simulations would yield an acceptable ICER (see Figure 8 below).

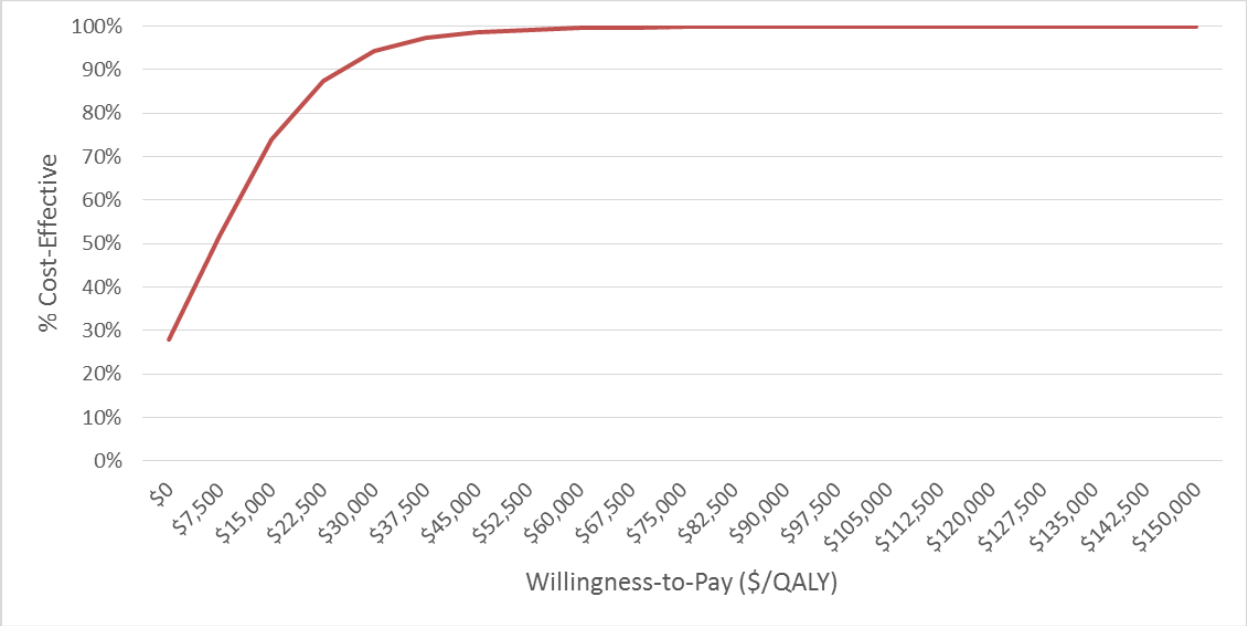
Figure 8: Cost-effectiveness Acceptability Curve for LDV/SOF 8/12 weeks, Treatment-naive, "Treat All" (Compared to PR Alone)



Treat at F3 and F4 only

Similar to the "treat all" strategy, over 99% of simulations for the "treat at F3, F4" strategy also yield an ICER of $50,000 or less (see Figure 9 below).

Figure 9: Cost-effectiveness Acceptability Curve for LDV/SOF 8/12 weeks, Treatment-naive, "Treat at F3, F4 Only" (Compared to PR Alone)



7.4 Health-System Value Analysis: Methods

As mentioned in the beginning of this section, we also assessed the potential budgetary impact of new hepatitis C therapy over three periods of follow-up: one, five, and 20 years after treatment initiation. As with the cost-effectiveness analyses, the regimen of interest for genotype 1 was the LDV/SOF strategy (8/12 weeks for treatment-naïve, 12/24 for treatment-experienced), as this represents the cost-effective strategy that is currently available and most likely to receive widespread use. For each of these time points, we used outputs from the care value model to inform expected numbers (per 1,000 treated) of patients experiencing HCV-related complications (cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant) and dying of HCV-related causes. Costs of treatment and all other care were calculated on a per patient basis, as were total costs. Results for treatment-naïve and treatment-experienced patients were combined and weighted according to an assumed distribution of 79% and 21% for these two subpopulations respectively, as used in the care value analysis.[176]

We then combined these results with findings from the initial CTAF review for genotypes 2 and 3[180] to assess the one-year budgetary impact to California state agencies (Medi-Cal and the Department of Corrections) of adopting LDV/SOF for genotype 1 and the most effective therapies that are FDA-approved for genotypes 2 and 3 (SOF + R for 12 weeks for genotype 2 and 24 weeks for genotype 3). The number of individuals with chronic hepatitis C in Medi-Cal and the California Department of Corrections was recently estimated to total 93,000,[177] of which 70%, 16%, and 12% were assumed to have genotypes 1, 2, and 3 respectively.[178] Cost offsets at five and 20 years were also included in this evaluation to provide additional context for the initial expenditures.

Finally, we conducted analyses to examine the drug prices at which benchmark thresholds of insurer premium increases would not be crossed. In conversation with a variety of health plan professionals and pharmacy benefit managers, we were advised that these thresholds tend to fall in the range of a 0.5-1.0% increase in the per-member per-month (PMPM) premium. Payers believe that the introduction of a single intervention that could potentially cause an increase in PMPM beyond this level requires some form of management in order to modulate the immediate budget impact. If a budget impact of this magnitude cannot be managed, payers believe that there is a significant likelihood that care of equal or greater value will be displaced and/or that health insurance premiums will rise in a fashion that would adversely affect access to affordable care for all patients. The base PMPM was assumed to be $611, based on a recent reporting of Medi-Cal rates from the state Department of Health Care Services (DHCS).[179]

In addition to a full analysis of the prevalent population, the latter two analyses were also conducted under a scenario in which only those currently at F3 and F4 would be prioritized for treatment. All budget impact analyses were conducted using Microsoft Excel.

7.5 Health-System Value Analysis: Results

Budgetary Impact: Per 1,000 Patients Treated

Findings for the performance of LDV/SOF vs. PR are presented in Table 21 below; results are weighted for the combined treatment-naïve and treatment-experienced populations (individual results for these populations are presented in Appendix Tables G1 and G2). As shown in the table, LDV/SOF produces incremental clinical benefits very soon after treatment initiation; for example, compared with PR alone, LDV/SOF prevents approximately six cases of cirrhosis and two HCV-related deaths per 1,000 patients treated in the first year alone.

Table 21. Clinical Outcomes (per 1,000 patients treated) and Costs for LDV/SOF and PR Therapy over One, Five, and 20 Years of Follow-up

	Liver-Related Complications				HCV	*Costs (per patient, $)*		
Timeframe/Regimen	**Cirrhosis**	**Decompensation**	**HCC**	**Transplant**	**Death**	**Treatment**	**Other**	**Total**
1 Year								
PR	6.8	3.5	1.8	0.0	5.4	$34,966	$1,636	$36,602
LDV/SOF	0.8	0.6	1.2	0.0	3.4	$84,341	$696	$85,037
Difference (LS-PR)	*(5.9)*	*(3.0)*	*(0.6)*	*0.0*	*(2.0)*	*$49,375*	*($940)*	*$48,435*
5 Years								
PR	34.8	18.7	11.9	0.4	35.3	$34,966	$6,681	$41,647
LDV/SOF	6.1	3.4	6.7	0.3	18.7	$84,341	$3,260	$87,601
Difference (LS-PR)	*(28.8)*	*(15.3)*	*(5.1)*	*(0.1)*	*(16.5)*	*$49,375*	*($3,421)*	*$45,954*
20 Years								
PR	120.9	66.8	45.3	4.9	248.8	$34,966	$23,442	$58,409
LDV/SOF	21.5	11.8	23.0	1.5	109.1	$84,341	$10,214	$94,555
Difference (LS-PR)	*(99.4)*	*(55.0)*	*(22.3)*	*(3.3)*	*(139.7)*	*$49,375*	*($13,229)*	*$36,146*

LS-PR: Difference between LDV/SOF and PR therapy

However, treatment costs are more than doubled with the newer regimen, and only a small portion of costs are offset by reduced complications. The incremental cost required to avert one HCV-related death at one year is approximately $24 million (i.e., $49,375 / 0.002).

Benefits are more fully realized at later time points. At five years, LDV/SOF would avoid 44 cases of cirrhosis (15 of which would be decompensated), five cases of HCC, and 17 HCV-related deaths per 1,000 treated. Cost offsets would total approximately 7% of incremental treatment costs, but the cost to prevent one HCV-related death would still be nearly $3 million. At 20 years, there would be a nearly six-fold reduction in the incidence of cirrhosis, HCC incidence would be reduced by about half, and 140 HCV-related deaths would be averted per 1,000 treated. Over 25% of treatment costs would be offset by these reductions, and the cost per HCV death averted would be reduced to $260,000.

Budgetary Impact: Medi-Cal/Department of Corrections Population

Our estimates of the budgetary impact of adoption of new hepatitis C treatments to Medi-Cal and the Department of Corrections is summarized in Figure 10 on the following page and in detail in Appendix Table G3. As described previously, LDV/SOF 8/12 or 12/24 was assumed to be the therapy of choice for genotype 1, while SOF + R for 12 weeks and 24 weeks was assumed for genotypes 2 and 3, respectively. A total of 91,140 of the 93,000 total patients would have chronic hepatitis C and genotypes 1, 2, and 3, 50% of whom would be expected to be aware of infection and present for treatment (n=45,570). Total health plan expenditures for all medical care would be approximately $56 billion (i.e., $611 PMPM).

Our model suggests that full uptake of new HCV treatments among known-infected patients would increase costs by approximately $1.6 billion, $545 million, and $901 million for genotypes 1, 2, and 3 respectively (see Figure 10), resulting in a total increase of $3 billion, or $33 PMPM. This represents a 5% increase over the base PMPM of $611. Cost offsets after five years would total $254 million, reducing net expenditures (i.e., initial expenditures less downstream cost offsets) modestly to $2.8 billion. More substantial offsets after 20 years ($1.2 billion) would reduce net expenditures further to $1.8 billion.

Figure 10. Budgetary Impact of New Hepatitis C Treatments in the Medi-Cal/Department of Corrections Hepatitis C Population in California, with and without Cost Offsets from Reduced Liver-related Complications

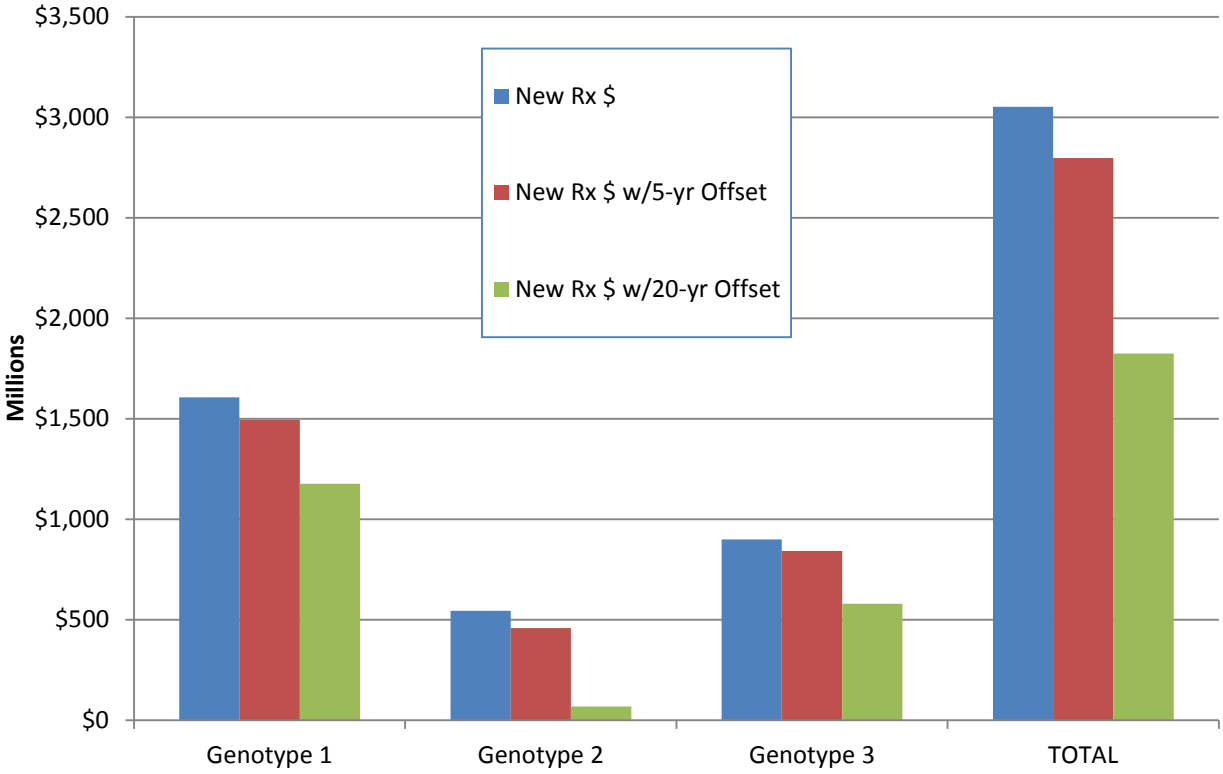
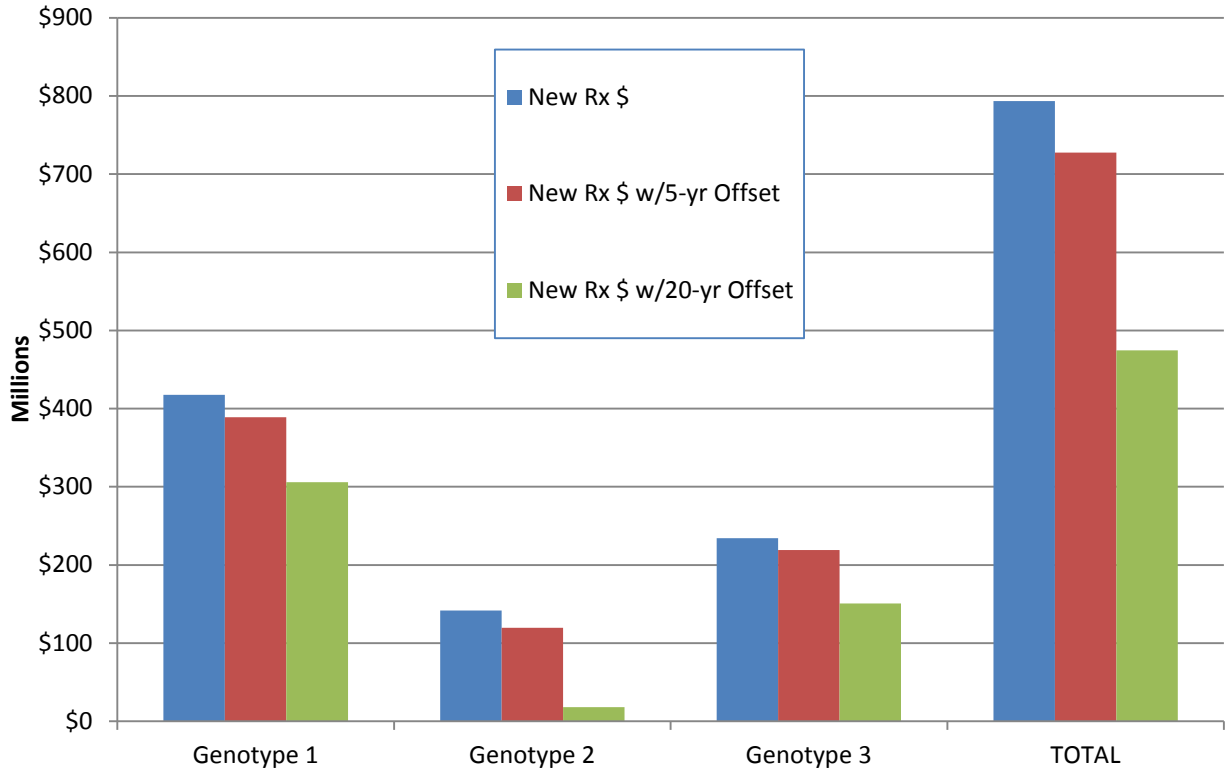


Figure 11 on the following page illustrates the budgetary impact with treatment commenced only for patients at fibrosis levels of F3 and F4 (approximately one-quarter of the potential patient pool). The initial expenditures for new therapies are reduced to approximately $800 million (~$9 PMPM, a 1.4% increase). Total net expenditures after 20 years are $475 million, an increase of less than 1%.

Figure 11. Budgetary Impact of New Hepatitis C Treatments in the Medi-Cal/Department of Corrections Hepatitis C Population in California, with and without Cost Offsets from Reduced Liver-related Complications: Treatment of Patients Currently at F3 and F4 Only



Additional Analyses Following the 12/18/14 CTAF Meeting

Comments made leading up to and at the December 18, 2014 CTAF meeting provided two important critiques of the budgetary impact analyses. The first concern related to the use of wholesale acquisition costs (WAC) to estimate payments by Medi-Cal and the California Department of Corrections. The commenters acknowledged that the true price paid by these entities is unknown, given supplemental rebates offered by manufacturers and other pricing adjustments. Nevertheless, we conducted an alternative analysis in which the WAC costs were reduced by 23.1% to reflect the mandated rebate that must be offered to all Medicaid programs for brand-name, "innovator" drugs. In this analysis, overall budget impact declined from $3 billion to $2.3 billion, or from $33 to $25 PMPM. The latter reflected a 4% increase over the base PMPM of $611, rather than a 5% increase in the original analysis.

The other criticism related to our estimate of the percentage of patients eligible for treatment who would be aware of their infection (50 %); many commenters felt that the percentage who would be aware and present for treatment would not exceed 15 % given challenges with many sectors of the HCV population as well as system capacity constraints. However, we also acknowledge that our initial estimate of the prevalent HCV population in Medi-Cal and the CA Department of Corrections

(N=93,000, or 1.2%) was overly conservative. When we used widely-circulated estimates for prevalence in Medicaid (3.8%) and prison (30.0%) populations,[184] a more likely number of infected individuals in these two California populations is approximately 300,000. Coincidentally, 15% of 300,000 is 45,000 individuals, which is essentially the same figure we used initially (50% of 93,000).

Drug Pricing to Meet Per-Member Per-Month Benchmarks

As mentioned previously, PMPM increases of 0.5%-1.0% in a given year were used in this report as a range of potential budget impact that is likely to warrant specific efforts to manage the costs of a new health care intervention. We examined the incremental drug expenditures at which PMPM increases of 0.5% and 1.0% would be met for genotype 1, the patient subpopulation of interest in this review. Historical treatment costs were estimated based on the cost of PR (approximately $42,000 per treatment course) weighted by the assumed proportion of patients eligible for such therapy (60%); no treatment at baseline was assumed for the 40% of patients who would be ineligible for interferon-based therapy. Thus, historical treatment costs were estimated to total approximately $25,000 per patient with genotype 1 disease.

Based on the assumed baseline PMPM in this analysis ($611) as well as the size of the population to be treated (approximately 33,000 patients in the Medi-Cal/Department of Corrections population in California if 50% of genotype 1 patients present for treatment), a course of treatment with a new agent would need to be priced at $34,000 - $42,000 to meet the 0.5% and 1% thresholds respectively.

We also conducted a hypothetical analysis of the number of treatment-naïve Medi-Cal/Department of Corrections patients who could be treated without exceeding a 1% PMPM threshold, based on the current wholesale acquisition costs of LDV/SOF (approximately $63,000 and $95,000 for 8 and 12 weeks, respectively). As with other model analyses, we assumed that 79% of genotype 1 patients presenting for treatment would be treatment-naïve (i.e., ~26,000 of 33,000 in the Medi-Cal/Department of Corrections population), and that 67% of treatment-naïve non-cirrhotic patients would receive 8 weeks of treatment.

Based on these assumptions, only two-thirds of these patients (approximately 16,500 of the 26,000 patients with known infections) could receive treatment at these prices if the one-year PMPM increase were to be held to less than 1% (i.e., ≤$6.11), leaving nearly 10,000 Medi-Cal/Department of Corrections patients without access to new therapy. When considering a 0.5% threshold for PMPM increase (≤$3.06), less than half of eligible patients (12,600 of 26,000) could be treated at current prices.

We conducted an alternative analysis in which the percentage of treatment-naïve non-cirrhotic patients eligible for 8 weeks of therapy was adjusted upward to 90%. Even with this adjustment, the percentages of genotype 1 patients who could receive treatment increases to only 54% and 71%

at the 0.5% and 1% PMPM thresholds respectively, leaving nearly 12,000 and 8,000 patients without access to treatment.

By contrast, if the population of treatment-naïve genotype 1 patients is restricted to those with F3 and F4 stage disease (n=~6,700), LDV/SOF could replace historical PR therapy in ***all*** of these patients at current prices and remain under the 1% threshold for PMPM increase. When considering a 0.5% increase in PMPM ($3.06), LDV/SOF could replace PR in 91% of F3/F4 patients (n=~6,100) at current prices. (*Note: if the percentage eligible for 8-week therapy is increased to 90%, then all F3/F4 patients could be treated below the 0.5% PMPM increase threshold*.)

7.6 Summary

Using the best available information on the costs and health consequences of drug therapies for the most common form of chronic hepatitis C (genotype 1), we modeled the net costs, health benefits (expressed in QALYs), and incremental cost-effectiveness of a range of sofosbuvir-based therapies as well as pegylated interferon and ribavirin alone. We also assessed these results in a comparison of a policy of treating HCV patients in all fibrosis stages against a policy of treating only those who reach F3 and F4, thus delaying the treatment for those initially in stages F0-F2. While estimates of what might be considered cost-effective vary, it is reasonable to rate an ICER of under $150,000 to be "cost-effective" and ICERs under $50,000 to be "very cost-effective". In the base-case analysis we found that LDV/SOF regimens for treatment-naïve and treatment-experienced patients were very cost-effective, producing ICERs ≤$20,000 per QALY gained regardless of the comparison (e.g., PR alone vs. next-least costly alternative, treat all vs. treat at F3, F4, weighted estimates for a combined treatment-naïve and treatment-experienced cohort).

Our analysis also found that, while treating patients at all fibrosis stages was more expensive in comparison to waiting to treat until patients reached F3 or F4, it was also more effective. For example, treating all naïve patients with LDV/SOF 8/12 or LDV/SOF 12 as well as PR alone produced ICERs <$40,000 per QALY gained in comparison to treating only at F3/F4. Among treatment-experienced patients, differences in effectiveness were more pronounced, with over two years of quality-adjusted life expectancy gained for sofosbuvir-based regimens relative to PR alone (generating ICERs of $10,000-$20,000 per QALY gained). Comparisons of the "treat all" vs. "treat at F3, F4" approaches in the treatment-experienced subgroup generated more costs (in part because sofosbuvir-based regimens are longer) but still produced estimates of cost-effectiveness of ~$50,000 per QALY gained. Model findings were robust to a range of sensitivity analyses, with changes in model results greatest in relation to variation in the weekly prices of sofosbuvir and PR therapy.

These findings stand in contrast, however, to those of our budget impact analysis, which suggest that the introduction of LDV/SOF would increase the cost of treatment over PR alone by $40,000-

$75,000 per patient depending on the duration of therapy. Some of these costs would be offset by reductions in the rate of serious liver complications but would offset 30-40% of additional treatment costs at most. As a result, the budgetary impact to the nearly 100,000 Californians being treated for HCV with state funds (i.e., Medi-Cal and Department of Corrections) would be substantial. Treatment costs would increase by $1.6 billion for genotype 1 alone if 50% of infected patients are treated; when estimates for genotypes 2 and 3 from our March 2014 report are included, the total budgetary impact would be over $3 billion, or $33 per member per month (PMPM).

Based on a recent estimate of PMPM costs for Medi-Cal ($611), this represents a 5% increase, far above the 0.5-1% increase that most insurers believe is the upper limit for a manageable increase in expenditures. This increase is reduced somewhat when downstream cost offsets are considered, but never approaches the 0.5-1% threshold. In fact, a new agent would need to be priced at $34,000 - $42,000 per course of treatment to fall within this range (approximately $9,000-$17,000 above the baseline cost of PR therapy). At current prices, LDV/SOF 8/12 could only be offered to approximately half of eligible patients presenting for treatment. If treatment were restricted only to patients at fibrosis stages F3 and F4, however, the budgetary impact is less pronounced. Treatment costs would rise by approximately $800 million in the Medi-Cal/Department of Corrections population (~$9 PMPM, a 1.4% increase) and would be $475 million after 20-year cost offsets were considered.

We note some limitation of our analyses. First, we did not model the effects of HCV treatments on patients co-infected with HIV, injection drug users, or in those treated following liver transplant. Clinical consequences and costs might be very different in these important subgroups. The analytic perspective was that of a third-party payer, and we therefore did not include the costs of transportation or other incidental costs associated with seeking and obtaining medical care, nor did we incorporate patients' financial contributions (e.g., copayments, deductibles) into these calculations. The FDA approval for the combination of sofosbuvir and simeprevir came after our analyses had been completed; as such, our modeled duration of therapy in treatment-experienced individuals was half that of the approved duration (12 vs. 24 weeks). While adjustment of treatment duration would have increased the cost of treatment for this combination in treatment-experienced individuals, it would not have appreciably changed major findings, namely that SMV + SOF is less effective and more expensive than LDV/SOF regimens.

We also did not include the benefits resulting from reduced secondary transmission of HCV due to reduced community HCV burden, which is a significant concern in some of the vulnerable populations mentioned above. We also did not model the risk of re-infection or relapse following SVR or non-adherence to treatment as well as their associated costs and health outcomes, due to a lack of comparative data between regimens. The simplified "snapshot" approach in the budget impact analysis also did not consider relapse, reinfection, or even incident infection in patients not treated at baseline. Finally, we obtained data from a variety of sources, many of them not perfectly suited to the demands of our models. For example, estimates of effectiveness as measured by SVR

were derived from clinical trial results. "Real world" effectiveness might diverge significantly from these estimates.

Finally, we recognize that the "benchmark" analysis as presented relies on a threshold standard (0.5-1% PMPM) for the budgetary impact of a new intervention that is not published or otherwise widely-circulated. This is in contrast to thresholds for cost-effectiveness analyses (e.g., $50,000 per QALY) which are widely known if not extensively validated. However, we do believe that use of a budget impact threshold promotes discussion about the challenges that payers face with regard to expensive interventions as well as the services that may be foregone to pay for them. For example, the $3 billion that may be required for Medi-Cal and the CA Department of Corrections to pay for new HCV agents represents payment for approximately 70 million well-child visits, or 18 visits for each of the 3.9 million children currently enrolled in Medi-Cal.

Nevertheless, our findings have important implications. In particular, model results suggest that the introduction of LDV/SOF for both treatment-naïve and treatment-experienced individuals would confer substantial clinical benefits in comparison to historical treatment standards and even in relation to other sofosbuvir-based regimens. While the use of this new regimen would increase treatment costs, such use appears to be cost-effective. However, the additional expenditures required to treat all patients with genotype 1 infection (even if only 50% of them are aware of their infection) are substantial; when added to the additional expenditures already required for genotypes 2 and 3, this represents a per-member per-month premium increase that is fivefold higher than frequently-discussed manageable thresholds for new interventions. It is clear that patients, physicians, insurers, and health systems will have to grapple with the budget impact of new, highly effective, and expensive treatments for hepatitis C. Whether this will result in prioritization of clinical care, new contracting and financing tactics, evolving market dynamics, or policy actions remains to be seen.

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This is the first review of these technologies by the California Technology Assessment Forum and the second review of treatment alternatives for chronic hepatitis C.

8. Questions and Discussion

8.1 About the CTAF Process

During CTAF public meetings, the CTAF Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, a cost analysis of the applications of the medical technologies or treatments under examination, and the supplementary information presented. Panel members typically serve for two or more years and are intentionally selected to represent a range of expertise and diversity in perspective. To maintain the objectivity of the CTAF Panel and ground the conversation in the interpretation of the published evidence, they are not pre-selected based on the topic being addressed. Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to CTAF Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the CTAF Panel during their deliberation, and they help form recommendations with CTAF on ways the evidence can be applied to policy and practice.

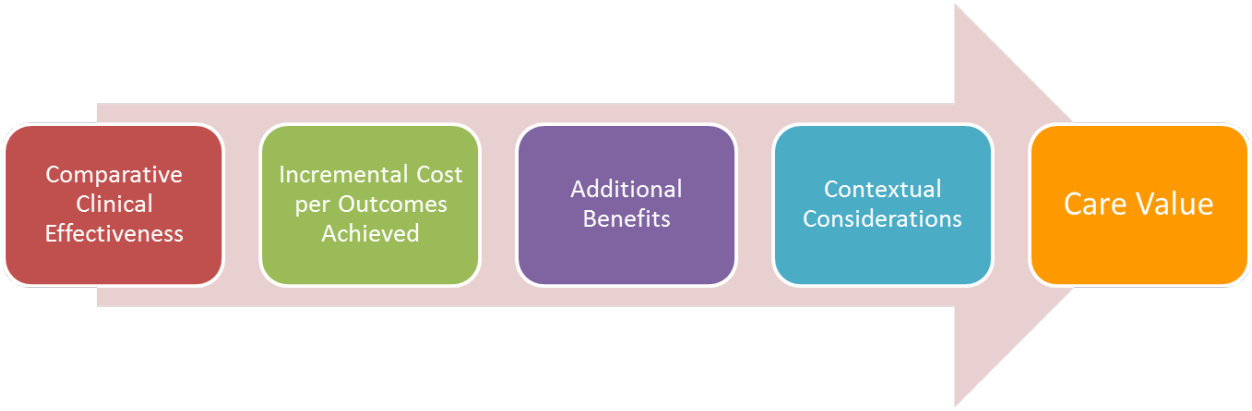
At each meeting, after the CTAF Panel vote, a policy roundtable discussion is held with the CTAF Panel, clinical experts, and representatives from provider groups, payers, and patient groups. This is intended to bring stakeholders into the discussion on how best to apply the evidence to guide patient education, clinical practice, and coverage policies. For this meeting, CTAF held an additional policy roundtable discussion on pricing and payment considerations, which was composed of a broader set of stakeholders. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the December 18, 2014 meeting, the CTAF Panel discussed issues regarding the application of the available evidence to help patients, providers, and payers address the important questions related to the newest, all-oral treatments for hepatitis C. Following the evidence presentation and public comments, the CTAF Panel voted on key questions concerning the comparative clinical effectiveness and comparative value of the newest treatments for hepatitis C. These questions are developed by the ICER research team for each assessment, with input from the CTAF Advisory Board to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice and medical policy decisions. The voting results are presented below, along with comments reflecting considerations mentioned by CTAF Panel members during the voting process.

In its deliberations and voting related to value, the CTAF Panel made use of a new value assessment framework with four different components of *care value*, which they considered in assigning an overall rating of low, reasonable, or high care value. The four components of care value are comparative clinical effectiveness, incremental cost per outcomes achieved, additional benefits, and contextual considerations regarding the illness or therapy. Once they made an overall

assessment of care value considering these four components, the CTAF panel then explicitly considered the affordability of the newest, all-oral hepatitis C treatments in assessing health system value as low, reasonable, or high (see Figure 12 below and Figure 13 on the next page, as well as the detailed explanation that follows).

Figure 12. Care Value Framework



***Care value* is a judgment comparing the clinical outcomes, average per-patient costs, and broader health effects of two alternative interventions or approaches to care.**

There are four elements to consider when deliberating on care value:

1. ***Comparative clinical effectiveness*** is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. CTAF now uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.
2. ***Incremental cost per outcomes achieved*** is the average per-patient incremental cost of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a ratio: a "cost per outcome achieved." Relative certainty in the cost and outcome estimates continues to be a consideration.
3. ***Additional benefits*** refers to any significant benefits offered by the intervention to caregivers, the delivery system, or other patients in the health care system that would not have been captured in the available "clinical" evidence. Examples of additional benefits include mechanisms of treatment delivery that require many fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions (e.g., mental illness) that have demonstrated low rates of response to currently available therapies. For each intervention evaluated, it will be open to discussion whether additional benefits such as these are important enough to factor into the overall judgment of care value. There is no quantitative measure for additional benefits.

4. ***Contextual considerations*** can include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether the condition affects priority populations. There is no quantitative measure for the role of contextual considerations in an overall judgment of care value.

CTAF uses this conceptual description of the elements of care value when deliberating on the evidence and voting. The CTAF Panel was asked to vote whether interventions represent a "high," "reasonable," or "low" care value vs. a comparator from the generalized perspective of a state Medicaid program.

Figure 13. Health System Value Framework

Health system value **is a judgment of the affordability of the short-term budget impact that would occur with a change to a new care option for all eligible patients, assuming the current price and payment structure.**

Usually, the care value and the health care system value of an intervention or approach to care will align, whether it is "high," "reasonable," or "low." For example, a treatment that is judged to represent high care value from the perspective of per-patient costs and benefits will almost always represent a high health system value as well. But health system value also takes into consideration the short-term effects of the potential budget impact of a change in care across the entire population of patients. Rarely, when the additional per-patient costs for a new care option are multiplied by the number of potential patients treated, the short-term budget impact of a new intervention of reasonable or even high care value could be so substantial that the intervention would be "unaffordable" unless the health system severely restricts its use, delays or cancels other valuable care programs, or undermines access to affordable health insurance for all patients by sharply increasing health care premiums. Under these circumstances, unmanaged change to a new care option could cause significant harm across the entire health system, in the short-term possibly even outweighing the good provided by use of the new care option itself.

To consider this possibility, CTAF reviews estimates of the potential budget impact for a change in care as measured by the estimated increase in "per-member-per-month" health care premiums

that would be needed to fund a new care option in its first year of use were all eligible patients to be treated. The CTAF Panel was asked to consider affordability from the generalized perspective of a state Medicaid program. It should be noted that if, after considering potential budget impact, a health intervention judged to have high care value receives a judgment of "low" health system value from the CTAF Panel, this does not imply that the health system should not adopt the intervention; rather, the vote indicates that policy makers should consider implementing mechanisms related to patient selection, step therapy, pricing, and/or financing to ensure that the short-term budget impact of a high care value intervention does not lead to more harm than good. CTAF votes on health system value will therefore serve an important function by highlighting situations when policymakers need to take action and work together to align care value with health system value.

8.2 Summary of the Votes and Considerations for Policy

Clinical Effectiveness (based on the evidence presented)

1. For patients with genotype 1 chronic hepatitis C infection, is the evidence adequate to demonstrate that clinical outcomes with *ledipasvir/sofosbuvir* are superior to those provided by treatment with *pegylated interferon plus ribavirin*?
   CTAF Panel Vote: 12 yes (100%) 0 no (0%)

2. For patients with genotype 1 chronic hepatitis C infection, is the evidence adequate to demonstrate that clinical outcomes with *ledipasvir/sofosbuvir* are superior to those provided by treatment with *sofosbuvir plus pegylated interferon plus ribavirin*?
   CTAF Panel Vote: 10 yes (83%) 2 no (17%)

3. For patients with genotype 1 chronic hepatitis C infection, is the evidence adequate to demonstrate that clinical outcomes with *ledipasvir/sofosbuvir* are superior to those provided by treatment with *simeprevir plus sofosbuvir*?[g]
   CTAF Panel Vote: 1 yes (8%) 11 no (92%)

4. For patients with genotype 1 chronic hepatitis C infection, is the evidence adequate to demonstrate that clinical outcomes with *ledipasvir/sofosbuvir* are superior to those provided by treatment with *3D + R (combination of paritaprevir, ritonavir, ombitasvir, and dasabuvir with ribavirin)*?
   CTAF Panel Vote: 1 yes (8%) 11 no (92%)

[g] At the meeting after the automated voting was completed, two panel members indicated that they voted for a different option than they had intended. As a result, the votes shown here differ from those shown on-screen at the meeting.

Value

5. If yes to question 1, given the prices presented in the report, what is the ***care value*** of *ledipasvir/sofosbuvir* vs. *pegylated interferon plus ribavirin*?[h]
   CTAF Panel Vote: 6 high (50%) 6 reasonable (50%) 0 low (0%)

   Comment: In written notes, CTAF Panel members offered insights into their assessments of each of the four components of care value. With regard to the evidence on *comparative clinical effectiveness,* CTAF Panel members had moderate to high certainty that the new drugs offered clinical benefits both in terms of high SVRs and fewer side effects. In terms of *incremental cost per outcomes achieved*, it was noted that the commonly-used $50,000 per QALY cost-effectiveness threshold was met for most comparisons, although there were some concerns that cost-effectiveness would be adversely affected if real-world SVRs did not match those of clinical trials. With respect to *additional benefits*, factors discussed included potential decreased transmission ("treatment as prevention"), future eradication of disease, presumed greater adherence given fewer side effects, and enhanced quality of life. In terms of *contextual considerations,* the public health impact of decreased transmission, potential reduction of disease in the community, quality of life, and high impact on a vulnerable/disadvantaged population were mentioned. One CTAF Panel member questioned the benefit of treatment for asymptomatic patients, noting that although there is the ability to stratify patients and prioritize treatment based on level of liver disease, this is not routinely done and current science does not allow us to predict which patients will suffer progressive liver disease. Thus, some patients will undergo treatment who would not have ever developed significant disease.

   CTAF Panel members who voted that the newest treatments were ***high*** care value cited high SVRs and fewer side effects of the new drugs paired with incremental costs per life year gained commonly considered "cost-effective". Those voting ***reasonable*** care value pointed to price as well as the issue of treating asymptomatic patients who may not progress to liver disease.

6. Assuming no changes to pricing or to payment mechanisms, if a policy strategy to treat all known infected patients was adopted, what would be the ***health system value*** of *ledipasvir/sofosbuvir* for a state Medicaid program?
   CTAF Panel Vote: 0 high (0%) 2 reasonable (17%) 10 low (83%)

   Comment: In considering ***health system value***, CTAF Panel members noted challenges due to the price of treatment and expressed concerns about the impact of these prices on the overall health care system. They highlighted the combination of high price and high prevalence, resulting in a dramatic and unaffordable budget impact that they viewed as

[h] See footnote g on the previous page.

unsustainable in the long term. Several CTAF Panel members made strong statements that this is ultimately a pricing problem, and additional comments referenced the impact of high drug prices in settings with fixed resources and the resulting forced reallocation of resources (effectively pitting one group of patients against another for resources).

The two CTAF Panel members who voted ***reasonable*** health system value noted the high prevalence of hepatitis C, the fact that it is an infectious disease and thus a public health problem, that treatment should be offered for those who desire it, and that there should be a push toward a sustainable balance of treatment and affordability.

Roundtable Discussions and Key Policy Implications

Following its deliberation on the evidence and subsequent voting, the CTAF Panel engaged in moderated discussions with two Policy Roundtables. The first focused on clinical and coverage considerations related to treatment with the newest, all-oral hepatitis C treatments and was composed of clinical experts, a patient advocate, representatives of one private and two public payers, and representatives from two manufacturers of the newest hepatitis C drugs. The policy roundtable discussions with the CTAF Panel reflected multiple perspectives and opinions, and therefore, none of the recommendations below should be taken as a consensus view held by all participants. The names of the participants on the first Policy Roundtable are shown in Table 22 below.

Table 22. Clinical Considerations Policy Roundtable Participants

Rena Fox, MD	Professor of Clinical Medicine, Division of General Internal Medicine, UCSF
Bill Guyer, PharmD	Vice President of Medical Affairs, Gilead Sciences
Mitch Katz, MD	Director, Los Angeles County Department of Health Services
Jim Kiley, MD	Interim Chair, Medical Policy Committee, Blue Shield of California
Neal D. Kohatsu, MD, MPH	Medical Director, California Department of Health Care Services
Juan Carlos Lopez-Talavera, MD	Vice President and Medical Affairs Head, Hepatology, AbbVie
The Reverend Margaret Moore, RN	Priest (Retired), Episcopal Church; Facilitator, North Oakland Hepatitis C Support Group
Joanna Ready, MD	Chief, Department of Gastroenterology, The Permanente Medical Group

The second policy roundtable focused on specialty drug pricing and payment, examining the affordability concerns raised by the newest hepatitis C drugs as a case of a more general policy challenge faced by the US health care system. Participants in this second policy roundtable included policy experts from diverse organizations with a wide variety of perspectives, as shown in Table 23 on the next page:

Table 23. Specialty Drug Pricing and Payment Policy Roundtable Participants

Tony Barrueta, JD	Senior Vice President of Government Relations, Kaiser Foundation Health Plan, Inc.
David Gollaher, PhD	Vice President Policy and Public Health, Gilead Sciences
Newell McElwee, PharmD, MSPH	Executive Director of US Outcomes Research, Merck & Co
Steve Miller, MD	Senior Vice President & Chief Medical Officer, Express Scripts
Steven Pearson, MD, MSc	President, Institute for Clinical and Economic Review
Matt Salo	Executive Director, National Association of Medicaid Directors
Sean Sullivan, BScPharm, PhD	Professor and Dean, School of Pharmacy, University of Washington

Both roundtable discussions were facilitated by Jed Weissberg, MD, Senior Fellow at ICER. The main themes and recommendations from the discussions are summarized below.

Clinical Considerations Policy Roundtable

1. *Because the newest treatment regimens avoid the need for interferon and therefore are associated with far fewer side effects, there is growing hope among patients and many clinical experts and policy makers that treatment can be expanded to all patients who seek treatment for hepatitis C. Treating all who desire treatment will be costly, however, and in many care settings, there are still infrastructure and financial constraints that highlight the importance of giving priority to identifying patients with advanced liver fibrosis (symptomatic or asymptomatic) or who are at high risk of infecting others and bringing them into treatment as quickly as possible.*

Given the effectiveness of the newest, all-oral treatments and the health benefits of treatment for individuals infected with hepatitis C and for society, the CTAF Panel and several participants on the policy roundtable stated that there is a societal imperative to treat all infected patients. Nonetheless, there are a limited number of physicians with expertise in treating hepatitis C, and even with non-specialist physicians beginning to prescribe these new treatments, the infrastructure to treat all patients immediately does not exist in most care settings. Further, even though the treatments represent a high care value, the budget impact will be significant, especially for health care systems with fixed annual budgets or otherwise limited financial resources.

Prioritization of patients for treatment is therefore still a reasonable policy approach, especially since there remain many patients with advanced liver fibrosis who have not been identified and brought into treatment. One suggestion to help health systems manage the budget impact of these treatments was that they identify patients who have hepatitis C, create registries to track their illness, and prioritize treatment for those patients who need treatment most urgently in a systematic way.

In the oral public comments given at the meeting, it was suggested that injection drug users (IDUs) be treated as a priority population to reduce disease transmission. It was agreed that health care systems should ensure that IDUs are actively screened for hepatitis C infection and that a holistic approach be taken to viewing the best way to prioritize patients' needs for psychosocial support, as well as treatment for hepatitis C, substance abuse, and other conditions.

2. *Given that the newest treatment regimens are much simpler and have fewer side effects than older treatment regimens, physician groups and payers should consider allowing non-specialist physicians to prescribe them.*

Because there is a desire to treat more patients with the newest, all-oral treatment regimens, the clinical experts on the policy roundtable suggested that non-specialist physicians could effectively prescribe these newest treatments as long as they had ready access to specialty consultation. They also suggested that other health care providers such as nurse practitioners and pharmacists could help to manage the treatment process. Demonstration projects of clinician education, coordination between primary care providers and specialists, and expanded prescribing privileges built into health plan or pharmacy benefits manager preauthorization criteria were suggested as a longer term strategy to increase provider treatment capacity.

3. *Patients with hepatitis C and their families need guidance and support through the treatment process.*

Although the newest treatments for hepatitis C are shorter in duration and have fewer side effects than older treatments, many patients may still have side effects that are frightening or disruptive. However, rigorous adherence to the treatment regimen is essential in assuring that patients receive the benefits of treatment and in reducing the risk of promoting resistant strains of the virus. The clinical experts on the policy roundtable indicated that they offer intensive guidance and support throughout the treatment process, but they also advised that clinicians should prioritize for early treatment patients who are likely to be able to follow through on their commitment to work in partnership with the clinical team to complete the treatment regimen.

4. *Patients and their families, as well as payers, experience the financial impact resulting from the high cost of these new hepatitis C treatments.*

While some patients have comprehensive health insurance with manageable copayments for the newest hepatitis C treatments, many other patients and their families face a much higher financial burden for treatment due to high deductibles, copayments, or coinsurance. Some patients may be able to obtain help with drug costs through patient assistance programs offered by manufacturers. Although some public agencies such as Medi-Cal and the US Department of Veterans Affairs obtain mandatory price reductions for these new drugs, and private payers can try to negotiate discounts with manufacturers, all face budget constraints that require them to divert resources from other health care services to cover the cost of the newest hepatitis C treatments.

Specialty Drug Pricing and Payment Policy Roundtable

1. *Hepatitis C deserves a focused, national strategy for treatment and financing.*

Several CTAF Panel members and policy roundtable participants stated that there is a compelling public interest because hepatitis C is an infectious and communicable disease with 3 million or more infected individuals in the US. A national approach that addresses the challenges of treatment and financing could more effectively solve this public health problem than the current model of individual states, payers, provider groups, or others independently negotiating for the best prices for the newest, all-oral hepatitis C drugs.

2. *Given the growing trend of effective but expensive new therapies like the new treatments for hepatitis C, inflammatory diseases, and cancer, a variety of mechanisms should be explored so that patients can benefit from treatments of high care value in a manner that also ensures high health system value.*

The CTAF Panel and policy roundtable participants agreed that a variety of innovative ideas should be considered to help manage the affordability of new, highly effective therapies that raise serious concerns about affordability. Specific suggestions could be grouped into three categories of payment, policy, and care redesign as shown below:

Payment

- Pay for outcomes rather than for the treatment (e.g., if a patient doesn't achieve the desired clinical benefit, the manufacturer refunds the payment; alternatively, the manufacturer receives payment only when a patient achieves the desired clinical outcome)
- Negotiate price volume agreements with manufacturers so that prices continue to decrease with increasing volume
- Mortgage/amortize the cost of treatment over several years to reduce the immediate budget impact (this was described by payers as unrealistic since they have 1- or 2-year budget windows, and since there will be other new/innovative therapies to pay for in the future)
- Use mechanisms such as reinsurance or risk corridors to help manage unexpectedly high costs

Policy

- Target federal funding to provide access to care for those who need it but do not have health insurance coverage or other financial resources to obtain care (akin to Ryan White Act for HIV/AIDS)
- Guide the FDA to provide accelerated pathways for approval for competing drugs in order to maximize market forces that can stimulate price competition
- Engage stakeholders and the public in a broad discussion of manufacturer pricing

- Establish a prize or award fund for a cure that provides a financial reward for innovation and allows treatments to be spread widely and quickly (e.g., the government could buy the patent for a cure and make the product available to everyone at very low cost)
- Explore the existing public health emergency powers of the states, along with their purchasing power, to create statewide plans to identify and treat all infected individuals
- Mandate at the federal level that important drugs not priced reasonably be placed in the public domain so other manufacturers can make generics, as is done in India
- Identify a mechanism that would allow more anticipatory, collaborative policymaking between manufacturers, payers, and other stakeholders as drugs with large budget impacts are coming through the system so there can be earlier conversations with policy options identified and implemented

Care Redesign

- Use data to collaboratively identify opportunities to disinvest from low value care and eliminate waste in the health care system, so that the savings can be redirected to higher value options now and in the future

3. *Payers should develop transparent approaches for identifying pragmatic thresholds for incremental cost-effectiveness and budget impact that represent both reasonable care and health system value. Efforts to establish and justify price points for new therapies should require dialogue among payers, providers, manufacturers, and other stakeholders.*

This report presented price ranges for new treatments for hepatitis C that were based on commonly accepted thresholds for incremental cost-effectiveness and a budget impact threshold of 0.5%-1.0% PMPM. One implication is that these price ranges could be construed as reflecting "reasonable" value. While health economists and public policy experts have long debated thresholds for incremental cost-effectiveness, many questions remain about the appropriate development and application of these thresholds. Budget impact thresholds are less well rooted in the health policy arena. The suggested 0.5%-1.0% threshold used in this study arose through communication with a variety of public and private payers in the United States, but this threshold has not routinely been modeled or used in policy discussions. Further work will be needed to document the validity and utility of these thresholds across settings, and all stakeholders will need to contribute to identifying both thresholds and suitable payment and policy options if we wish to promote high value in the US health care system.

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APPENDICES

Appendix A: Coverage Policies

Appendix Table A1: Coverage Policies for LDV/SOF

	Medi-Cal	Aetna	Anthem	CVS/Caremark	Health Net	Humana	UHC
METAVIR or equivalent score	N/A	Covered with documentation of HCV diagnosis, genotype, and subtype	Covered if ≥F3	N/A	Covered if ≥F2	N/A	Covered if ≥F3
Patients with severe renal impairment	N/A	--	Not covered	N/A	--	N/A	--
Extrahepatic manifestations	N/A	--	Covered	N/A	--	N/A	Covered
Decompensated liver disease	N/A	Not covered	Not covered	N/A	Not covered	N/A	--
Post-liver transplant	N/A	Not covered	Covered	N/A	--	N/A	Covered
Hepatocellular carcinoma	N/A	Not covered	--	N/A	--	N/A	--
Eligible if treatment experienced?	N/A	Not eligible if previous SOF failure	Not eligible if previous LDV or SOF failure	N/A	Not eligible if previous SOF failure	N/A	Yes, including any protease inhibitor or SOF failure
Treatment continuation based on reduced HCV RNA levels	N/A	Yes	--	N/A	--	N/A	--
Treatment restrictions related to abuse of illicit drugs and/or alcohol	N/A	--	Yes	N/A	--	N/A	Yes
Require specialist to prescribe or consult	N/A	--	--	N/A	Yes	N/A	Yes
Other criteria	N/A	For patients meeting clinical criteria, use of LDV/SOF is required unless patient is contraindicated or intolerant to any of its ingredients	Not to be used in combination with other NS5B polymerase or NS5A inhibitors	N/A	Non-FDA-approved indications are covered only with sufficient documentation in published literature	N/A	--

Maximum duration authorized	N/A	8 weeks: tx-naïve w/o cirrhosis, viral load <6M; 12 weeks: tx-naïve w/o cirrhosis and viral load ≥6M OR tx-naïve w/ cirrhosis OR tx-experienced w/o cirrhosis; 24 weeks: tx-experienced w/ cirrhosis	8 weeks: tx-naïve w/o cirrhosis, viral load <6M; 12 weeks: tx-naïve w/o cirrhosis and viral load ≥6M OR tx-naïve w/ cirrhosis OR tx-experienced w/o cirrhosis; 24 weeks: tx-experienced w/ cirrhosis	N/A	8 weeks: tx-naïve w/o cirrhosis, viral load <6M; 12 weeks: tx-naïve w/o cirrhosis and viral load ≥6M OR tx-naïve w/ cirrhosis OR tx-experienced w/o cirrhosis; 24 weeks: tx-experienced w/ cirrhosis	N/A	8 weeks: tx-naïve w/o cirrhosis, viral load <6M; 12 weeks: tx-naïve w/o cirrhosis and viral load ≥6M OR post-liver transplant OR tx-naïve w/ cirrhosis OR tx-experienced w/o cirrhosis; 24 weeks: tx-experienced w/ cirrhosis
Published/revised/effective date	N/A	10/31/2014	10/15/2014	N/A	10/28/2014	N/A	10/15/2014

Abbreviations: HCC = hepatocellular carcinoma; P = pegylated interferon; R = ribavirin; tx = treatment; -- = not specified in coverage policy; N/A = no online coverage policy available

Note: The information in this table is extracted from publicly available documents as of November 3, 2014 and is not intended to be a definitive source on coverage policies, as these are being updated regularly and contain details that cannot reasonably be reflected in this summary table. Interested parties should obtain current, specific coverage policy information from individual payers.

Appendix Table A2: Coverage Policies for Sofosbuvir + PR

	Medi-Cal	Aetna	Anthem	CVS/Caremark	Health Net	Humana	UHC
METAVIR or equivalent score	Covered if ≥F3 or if F0-F2 with severe extrahepatic manifestations	Covered with documentation of HCV diagnosis, genotype, and subtype	Covered if ≥F3	-	Covered if ≥F2	-	Covered if ≥F3
Patients with severe renal impairment	Not covered	--	Not covered	Not covered	--	--	--
Extrahepatic manifestations	Covered	--	Covered	--	--	--	Covered
Decompensated liver disease	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered
Post-liver transplant	Must meet DHCS investigational services criteria	Covered	SOF covered but treatment regimen not specified	Not covered	Covered	Covered for patients with compensated liver disease	Covered
Hepatocellular carcinoma	Not covered	Not covered	Not covered	Not covered	Not covered	--	Not covered
Eligible if treatment experienced?	Yes	Yes in most cases, see policy for details	Not eligible if previous PR + protease or polymerase inhibitor failure	--	--	--	Not eligible if previous SOF failure
Treatment continuation based on reduced HCV RNA levels	Recommended	Yes	--	--	--	--	--
Treatment restrictions related to abuse of illicit drugs and/or alcohol	Yes	--	Yes	--	--	--	Yes
Require specialist to prescribe or consult	Recommended	--	--	--	Yes	--	Yes

Other criteria	All non-FDA approved indications must meet DHCS investigational services criteria	Intolerance/contraindication to or nonfulfillment of criteria for LDV/SOF required	--	--	Failure/contraindication to LDV/SOF required; non-FDA-approved use must be supported by published literature	Investigational/ experimental SOF regimens must be supported by published literature or CMS compendia	--
Maximum duration authorized	12 weeks	24 weeks for post-liver transplant; otherwise 12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks
Published/revised/ effective date	6/30/2014	10/31/2014	10/17/2014	--	10/28/2014	3/6/2014	9/1/2014

Abbreviations: HCC = hepatocellular carcinoma; P = pegylated interferon; R = ribavirin; tx = treatment; -- = not specified in coverage policy; N/A = no online coverage policy available

Note: The information in this table is extracted from publicly available documents as of November 3, 2014 and is not intended to be a definitive source on coverage policies, as these are being updated regularly and contain details that cannot reasonably be reflected in this summary table. Interested parties should obtain current, specific coverage policy information from individual payers.

Appendix Table A3: Coverage Policies for Sofosbuvir + R

	Medi-Cal	Aetna	Anthem	CVS/Caremark	Health Net	Humana	UHC
METAVIR or equivalent score	Covered if ≥F3 or if F0-F2 with severe extrahepatic manifestations	Covered with documentation of HCV diagnosis, genotype, and subtype	Covered if ≥F3	--	Covered if ≥F2	--	Covered if ≥F3
Patients with severe renal impairment	Not covered	--	Not covered	Not covered	--	--	--
Extrahepatic manifestations	Covered	--	Covered	--	--	--	Covered
Decompensated liver disease	Covered, patient must be referred to specialist	Covered	Covered if decompensation is reason for interferon-ineligibility	Covered if decompensation is reason for interferon-ineligibility	Not covered	Covered	Covered
Post-liver transplant	Must meet DHCS investigational services criteria	Covered	SOF covered but treatment regimen not specified	Not covered	Covered	Covered for patients with decompensated liver disease	Covered
Hepatocellular carcinoma	Covered	Covered if awaiting liver transplant	Covered if awaiting liver transplant	Covered if awaiting liver transplant	Covered if awaiting liver transplant	--	Covered if patient is on waiting list for liver transplant and being managed in a liver transplant center
Eligible if treatment experienced?	Yes in most cases, see other criteria for details	--	Not eligible if previous PR + protease or polymerase inhibitor failure	Not eligible if previous SOF failure	--	Yes	Not eligible if previous SOF failure
Treatment continuation based on reduced HCV RNA levels	Recommended	Yes	--	--	--	--	--
Treatment restrictions related to abuse of illicit drugs and/or alcohol	Yes	--	Yes	--	--	--	Yes

Require specialist to prescribe or consult	Recommended	--	--	--	Yes	--	Yes
Other criteria	Must be interferon-ineligible; must meet DCHS investigational services criteria for non-FDA approved indications including treatment-experienced, advanced fibrosis/ compensated cirrhosis, interferon-eligible	Intolerance/contraindication to or nonfulfillment of criteria for LDV/SOF required; must be interferon-ineligible	Must be interferon-ineligible	Must be interferon-ineligible	Failure/contraindication to LDV/SOF required; must be interferon-ineligible; non-FDA approved use must be supported by published literature	Investigational/ experimental SOF regimens must be supported by published literature or CMS compendia	Must be interferon-ineligible; documented contraindication to SMV required unless patient has HCC or decompensated liver disease
Maximum duration authorized	24-48 weeks or until liver transplant for HCC; otherwise 24 weeks	48 weeks or until liver transplantation for HCC or decompensated cirrhosis; otherwise 24 weeks	48 weeks or until liver transplantation for HCC; otherwise 24 weeks	48 weeks or until liver transplantation for HCC; otherwise 24 weeks	48 weeks or until liver transplantation for HCC; otherwise 24 weeks	48 weeks or until liver transplantation for decompensated cirrhosis or for decompensated liver disease post-liver transplant; otherwise 24 weeks	48 weeks for HCC or decompensated liver disease; otherwise 24 weeks
Published/revised/ effective date	6/30/2014	10/31/2014	10/17/2014	--	10/28/2014	3/6/2014	9/1/2014

Abbreviations: HCC = hepatocellular carcinoma; P = pegylated interferon; R = ribavirin; tx = treatment; -- = not specified in coverage policy; N/A = no online coverage policy available

Note: The information in this table is extracted from publicly available documents as of November 3, 2014 and is not intended to be a definitive source on coverage policies, as these are being updated regularly and contain details that cannot reasonably be reflected in this summary table. Interested parties should obtain current, specific coverage policy information from individual payers.

Appendix Table A4: Coverage Policies for Simeprevir + Sofosbuvir ± R

	Medi-Cal	Aetna	Anthem	CVS/Caremark	Health Net	Humana	UHC
METAVIR or equivalent score	Covered if ≥F3 or if F0-F2 with severe extrahepatic manifestations and interferon-ineligible	Covered with documentation of HCV diagnosis, genotype, and subtype	Covered if ≥F3	Covered if ≥F3	N/A	--	Covered if ≥F3
Patients with severe renal impairment	Not covered	--	--	--	N/A	--	--
Extrahepatic manifestations	Covered	--	Covered	--	N/A	--	Covered
Decompensated liver disease	Covered, patient must be referred to specialist	Not covered	Covered if decompensation is reason for interferon-ineligibility	Covered if decompensation is reason for interferon-ineligibility	N/A	Covered if decompensation is reason for interferon-ineligibility	Not covered
Post-liver transplant	Must meet DHCS investigational services criteria	Covered	SOF covered but treatment regimen not specified	Covered only if treatment-naïve post-transplant	N/A	Covered for patients with compensated liver disease	Covered
Hepatocellular carcinoma	Not covered	Not covered	Not covered	Covered if HCC is reason for interferon-ineligibility	N/A	--	--
Eligible if treatment experienced?	Yes	Yes if previous PR failure	Not eligible if previous PR + protease or polymerase inhibitor failure	Yes if previous failure of PR therapy without a protease inhibitor	N/A	Yes	Not eligible if previous SOF failure, unless discontinuation due to PR intolerance
Treatment continuation based on reduced HCV RNA levels	Recommended	Yes	--	Yes	N/A	--	--
Treatment restrictions related to abuse of illicit drugs and/or alcohol	Yes	--	Yes	--	N/A	--	Yes

Require specialist to prescribe or consult	Recommended	--	--	--	N/A	--	Yes
Other criteria	All non-FDA-approved indications must meet DHCS investigational services criteria	Intolerance/contraindication to or nonfulfillment of criteria for LDV/SOF required; must be interferon-ineligible or post-liver transplant	Patient must be interferon-ineligible OR have had a previous partial or nonresponse to PR therapy	Patient must be treatment naïve and interferon-ineligible OR have had a previous PR failure	N/A	Patient must be interferon-ineligible or treatment experienced; investigational/ experimental SOF regimens must be supported by published literature or CMS compendia	Must be interferon-ineligible
Maximum duration authorized	12 weeks	12-24 weeks for post-liver transplant; otherwise 12 weeks	12 weeks	24 weeks for post-liver transplant; otherwise 12 weeks	N/A	12-24 weeks for post-liver transplant; otherwise 12 weeks	12 weeks
Published/revised/ effective date	6/30/2014	10/31/2014	10/17/2014	--	N/A	3/6/2014	9/1/2014

Abbreviations: HCC = hepatocellular carcinoma; P = pegylated interferon; R = ribavirin; tx = treatment; -- = not specified in coverage policy; N/A = no online coverage policy available

Note: The information in this table is extracted from publicly available documents as of November 3, 2014 and is not intended to be a definitive source on coverage policies, as these are being updated regularly and contain details that cannot reasonably be reflected in this summary table. Interested parties should obtain current, specific coverage policy information from individual payers.

Appendix Table A5: Coverage Policies for Simeprevir + PR

	Medi-Cal	Aetna	Anthem	CVS/Caremark	Health Net	Humana	UHC
METAVIR or equivalent score	Covered if ≥F3 or if F0-F2 with severe extrahepatic manifestations	Covered with documentation of HCV diagnosis, genotype, and subtype	Covered if ≥F3	--	Covered if ≥F2	--	--
Patients with severe renal impairment	--	--	--	--	--	--	--
Extrahepatic manifestations	Covered	--	--	--	--	--	--
Decompensated liver disease	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered
Genotype 1a NS3 Q80k polymorphism	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered	Not recommended
Post-liver transplant	--	Not covered	--	Not covered	--	--	--
Hepatocellular carcinoma	Not covered	--	--	--	--	--	--
Eligible if treatment experienced?	Not eligible if previous protease inhibitor failure	Not eligible if previous protease inhibitor failure	Not eligible if previous PR + protease or polymerase inhibitor failure	Not eligible if previous PR + protease inhibitor failure	Not eligible if previous protease inhibitor failure	Not eligible if previous protease inhibitor failure	Not eligible if previous protease inhibitor failure
Treatment continuation based on reduced HCV RNA levels	Yes	Yes	--	Yes	Yes	Yes	--
Treatment restrictions related to abuse of illicit drugs and/or alcohol	Yes	--	Yes	--	--	--	--
Require specialist to prescribe or consult	--	--	--	--	--	--	--

Other criteria	Prior treatment failure with any protease inhibitor precludes use of SMV; all non-FDA-approved indications must meet DHCS investigational services criteria	Intolerance/contraindication to or nonfulfillment of criteria for LDV/SOF required	Not for use in combination with other protease inhibitors	--	Failure/contraindication to LDV/SOF required; non-FDA approved use must be supported by published literature	Investigational/ experimental SMV regimens must be supported by published literature or CMS compendia	--
Maximum duration authorized	SMV up to 12 weeks, R up to 48 weeks	SMV up to 12 weeks, R up to 48 weeks	--	SMV up to 12 weeks, R up to 48 weeks	SMV up to 12 weeks, R up to 48 weeks	SMV up to 12 weeks, R up to 48 weeks	SMV up to 12 weeks, R up to 48 weeks
Published/revised/ effective date	6/30/2014	10/31/2014	7/2/2014	--	10/16/2014	10/2/2014	9/1/2014

Abbreviations: HCC = hepatocellular carcinoma; P = pegylated interferon; R = ribavirin; tx = treatment; -- = not specified in coverage policy; N/A = no online coverage policy available

Note: The information in this table is extracted from publicly available documents as of November 3, 2014 and is not intended to be a definitive source on coverage policies, as these are being updated regularly and contain details that cannot reasonably be reflected in this summary table. Interested parties should obtain current, specific coverage policy information from individual payers.

Appendix B: Search Strategies

PubMed (NLM), run date 9/10/14
sofosbuvir OR simeprevir OR daclatasvir OR ombitasvir OR abt-450* AND English[la] NOT (review[pt] OR editorial[pt] OR news[pt]) AND (clinical trial[pt] OR clinical trials as topic[mh] OR random* OR study OR trial OR trials)
157 refs

Cochrane Library (Wiley), run date 9/10/14
sofosbuvir OR simeprevir OR daclatasvir OR ombitasvir OR "abt-450" OR "abt-450r"

All Results (58)
Cochrane Reviews (0) All Review Protocol Other Reviews (1) Trials (47) Methods Studies (0) Technology Assessments (9) Economic Evaluations (1) Cochrane Groups (0)

Cochrane Central Register of Controlled Trials (Central) Issue 8 of 12, August 2014

Embase (Elsevier), run date 9/10/14
sofosbuvir or simeprevir or daclatasvir or ombitasvir or 'abt-450' or 'abt-450r' and [english]/lim and ('clinical trial'/de or 'clinical trial (topic)'/de or 'controlled study'/de or 'double blind procedure'/de or 'major clinical study'/de or 'multicenter study'/de or 'multicenter study (topic)'/de or 'phase 2 clinical trial'/de or 'phase 2 clinical trial (topic)'/de or 'phase 3 clinical trial'/de or 'phase 3 clinical trial (topic)'/de or 'randomized controlled trial'/de or 'randomized controlled trial (topic)'/de or random* or study or trial or trials) not ('conference abstract'/it OR 'conference review'/it or 'editorial'/it or 'review'/it or 'short survey'/it)
404 refs

Appendix C: Supplemental Tables from Chapter 6

Simeprevir + PR

Appendix Table C1. Clinical Trials of Simeprevir + PR in Patients Infected with HCV Genotype 1

Study	Publication	Study drugs	Control	Treatment Naïve	Prevalence of Cirrhosis (%)
Phase 2					
PILLAR	Fried 2013[41]	SMV12/24 + PR48	PR48	Yes	0
ASPIRE	Zeuzem 2014[63]	SMV12/24/48 + PR48	PR48	No	18
Phase 3					
QUEST 1	Jacobson 2014[61]	SMV12 + PR24/48	PR48	Yes	12
QUEST 2	Manns 2014[62]	SMV12 + PR24/48	PR48	Yes	9
PROMISE	Forns 2013[60]	SMV12 + PR24/48	PR48	No	15
Japan					
CONCERTO-1	Hayashi 2014b[64]	SMV12 + PR24/48	PR48	Yes	0
CONCERTO-2	Izumi 2014[66]	SMV12 + PR24/48 or SMV24 + PR24/48	PR48	No	0
CONCERTO-3	Izumi 2014[66]	SMV12 + PR24/48	None	No	0
CONCERTO-4	Kumada 2014[67]	SMV12 + PR24/48	None	Both	0
DRAGON	Hayashi 2014a[65]	SMV12 + PR24	PR48	Yes	0

Appendix Table C2. Summary of the Outcomes of Simeprevir + PR in Patients Infected with HCV Genotype 1

FDA approved or probable treatment dose/duration only

Study	Treatment Naïve	Cirrhosis	Treatment	N	SVR (%)	DR (%)
QUEST 1	Yes	No	SMV12 + PR24/48	233	82.4	8.2
QUEST 2	Yes	No	SMV12 + PR24/48	240	82.5	4.6
QUEST 1	Yes	Yes	SMV12 + PR24/48	31	58.1	6.5
QUEST 2	Yes	Yes	SMV12 + PR24/48	17	64.7	5.9
ASPIRE	No	No	SMV12 + PR48	53	66.0	7.5
PROMISE	No	No	SMV12 + PR24/48	221	80.1	0.9
ASPIRE	No	Yes	SMV12 + PR48	13	69.2	7.7
PROMISE	No	Yes	SMV12 + PR24/48	39	74.4	20.5

Sofosbuvir + PR

Appendix Table C3. Clinical Trials of Sofosbuvir + PR in Patients Infected with HCV Genotype 1

Study	Publication	Study drugs	Control	Treatment Naïve	Prevalence of Cirrhosis (%)
Phase 2					
PROTON	Lawitz 2013a[69]	SOF12 + PR24/48	PR24/48	Yes	0
ATOMIC	Kowdley 2013[68]	SOF12 + PR12 or SOF24 + PR24	None	Yes	0
Phase 3					
NEUTRINO	Lawitz 2013b[70]	SOF12 + PR12	None	Yes	17

Appendix Table C4. Summary of the Outcomes of Sofosbuvir + PR in Patients Infected with HCV Genotype 1

FDA approved or probable treatment dose/duration only

Study	Treatment Naïve	Cirrhosis	Treatment	N	SVR (%)	DR (%)
PROTON	Yes	No	SOF12 + PR24/48	47	89.4	17.0
ATOMIC	Yes	No	SOF12 + PR12	52	88.5	9.6
NEUTRINO	Yes	No	SOF12 + PR12	249	92.8	9.6
NEUTRINO	Yes	Yes	SOF12 + PR12	43	81.4	11.6

Sofosbuvir + R

Appendix Table C5. Clinical Trials of Sofosbuvir + R in Patients Infected with HCV Genotype 1

Study	Publication	Study drugs	Control	Treatment Naïve	Prevalence of Cirrhosis (%)
Phase 2					
QUANTUM	Abstract[72]	SOF24 + R24	None	Yes	6
NIH SPARE	Osinusi 2013[73]	SOF24 + R24	None	Yes	23
ELECTRON	Gane 2013[71]	SOF12 + R12	None	Both	0

Appendix Table C6. Summary of the Outcomes of sofosbuvir + R in Patients Infected with HCV Genotype 1

FDA approved or probable treatment dose/duration only

Study	Treatment Naïve	Cirrhosis	Treatment	N	SVR (%)	DR (%)
NIH SPARE	Yes	No	SOF24 + R24	10	90.0	10.0
NIH SPARE	Yes	No	SOF24 + R24	19	73.7	10.5
QUANTUM	Yes	No	SOF24 + R24	19	47.4	5.3
NIH SPARE	Yes	Yes	SOF24 + R24	6	50.0	0.0

Simeprevir + Sofosbuvir

Appendix Table C7. Clinical Trials of Simeprevir + Sofosbuvir in Patients Infected with HCV Genotype 1

Study	Publication	Study drugs	Control	Treatment Naïve	Prevalence of Cirrhosis (%)
Phase 2					
COSMOS	Lawitz 2014[58]	SMV + SOF12 ± R12 or SMV + SOF24 ± R24	None	Both	25

Appendix Table C8. Summary of the Outcomes of Simeprevir + Sofosbuvir in Patients Infected with HCV Genotype 1

FDA approved or probable treatment dose/duration only

Study	Treatment Naïve	Cirrhosis	Treatment	N	SVR (%)	DR (%)
COSMOS	Yes	No	SMV + SOF12	4	100	0
COSMOS	Yes	Yes	SMV + SOF24	6	100	16.7
COSMOS	No	No	SMV + SOF12	14	92.9	0
COSMOS	No	No	SMV + SOF12	3	100	0
COSMOS	No	Yes	SMV + SOF24	4	100	0

Ledipasvir/Sofosbuvir

Appendix Table C9. Clinical Trials of Ledipasvir/Sofosbuvir in Patients Infected with HCV Genotype 1

Study	Publication	Study drugs	Control	Treatment Naïve*	Prevalence of Cirrhosis (%)
Phase 2					
LONESTAR	Lawitz 2014[78]	LDV/SOF8 or 12 ± R	None	Both	22
ELECTRON	Gane 2014[76]	LDV/SOF6 or 12 ± R ± GS-9669	None	Both	17
ELECTRON 2	Abstract[80]	LDV/SOF12	None	No	0
NIH SPARE 2	Osinusi 2014[79]	LDV/SOF12	None	No	50
SYNERGY	Abstract[81]	LDV/SOF12 ± GS-9451	None	Yes	30
Phase 3					
ION-1	Afdhal 2014[75]	LDV/SOF12 ± R12 or LDV/SOF24 ± R24	None	Yes	16
ION-2	Afdhal 2014[74]	LDV/SOF12 ± R12 or LDV/SOF24 ± R24	None	No	20
ION-3	Kowdley 2014[77]	LDV/SOF8 ± R8 or LDV/SOF12 ± R12	None	Yes	0

* "Both" means both treatment naïve and treatment-experienced were included in the study

Appendix Table C10. Summary of the Outcomes of Ledipasvir/Sofosbuvir in Patients Infected with HCV Genotype 1

FDA approved or probable treatment dose/duration only

Study	Treatment Naïve	Cirrhosis	Treatment	N	SVR (%)	DR (%)
LONESTAR	Yes	No	LDV/SOF8	20	95.0	0.0
ION-3	Yes	No	LDV/SOF8	215	94.0	0.9
LONESTAR	Yes	No	LDV/SOF12	19	94.7	5.3
SYNERGY	Yes	No	LDV/SOF12	17	100	0.0
ION-1	Yes	No	LDV/SOF12	180	99.4	0.6
ION-3	Yes	No	LDV/SOF12	216	95.4	4.2
SYNERGY	Yes	Yes	LDV/SOF12	3	100	0.0
ELECTRON-2*	Yes	Yes*	LDV/SOF12	20	65.0	0.0
ION-1	Yes	Yes	LDV/SOF12	34	94.1	2.9
LONESTAR	No	No	LDV/SOF12	8	100	0.0
ION-2	No	No	LDV/SOF12	87	95.4	0.0
ION-2	No	Yes	LDV/SOF24	22	100	0

* ELECTRON-2 includes patients with decompensated cirrhosis (Child-Turcotte-Pugh Class B cirrhosis). No other study includes patients with decompensated cirrhosis.

Daclatasvir + Sofosbuvir

Appendix Table C11. Clinical Trials of Daclatasvir + Sofosbuvir in Patients Infected with HCV Genotype 1

Study	Publication	Study drugs	Control	Treatment Naïve*	Prevalence of Cirrhosis (%)
Phase 2					
AI444040	Sulkowski 2014[59]	DCV + SOF12 ± R12 or DCV + SOF24 ± R24	None	Both	16

* "Both" means both treatment naïve and treatment-experienced were included in the study

Appendix Table C12. Summary of the Outcomes of Daclatasvir + Sofosbuvir in Patients Infected with HCV Genotype 1

FDA approved or probable treatment dose/duration only

Study	Treatment Naïve	Cirrhosis	Treatment	N	SVR (%)	DR (%)
AI444040	Yes	No	DCV + SOF12	35	100	0.0
AI444040	Yes	No	DCV + SOF24	25	100	4.0
AI444040	Yes	Yes	DCV + SOF12	6	100	0.0
AI444040	Yes	Yes	DCV + SOF24	4	100	0.0
AI444040	No	No	DCV + SOF24	18	92.9	0.0
AI444040	No	Yes	DCV + SOF24	3	100	0.0

Daclatasvir + Asunaprevir

Appendix Table C13. Clinical Trials of Daclatasvir + Asunaprevir in Patients Infected with HCV Genotype 1

Study	Publication	Study drugs	Control	Treatment Naïve*	Prevalence of Cirrhosis (%)
Phase 2					
NCT01012895	Lok 2012[85]	DCV + ASV24 ± PR24	None	No	0
	Lok 2014[84]	DCV + ASV24 ± PR24	None	No	0
Phase 3					
HALLMARK-DUAL GT1b only	Manns 2014[86]	DCV + ASV24	Placebo	Both	30
Japan					
GT1b only	Chayama 2012[82]	DCV + ASV24	None	No	0
GT1b only	Suzuki 2013[87]	DCV + ASV24	None	Both	0
GT1b only	Kumada 2014[83]	DCV + ASV24	None	Both	10

* "Both" means both treatment naïve and treatment-experienced were included in the study

The dosing used in the US Phase 3 clinical trial HALLMARK-DUAL[86] (daclatasvir 60 mg once daily plus asunaprevir 100 mg twice daily) was only used in one of the other clinical trials.[83] In early studies, asunaprevir was dosed at 600 mg twice daily and reduced to 200 mg twice daily due to elevations in liver enzymes.[82,85,87] It is worth noting that the combination of daclatasvir and asunaprevir was not as effective in HCV genotype 1a and the later, larger Phase 3 studies are limited to genotype 1b. This is the primary genotype in Japan.

Appendix Table C14. Summary of the Outcomes of Daclatasvir + Asunaprevir in Patients Infected with HCV Genotype 1

FDA approved or probable treatment dose/duration only

Study	Treatment Naïve	Cirrhosis	Treatment	N	SVR (%)	DR (%)
Kumada 2014	Yes	No	DCV + ASV24	124	87.1	10.4
HALLMARK-DUAL	Yes	No	DCV + ASV24	171	89.5	7.4
Kumada 2014	Yes	Yes	DCV + ASV24	11	90.9	10.4
HALLMARK-DUAL	Yes	Yes	DCV + ASV24	32	90.6	7.4
Kumada 2014	No	No	DCV + ASV24	76	78.9	16.1
HALLMARK-DUAL	No	No	DCV + ASV24	142	79.6	13.7
Kumada 2014	No	Yes	DCV + ASV24	11	90.9	16.1
HALLMARK-DUAL	No	Yes	DCV + ASV24	63	87.3	13.7

Paritaprevir, Ritonavir, Ombitasvir, and Dasabuvir (3D) ± Ribavirin

Appendix Table C15. Clinical Trials of 3D ± R in Patients Infected with HCV Genotype 1

Study	Publication	Study drugs	Control	Treatment Naïve*	Prevalence of Cirrhosis (%)
Phase 2					
AVIATOR	Kowdley 2014[91]	3D12 ± R12 or 3D24 ± R24 14 groups	None	Both	0
Phase 3					
PEARL-II GT1b only	Andreone 2014[88]	3D12 ± R12	None	No	0
PEARL-III GT1b only	Ferenci 2014[90]	3D12 ± R12	None	Yes	0
PEARL-IV GT1a only	Ferenci 2014[90]	3D12 ± R12	None	Yes	0
SAPPHIRE-I	Feld 2014[89]	3D12 + R12	Placebo	Yes	0
SAPPHIRE-II	Zeuzem 2014[93]	3D12 + R12	Placebo	No	0
TURQUOISE-II	Poordad 2014[92]	3D12 + R12 or 3D24 + R24	None	No	100

* "Both" means both treatment naïve and treatment-experienced were included in the study

Appendix Table C16. Summary of the Outcomes of 3D + R in Patients Infected with HCV Genotype 1

FDA approved or probable treatment dose/duration only

Study	Treatment Naïve	Cirrhosis	Treatment	N	SVR (%)	DR (%)
AVIATOR	Yes	No	3D24 + R24	40	90.0	7.5
AVIATOR	Yes	No	3D12 + R12	40	95.0	5.0
PEARL-III	Yes	No	3D12 + R12	210	99.5	0.5
PEARL-IV	Yes	No	3D12 + R12	100	97.0	0.0
SAPPHIRE-I	Yes	No	3D12 + R12	473	96.2	1.7
TURQUOISE-II	Yes	Yes	3D12 + R12	86	94.2	2.3
TURQUOISE-II	Yes	Yes	3D24 + R24	74	94.6	5.4
AVIATOR	No	No	3D12 + R12	22	95.5	0.0
AVIATOR	No	No	3D24 + R24	20	100	0.0
PEARL-II	No	No	3D12 + R12	95	95.8	4.2
SAPPHIRE-II	No	No	3D12 + R12	297	96.3	1.3
TURQUOISE-II	No	Yes	3D12 + R12	122	90.2	1.6
TURQUOISE-II	No	Yes	3D24 + R24	98	96.9	5.1

HIV Co-infection

Appendix Table C17. Clinical Trials of the Treatment of HCV in HIV Co-infected Patients

Study	Publication	Study drugs	Control	Treatment Naïve*	Prevalence of Cirrhosis (%)
C212	Dieterich 2014[104]	SMV12 + PR24/48	None	Both	13
PHOTON-1	Sulkowski 2014[106]	SOF24 + R24	None	Yes for GT1	4
ERADICATE	Abstract[105]	LDV/SOF12	None	Yes	0

* "Both" means both treatment naïve and treatment-experienced were included in the study

Appendix Table C18. Summary of the Outcomes in Patients Co-infected with HCV Genotype 1 and HIV

FDA approved or probable treatment dose/duration only

Study	Treatment Naïve	Cirrhosis	Treatment	N	SVR (%)	DR (%)
C212	Yes	~6%	SMV12 + PR24/48	53	79.2	17.0
C212	No	~11%	SMV12 + PR24/48	53	67.9	34.0
C212	Both	Yes	SMV12 + PR48	9	77.8	-
PHOTON-1	Yes	No	SOF24 + R24	109	77.1	11.4
PHOTON-1	Yes	Yes	SOF24 + R24	5	60.0	11.4
ERADICATE	Yes	No	LDV/SOF12	50	98.0	0.0

Pre- or post-liver transplant

Appendix Table C19. Clinical Trials of the Treatment of HCV Pre- or Post-liver Transplant

Study	Publication	Study drugs	Control	Treatment Naïve*	Prevalence of Cirrhosis (%)
P7977-2025 Pre-transplant	Curry 2014[108]	SOF48 + R48	None	Both	100% with HCC
Post-transplant	Charlton 2014[107]	SOF24 + R24	None	Both	40
Post-transplant	Pellicelli 2014[109]	DCV + SOF24 ± R24	None	NR	75
Post-transplant CORAL-I	Kwo 2014[185]	3D + R24	None	Both	0

* "Both" means both treatment naïve and treatment-experienced were included in the study

Appendix Table C20. Summary of the Outcomes in Patients with HCV Genotype 1 Pre- and Post-liver Transplant

FDA approved or probable treatment dose/duration only

Study	Transplant	Cirrhosis	Treatment	N	SVR (%)	DR (%)
Curry 2014[108]	Pre	100% with HCC	SOF48 + R48	45	17/31 54.8% 12 weeks after transplant	24.6
Charlton 2014[107]	Post	40	SOF24 + R24	53	67.9	34.0
Pellicelli 2014[109]	Post	75	DCV + SOF24 ± R24	12	5/5 SVR4	3 unrelated deaths
Kwo 2014	Post	0	3D + R24	34	97% SVR24	2.9

Appendix D: Supplementary Tables for Chapter 7

Table D1: METAVIR Score for Classification of Liver Damage Due to HCV and Distribution of Fibrosis Stages in CHC Population

Stage of Fibrosis	Histological definition	Distribution of fibrosis	Reference
F0	No fibrosis	0.17 (0.14-0.19)	[134]
F1	Portal fibrosis without septa	0.35 (0.26-0.39)	[134]
F2	Portal fibrosis with rare septa	0.22 (0.18-0.24)	[134]
F3	Numerous septa without cirrhosis	0.14 (0.12-0.15)	[134]
F4 (CC)	Compensated Cirrhosis	0.12 (0.11-0.13)	[134]

CHC – Chronic Hepatitis C; F0-F4 – METAVIR fibrosis score; CC – Compensated Cirrhosis

Table D2: Chronic Hepatitis C Annual Post-SVR Transition Probabilities, and Regression Proportions

Source State	Target State	Base case	Lower limit	Upper	Reference
CHC Progression Post-SVR					
F0	F1	0.010023	0.005012	0.015035	Calculated*
F1	F2	0.007282	0.003641	0.010923	Calculated*
F2	F3	0.01028	0.00514	0.01542	Calculated*
F3	F4	0.009937	0.004969	0.014906	Calculated*
	Decompensated Cirrhosis	0.001028	0.0005	0.0015	[140]
	Hepatocellular Carcinoma	0.004753	0.001	0.007	[140]
F4	Decompensated Cirrhosis	0.003342	0.002	0.005	[140]
	Hepatocellular Carcinoma	0.012449	0.006	0.019	[140]
Decompensated Cirrhosis	Hepatocellular Carcinoma	0.010	0.008	0.017	[126]
	Liver Transplant	0.012	0.007	0.016	[141]
	Death	0.09	0.07	0.15	[126]
Fibrosis Regression Post-SVR (Proportions)					
F1	F0	0.35	0.17	0.52	[142-145]
F2	F0	0.12	0.06	0.18	[142-145]
	F1	0.58	0.29	0.87	[142-145]
F3	F1	0.24	0.12	0.36	[142-145]
	F2	0.46	0.23	0.69	[142-145]
F4	F1	0.09	0.05	0.14	[142-149]
	F2	0.14	0.07	0.21	[142-149]
	F3	0.22	0.11	0.33	[142-146,148,150]

* – calculated post-SVR F0 to F4 transition probabilities (using non-SVR probabilities from meta-analysis by Thein et al.) based on a 91% reduction observed in progression from F3 to decompensated cirrhosis post-SVR

Table D3: SVR and Discontinuation Rates of Sofosbuvir-based Treatments

Therapy	Subgroup	Treatment Duration	SVR (95% CI)	DR (95% CI)
SOF + PR	Naïve, no cirrhosis	12 weeks	.920 (.888-.948)	.103 (.072-.139)
	Naïve, + cirrhosis	12 weeks	.814 (.666-.916)	.116 (.039-.251)
	Experienced, no cirrhosis	12 weeks	.780 (0.390-1.00) †	.103 (.072-.139) ‡
	Experienced, + cirrhosis	12 weeks	.710 (.570-0.830)	.116 (.039-.251) ‡
SOF + R	Naïve, no cirrhosis	24 weeks	.750 (.675-.819)	.078 (.036-.131)
	Naïve, + cirrhosis	24 weeks	.545 (.227-.484)	.000 (.000-.013)
SMV + SOF	Naïve, no cirrhosis	12 weeks	1.00 (.398-1.00)	.000 (.000-.602)
	Naïve, + cirrhosis	12 weeks	.667 (.094-.992)	.333 (.008-.906)
	Experienced, no cirrhosis	12 weeks	.970 (.781-1.00)	.000 (.000-.083)
	Experienced, + cirrhosis	12 weeks	1.00 (.398-1.00)	.000 (.000-.602)
LDV/SOF*	Naïve, no cirrhosis	8 weeks	.948 (.913-.976)	.002 (.000-.018)
	Naïve, no cirrhosis	12 weeks	.985 (.968-.997)	.013 (.002-.029)
	Naïve, + cirrhosis	12 weeks	.892 (.778-.974)	.000 (.000-.043)
	Experienced, no cirrhosis	12 weeks	.977 (.924-1.00)	.000 (.000-.004)
	Experienced, + cirrhosis	24 weeks	1.00 (.846-1.00)	.000 (.000-.154)

* – For base-case 67% of patients were allocated to receive LDV/SOF 8, while the remaining received 12 weeks of LDV/SOF therapy. This value was varied in probabilistic sensitivity analysis using a range of (30% to 90%).

† – CI selected by authors (lower limit 50% of base-case, upper limit 100%)

‡ – Due to lack of data, discontinuation rates modeled to be the same as treatment-naïve group.

Table D4: SVR and Discontinuation Rates for PR (48 weeks)

Treatment Characteristics	Base case (%)	Lower limit*	Upper limit*	Reference
Treatment-naïve				
SVR – Overall	54.6	27	82	153, 154
Discontinuation rate	24.2	12	36	154, 155
EVR12	79.9	40	100†	153, 154
SVR followed by EVR12	68.3	34	85†	153, 154
Treatment-experienced				
SVR – Overall	16.5	8	25	156, 157
Discontinuation rate	64.6	32	97	157
SVR by fibrosis	**Base case (%)**	**Lower limit***	**Upper limit***	**Reference**
Prior Relapse (0.53)				
Overall for Prior Relapse	22.1	11	33	156, 157
F0-F1	35	18	53	156, 157
F2	27.8	14	42	156, 157
F3	13.3	7	20	156, 157
F4	6.7	3	10	156, 157
Partial Response (0.19)				
Overall for Partial Response	18.2	9	27	156, 157
F0-F1	0	0	10‡	156, 157
F2	42.9	21	64	156, 157
F3	0	0	10‡	156, 157
F4	20	10	30	156, 157
Null Response (0.28)				
Overall for Null Response	5.4	3	8	156, 157
F0-F1	0.0	0	10‡	156, 157
F2	7.7	4	12	156, 157
F3	0	0	10‡	156, 157
F4	10	5	15	156, 157

* – Lower and upper bounds are 50% to 150% of base-case, unless otherwise noted.

† – Lower and upper bounds are 50% to 125% of base-case.

‡ – Upper limit selected by authors.

EVR = Early Virologic Response

Table D5: Frequency, by Week, of Follow-up/Testing/Management of Each Treatment Modality

Test and Office Visit	8-week therapy	12-week therapies					24-week therapies				48-week therapy
	LDV/SOF*	SOF + PR	LDV/SOF	SMV + SOF	3D	DCV + SOF	SOF + R	LDV/SOF	3D	DCV + SOF	PR
Anti-HCV (antibody) test	0 (#1)†,‡	0 (#1)					0 (#1)				0 (#1)
Genotype assay	0 (#1) ‡	0 (#1)					0 (#1)				0 (#1)
Fibrosis assessment	0 (#1) ‡	0 (#1)					0 (#1)				0 (#1)
HCV RNA quantification	0, 4, 8, 12 (#4) ‡	0, 4, 12, 24 (#4)					0, 4, 24, 36 (#4)				0, 4, 12, 24, 48, 60 (#6) §
CBC w/Differential	0, 4, 8, 12 (#4) ‡	0, 4, 8, 12, 24 (#5)					0, 4, 8, 12, 16, 24, 36 (#7)				0, 4, 8, 12, 16, 24, 48, 60 (#8)
Hepatic function panel	0, 4, 8, 12 (#4) ‡	0, 4, 8, 12, 24 (#5)					0, 4, 8, 12, 16, 24, 36 (#7)				0, 4, 8, 12, 16, 24, 48, 60 (#8)
Office visit (outpatient)	0, 4, 8, 12 (#4) ‡	0, 4, 8, 12, 24 (#5)					0, 4, 8, 12, 16, 24, 36 (#7)				0, 4, 8, 12, 16, 24, 48, 60 (#8)

– indicates the quantity of tests or office visits over the course of treatment.

***** – Treatment-naïve.

† – Week (0, 2, 4, etc.) at which the test or office visit takes place.

‡ – Per AASLD guidelines and an additional test at 12-weeks after end-of-treatment.[159]

§ – Increased number of tests based on response-guided therapy criteria for PR therapy.[160]

Table D6: Utility Loss with CHC Treatment

Treatment Modality	Annualized utility loss	Base case (during treatment)	Lower limit*	Upper limit*	Reference
Utility penalties during treatment					
PR (48 weeks)	-0.1931	-0.1782	-0.2896	0	Calculated
SOF + PR (12-weeks)	-0.1657	-0.0382	-0.2486	0	Calculated
SOF + R (24 weeks)	-0.0852	-0.0393	-0.1279	0	Calculated
SMV + SOF (12 weeks)	-0.0873	-0.0202	-0.1310	0	Calculated
LDV/SOF (8 weeks) †	-0.0754	-0.0116	-0.1130	0	Calculated
LDV/SOF (12 weeks)†	-0.0754	-0.0174	-0.1130	0	Calculated
LDV/SOF (24 weeks)†	-0.0754	-0.0348	-0.1130	0	Calculated

* – Lower Limit is 50% more than the annualized base-case. Upper Limit is no utility loss.

† – Annualized disutility represents an average of disutility across the various treatment durations.

Appendix E: Explanation of Disease Progression and Markov Model Details

Figure E1: Hepatitis C Natural History Markov Representation

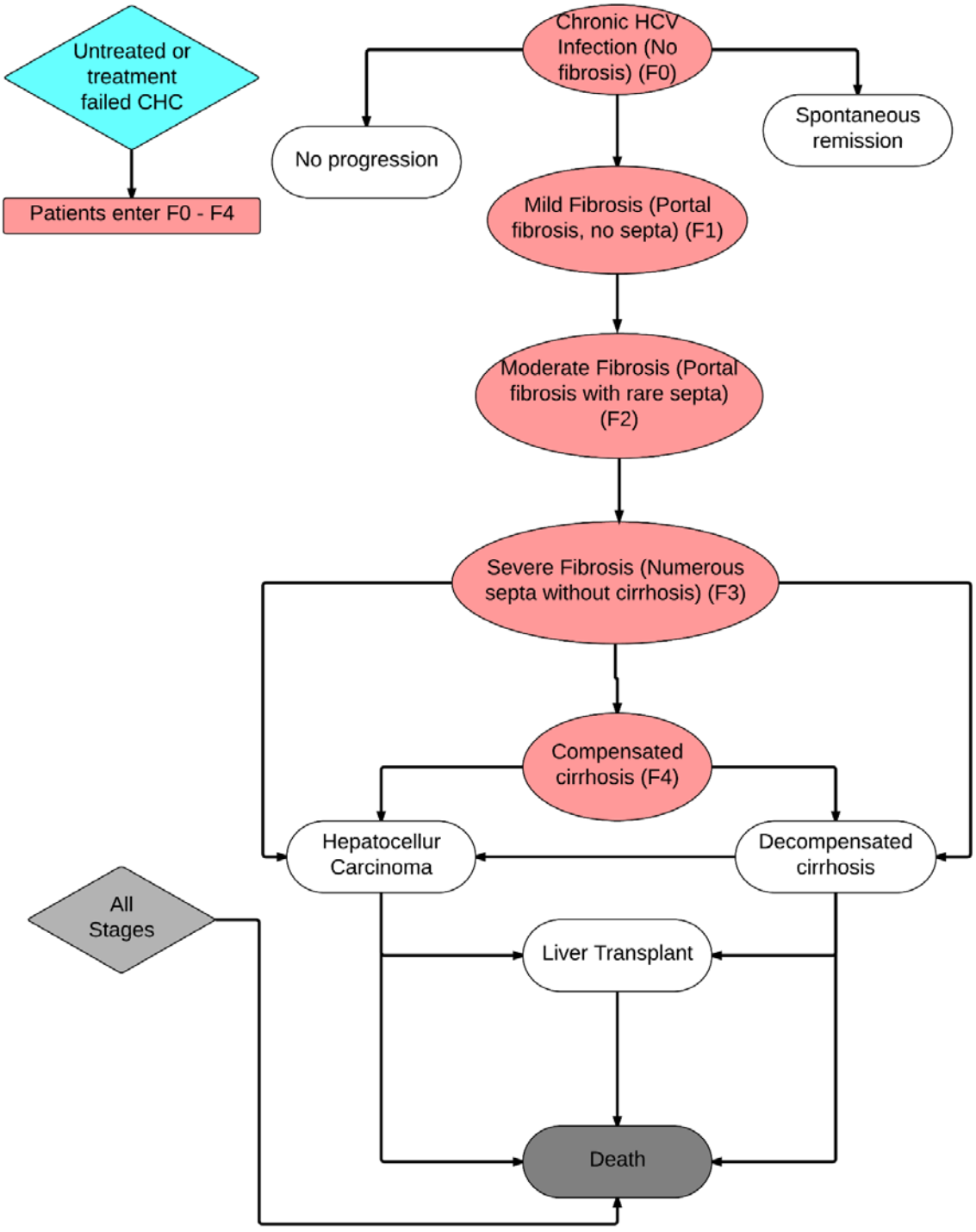

Figure E1 description: Patients enter the Markov model either when they receive no treatment, after unsuccessful therapy, or treatment discontinuation, in stages F0 through F4. The black arrows indicate annual progression of liver damage. The one time "no-progression" proportion from F0 fibrosis state is

removed from the progression cascade after that proportion of patients accrue the cost of treatment under the "treat all" strategy.

Post-SVR progression and regression model

To account for progression of liver disease and liver regeneration following SVR, this model allows patients to attain a worse or better health status after HCV eradication.[181] A graphical representation of post-SVR HCV history and health states is available in Figure E2. Following SVR, there exists the possibility of progression from F3 and F4 states to more advanced liver complications.[4,182] Therefore, patients will cycle through a set of post-SVR Markov states that have different transition probabilities than those of the natural history Markov states. The annual post-SVR progression probabilities are shown in Appendix Table D2 and are derived from published literature.[4,141]

Additionally, it is possible for the liver damage caused by HCV to be reversed, at least partially, in a subset of the patients following successful therapy.[4,153-157] The data for regression are determined from the literature as a proportion of patients achieving regression post-SVR.[4,153-157] Therefore, the model assumes that immediately after SVR, a certain percent of patients from F1 to F4 states regress to a lower fibrotic state as indicated by the proportions listed in Appendix Table D2.

Figure E2: Hepatitis C Post-SVR Markov Representation Showing Progression and Regression of CHC Following Successful Treatment

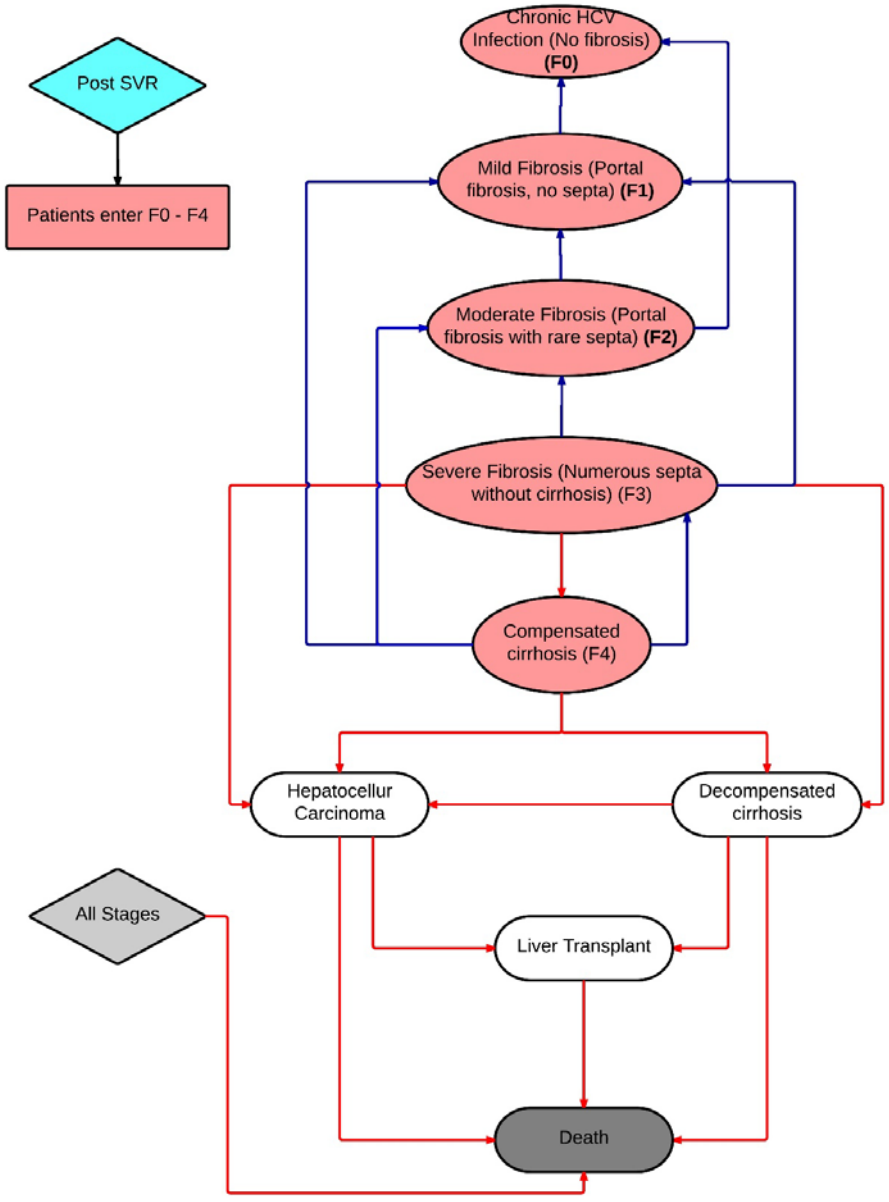

Figure E2 description: Patients enter the Markov model after successful therapy in stages F0 through F4. Blue arrows indicate proportional regression from source state to a lower fibrosis state. The regression data covers a wide time range, between 1 and 10 years post regression. In this model, the regression transition occurs immediately after successful treatment. Red arrows indicate annual progression of liver damage after achieving SVR.

Figure E3: Simplified Tree Structure of the HCV Cost-effectiveness Model

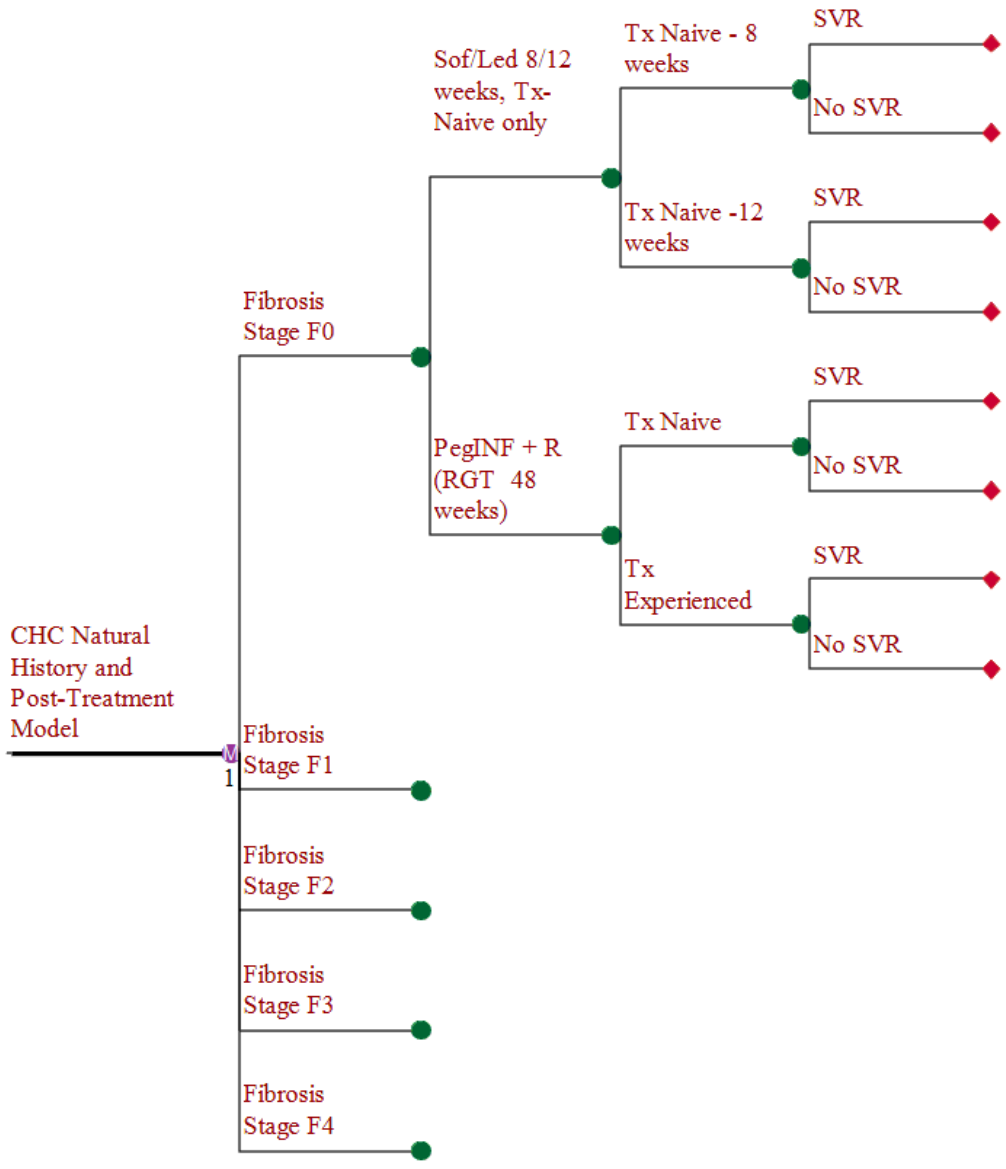

Figure E3 depicts a simplified tree of the model for illustrative purposes. This structure shows only five of 26 Markov states representing 15 health states. See Appendix Figures E1 and E2 for details of the Markov model. The Markov model is the same for all treatment policies. The policy analysis starts at the node marked with an "M." At the "M" node, a policy to treat all immediately or to wait until patients progress to F3 or F4 stages is selected. The terminal nodes (red diamonds) indicate the transition to other Markov states depending on the outcome of the cycle.

Appendix F: Scenario Analyses

Table F1: Scenario 1: Increased Discontinuation Rates

Scenario Analysis 1. Increased PR treatment experienced D/C rate increased by 1.5
Discontinuation rates 2. All others D/C rates doubled; including all treatmnt naïve.
3. For treatments with base-case of 0, lowest non-zero value of D/C rates from another treatment selected (0.013)

Incremental comparison of regimens						
Strategy	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**Comment**
Tx naïve, treat all						
No Treatment	$ 45,313	$ -	11.82	0.00	$ -	undominated
PR (48 weeks)	$ 64,875	$ 19,562	12.79	0.97	$ 20,160	ext. dominated
LDV/SOF (8/12 weeks)	$ 90,947	$ 45,634	14.72	2.90	$ 15,736	undominated
SOF + PR (12 weeks)	$ 106,417	$ 15,470	14.19	-0.53	$ (29,139)	abs. dominated
LDV/SOF (12 weeks)	$ 108,436	$ 17,489	14.77	0.04	$ 411,659	undominated
SMV + SOF (12 weeks)	$ 161,849	$ 53,412	14.50	-0.27	$ (199,644)	abs. dominated
SOF + R (24 weeks)	$ 182,165	$ 73,729	13.82	-0.95	$ (77,799)	abs. dominated
Tx Naive, treat at F3, F4						
No Treatment	$ 45,313	$ -	11.82	0.00	$ -	undominated
PR (48 weeks)	$ 51,560	$ 6,247	12.57	0.75	$ 8,346	undominated
LDV/SOF (8/12 weeks)	$ 65,282	$ 13,721	14.00	1.43	$ 9,587	undominated
SOF + PR (12 weeks)	$ 70,863	$ 5,581	13.60	-0.40	$ (14,034)	abs. dominated
LDV/SOF (12 weeks)	$ 80,547	$ 15,265	14.03	0.03	$ 509,551	undominated
SMV + SOF (12 weeks)	$ 98,997	$ 18,450	13.77	-0.27	$ (69,134)	abs. dominated
SOF + R (24 weeks)	$ 113,421	$ 32,875	13.30	-0.73	$ (44,771)	abs. dominated
Tx exp, treat all						
No Treatment	$ 45,313	$ -	11.82	0.00	$ -	undominated
PR (48 weeks)	$ 70,069	$ 24,755	11.68	-0.14	$ (172,066)	abs. dominated
SOF + PR (12 weeks)	$ 110,196	$ 64,883	13.83	2.01	$ 32,273	ext. dominated
LDV/SOF (12/24 weeks	$ 119,079	$ 73,766	14.76	2.93	$ 25,147	undominated
SIM + SOF (12 weeks)	$ 164,649	$ 45,570	14.62	-0.13	$ (344,119)	abs. dominated
Tx exp, treat at F3, F4						
No Treatment	$ 45,313	$ -	11.82	0.00	$ -	undominated
PR (48 weeks)	$ 58,370	$ 13,057	11.74	-0.08	$ (161,345)	abs. dominated
SOF + PR (12 weeks)	$ 74,762	$ 29,449	13.26	1.44	$ 20,432	ext. dominated
LDV/SOF (12/24 weeks	$ 80,294	$ 5,532	14.02	0.76	$ 7,314	undominated
SMV + SOF (12 weeks)	$ 101,450	$ 21,156	13.94	-0.08	$ (278,207)	abs. dominated

Vs. PR			
Cost	**Eff**	**ICER**	
Tx naïve, treat all			
$ (19,562)	-0.970	$ 20,160	
$ 26,072	1.930	$ 13,511	
$ 41,542	1.399	$ 29,700	
$ 43,561	1.972	$ 22,089	
$ 96,974	1.705	$ 56,891	
$ 117,290	1.024	$ 114,494	
Tx Naive, treat at F3, F4			
$ (6,247)	-0.749	$ 8,346	
$ 13,721	1.431	$ 9,587	
$ 19,302	1.034	$ 18,676	
$ 28,986	1.461	$ 19,837	
$ 47,437	1.194	$ 39,717	
$ 61,861	0.727	$ 85,097	
Tx exp, treat all			
$ (24,755)	0.144	$ (172,066)	
$ 40,128	2.154	$ 18,627	
$ 49,010	3.077	$ 15,927	
$ 94,580	2.945	$ 32,117	
Tx exp, treat at F3, F4			
$ (13,057)	0.081	$ (161,345)	
$ 16,392	1.522	$ 10,769	
$ 21,924	2.279	$ 9,622	
$ 43,080	2.203	$ 19,559	

Vs. No Treatment		
Cost	**Eff**	**ICER**
$ 19,562	0.97	$ 20,160
$ 45,634	2.90	$ 15,736
$ 61,104	2.37	$ 25,793
$ 63,123	2.94	$ 21,453
$ 116,536	2.67	$ 43,566
$ 136,852	1.99	$ 68,606
$ 6,247	0.75	$ 8,346
$ 19,969	2.18	$ 9,161
$ 25,550	1.78	$ 14,337
$ 35,234	2.21	$ 15,945
$ 53,684	1.94	$ 27,631
$ 68,108	1.48	$ 46,160
$ 24,755	-0.14	$ (172,066)
$ 64,883	2.01	$ 32,273
$ 73,766	2.93	$ 25,147
$ 119,336	2.80	$ 42,605
$ 13,057	-0.08	$ (161,345)
$ 29,449	1.44	$ 20,432
$ 34,981	2.20	$ 15,918
$ 56,137	2.12	$ 26,460

Treat All vs. Treat at F3, F4		
cost	**Eff**	**ICER**
Tx naïve, treat all		
$ 13,315	0.22	$ 60,028
$ 25,665	0.72	$ 35,639
$ 35,554	0.59	$ 60,573
$ 27,889	0.73	$ 38,065
$ 62,852	0.73	$ 85,861
$ 68,744	0.52	$ 132,383
Tx exp, treat all		
$ 11,699	-0.06	$(185,847)
$ 35,434	0.57	$ 62,258
$ 38,785	0.74	$ 52,713
$ 63,199	0.68	$ 93,022

DR — Discontinuation Rate; Incr Net Cost — Incremental Net Cost; Eff — Effectiveness; Incr Eff — Incremental Effectiveness

Table F2: Scenario 2: Increased Portion of Cohort at Initial Stage F4

Scenario Analysis 1. Scenario Analysis Distribution: F0, F1, F2, F3, F4 = 0.15, 0.33, 0.20, 0.12, 0.20 = 1.0
Increased F4 Prevalence

Incremental comparison of regimens						
Strategy	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**Comment**
Tx naïve, treat all						
No Treatment	$ 50,227	$ -	11.46	0.00	$ -	undominated
PR (48 weeks)	$ 65,809	$ 15,582	13.02	1.56	$ 9,993	undominated
LDV/SOF (8/12 weeks)	$ 94,994	$ 29,185	14.44	1.42	$ 20,486	undominated
SOF + PR (12 weeks)	$ 110,430	$ 15,436	14.20	-0.24	$ (64,235)	abs. dominated
LDV/SOF (12 weeks)	$ 111,026	$ 16,032	14.50	0.06	$ 285,937	undominated
SMV + SOF (12 weeks)	$ 164,881	$ 53,854	14.34	-0.16	$ (345,454)	abs. dominated
SOF + R (24 weeks)	$ 190,636	$ 79,610	13.62	-0.88	$ (90,777)	abs. dominated
Tx Naive, treat at F3, F4						
No Treatment	$ 50,227	$ -	11.46	0.00	$ -	undominated
PR (48 weeks)	$ 52,871	$ 2,644	12.68	1.22	$ 2,169	undominated
LDV/SOF (8/12 weeks)	$ 71,450	$ 18,579	13.77	1.10	$ 16,937	undominated
SOF + PR (12 weeks)	$ 76,280	$ 4,830	13.59	-0.19	$ (25,976)	abs. dominated
LDV/SOF (12 weeks)	$ 85,452	$ 14,002	13.81	0.04	$ 356,143	undominated
SMV + SOF (12 weeks)	$ 106,551	$ 21,099	13.65	-0.16	$ (128,301)	abs. dominated
SOF + R (24 weeks)	$ 125,105	$ 39,653	13.10	-0.72	$ (55,302)	abs. dominated
Tx exp, treat all						
No Treatment	$ 50,227	$ -	11.46	0.00	$ -	undominated
PR (48 weeks)	$ 77,004	$ 26,777	11.76	0.30	$ 88,615	ext. dominated
SOF + PR (12 weeks)	$ 114,883	$ 37,880	13.80	2.04	$ 18,601	ext. dominated
LDV/SOF (12/24 weeks)	$ 128,890	$ 14,006	14.56	0.76	$ 18,358	undominated
SIM + SOF (12 weeks)	$ 167,600	$ 38,710	14.43	-0.13	$ (294,135)	abs. dominated
Tx exp, treat at F3, F4						
No Treatment	$ 50,227	$ -	11.46	0.00	$ -	undominated
PR (48 weeks)	$ 65,598	$ 15,371	11.55	0.09	$ 167,174	ext. dominated
SOF + PR (12 weeks)	$ 80,859	$ 15,260	13.20	1.65	$ 9,238	undominated
LDV/SOF (12/24 weeks)	$ 92,920	$ 12,061	13.86	0.66	$ 18,242	undominated
SMV + SOF (12 weeks)	$ 108,942	$ 16,022	13.79	-0.08	$ (204,469)	abs. dominated

Vs. PR			Vs. No Treatment		
Cost	**Eff**	**ICER**	**Cost**	**Eff**	**ICER**
Tx naïve, treat all					
-$15,582	-1.559	$ 9,993			
			$ 15,582	1.559	$ 9,993
$29,185	1.425	$ 20,486	$ 44,767	2.984	$ 15,003
$44,621	1.184	$ 37,676	$ 60,203	2.744	$ 21,943
$45,217	1.481	$ 30,537	$ 60,799	3.040	$ 20,000
$99,072	1.325	$ 74,781	$ 114,654	2.884	$ 39,754
$124,828	0.604	$ 206,759	$ 140,409	2.163	$ 64,914
Tx Naive, treat at F3, F4					
-$2,644	-1.219	$ 2,169			
			$ 2,644	1.219	$ 2,169
$18,579	1.097	$ 16,937	$ 21,223	2.316	$ 9,163
$23,409	0.911	$ 25,695	$ 26,053	2.130	$ 12,230
$32,581	1.136	$ 28,674	$ 35,225	2.355	$ 14,954
$53,680	0.972	$ 55,237	$ 56,324	2.191	$ 25,706
$72,234	0.419	$ 172,296	$ 74,878	1.638	$ 45,700
Tx exp, treat all					
-$26,777	-0.302	$ 88,615			
			$ 26,777	0.302	$ 88,615
$37,880	2.036	$ 18,601	$ 64,656	2.339	$ 27,648
$51,886	2.799	$ 18,535	$ 78,663	3.101	$ 25,363
$90,596	2.668	$ 33,960	$ 117,373	2.970	$ 39,521
Tx exp, treat at F3, F4					
-$15,371	-0.092	$ 167,174			
			$ 15,371	0.092	$ 167,174
$15,260	1.652	$ 9,238	$ 30,632	1.744	$ 17,566
$27,321	2.313	$ 11,812	$ 42,693	2.405	$ 17,752
$43,344	2.235	$ 19,396	$ 58,715	2.327	$ 25,236

Treat All vs. Treat at F3, F4		
cost	**Eff**	**ICER**
Tx naïve, treat all		
$12,938	0.340	$ 38,048
$23,544	0.668	$ 35,259
$34,150	0.613	$ 55,676
$25,574	0.684	$ 37,362
$58,330	0.693	$ 84,164
$65,532	0.525	$ 124,933
Tx exp, treat all		
$11,405	0.210	$ 54,254
$34,025	0.595	$ 57,208
$35,970	0.697	$ 51,643
$58,658	0.643	$ 91,189

DR — Discontinuation Rate; Incr Net Cost — Incremental Net Cost; Eff — Effectiveness; Incr Eff — Incremental Effectiveness

Table F3: Scenario 3: Modified F0-F3 Costs

Scenario Analysis 1. Applying the same costs across F0-F3 ($900 weighted by frequency = $1,023/stage)
F0-F3 costs 2. F4 cost remain the same ($2,516/year)

Incremental comparison of regimens						
Strategy	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**Comment**
Tx naïve, treat all						
No Treatment	$ 44,582	$ -	11.82	0.00	-	undominated
PR (48 weeks)	$ 62,208	$ 17,626	13.34	1.51	$ 11,649	undominated
LDV/SOF (8/12 weeks)	$ 90,962	$ 28,754	14.75	1.41	$ 20,347	undominated
SOF + PR (12 weeks)	$ 107,868	$ 16,906	14.52	-0.23	$ (73,376)	abs. dominated
LDV/SOF (12 weeks)	$ 108,608	$ 17,646	14.81	0.06	$ 284,212	undominated
SMV + SOF (12 weeks)	$ 163,336	$ 54,727	14.74	-0.08	$ (719,492)	abs. dominated
SOF + R (24 weeks)	$ 186,333	$ 77,724	13.99	-0.82	$ (94,800)	abs. dominated
Tx Naive, treat at F3, F4						
No Treatment	$ 44,582	$ -	11.82	0.00	$ -	undominated
PR (48 weeks)	$ 48,848	$ 4,266	12.97	1.14	$ 3,726	undominated
LDV/SOF (8/12 weeks)	$ 66,840	$ 17,992	14.02	1.06	$ 17,018	undominated
SOF + PR (12 weeks)	$ 72,105	$ 5,264	13.85	-0.17	$ (30,722)	abs. dominated
LDV/SOF (12 weeks)	$ 82,264	$ 15,424	14.07	0.04	$ 351,184	undominated
SMV + SOF (12 weeks)	$ 101,380	$ 19,115	13.98	-0.09	$ (224,046)	abs. dominated
SOF + R (24 weeks)	$ 116,053	$ 33,788	13.42	-0.65	$ (52,283)	abs. dominated
Tx exp, treat all						
No Treatment	$ 44,582	$ -	11.82	0.00	$ -	undominated
PR (48 weeks)	$ 71,645	$ 27,063	12.13	0.31	$ 88,254	ext. dominated
SOF + PR (12 weeks)	$ 112,017	$ 40,372	14.11	1.98	$ 20,357	ext. dominated
LDV/SOF (12/24 weeks	$ 119,586	$ 7,569	14.84	0.72	$ 10,467	undominated
SIM + SOF (12 weeks)	$ 165,749	$ 46,163	14.70	-0.14	$ (341,330)	abs. dominated
Tx exp, treat at F3, F4						
No Treatment	$ 44,582	$ -	11.82	0.00	$ -	undominated
PR (48 weeks)	$ 59,292	$ 14,710	11.90	0.08	$ 188,073	ext. dominated
SOF + PR (12 weeks)	$ 76,108	$ 16,816	13.47	1.57	$ 10,735	ext. dominated
LDV/SOF (12/24 weeks	$ 81,880	$ 5,772	14.08	0.61	$ 9,419	undominated
SMV + SOF (12 weeks)	$ 103,319	$ 21,439	14.00	-0.08	$ (276,706)	abs. dominated

Vs. PR			
Cost	**Eff**	**ICER**	
Tx naïve, treat all			
$ (17,626)	-1.51	$ 11,649	
$ 28,754	1.41	$ 20,347	
$ 45,660	1.18	$ 38,604	
$ 46,400	1.48	$ 31,452	
$ 101,127	1.40	$ 72,275	
$ 124,124	0.66	$ 189,391	
Tx Naive, treat at F3, F4			
$ (4,266)	-1.14	$ 3,726	
$ 17,992	1.06	$ 17,018	
$ 23,257	0.89	$ 26,251	
$ 33,416	1.10	$ 30,345	
$ 52,532	1.02	$ 51,711	
$ 67,205	0.45	$ 147,723	
Tx exp, treat all			
$ (27,063)	-0.31	$ 88,254	
$ 40,372	1.98	$ 20,357	
$ 47,941	2.71	$ 17,714	
$ 94,104	2.57	$ 36,601	
Tx exp, treat at F3, F4			
$ (14,710)	-0.08	$ 188,073	
$ 16,816	1.57	$ 10,735	
$ 22,588	2.18	$ 10,365	
$ 44,027	2.10	$ 20,948	

Vs. No Treatment		
Cost	**Eff**	**ICER**
$17,626	1.51	$ 11,649
$46,380	2.93	$ 15,849
$63,286	2.70	$ 23,475
$64,026	2.99	$ 21,425
$118,753	2.91	$ 40,776
$141,750	2.17	$ 65,366
$4,266	1.14	$ 3,726
$22,258	2.20	$ 10,108
$27,522	2.03	$ 13,554
$37,682	2.25	$ 16,778
$56,797	2.16	$ 26,288
$71,470	1.60	$ 44,679
$27,063	0.31	$ 88,254
$67,435	2.29	$ 29,449
$75,004	3.01	$ 24,894
$121,167	2.88	$ 42,105
$14,710	0.08	$ 188,073
$31,526	1.64	$ 19,169
$37,298	2.26	$ 16,522
$58,737	2.18	$ 26,944

Treat All vs. Treat at F3, F4		
Cost	**Eff**	**ICER**
Tx naïve, treat all		
$13,361	0.37	$ 36,259
$24,122	0.72	$ 33,301
$35,764	0.67	$ 53,754
$26,344	0.74	$ 35,479
$61,956	0.75	$ 82,411
$70,280	0.57	$ 123,533
Tx exp, treat all		
$12,353	0.23	$ 54,077
$35,909	0.65	$ 55,656
$37,706	0.76	$ 49,906
$62,430	0.70	$ 89,470

DR — Discontinuation Rate; Incr Net Cost — Incremental Net Cost; Eff — Effectiveness; Incr Eff — Incremental Effectiveness

Table F4: Scenario 4: Age Set to 50

Scenario Analysis
Age

1. Age set to 50 years old, all other values held constant

Incremental comparison of regimens						
Strategy	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**Comment**
Tx naïve, treat all						
No Treatment	$ 60,082	$ -	14.11	0.00	$ -	undominated
PR (48 weeks)	$ 70,995	$ 10,913	16.23	2.12	$ 5,141	undominated
LDV/SOF (8/12 weeks)	$ 94,297	$ 23,302	18.08	1.85	$ 12,562	undominated
LDV/SOF (12 weeks)	$ 111,704	$ 17,407	18.17	0.09	$ 201,418	undominated
SOF + PR (12 weeks)	$ 111,985	$ 282	17.78	-0.39	$ (720)	abs. dominated
SMV + SOF (12 weeks)	$ 166,603	$ 54,900	18.07	-0.10	$ (567,135)	abs. dominated
SOF + R (24 weeks)	$ 192,829	$ 81,126	17.07	-1.10	$ (73,829)	abs. dominated
Tx Naive, treat at F3, F4						
PR (48 weeks)	$ 59,419	$ -	15.74	0.00	$ -	undominated
No Treatment	$ 60,082	$ 664	14.11	-1.63	$ (407)	abs. dominated
LDV/SOF (8/12 weeks)	$ 74,728	$ 15,310	17.14	1.40	$ 10,917	undominated
SOF + PR (12 weeks)	$ 80,125	$ 5,397	16.91	-0.23	$ (23,251)	abs. dominated
LDV/SOF (12 weeks)	$ 93,788	$ 19,059	17.20	0.06	$ 308,063	undominated
SMV + SOF (12 weeks)	$ 111,212	$ 17,424	17.09	-0.11	$ (160,087)	abs. dominated
SOF + R (24 weeks)	$ 130,033	$ 36,245	16.33	-0.87	$ (41,749)	abs. dominated
Tx exp, treat all						
No Treatment	$ 60,082	$ -	14.11	0.00	$ -	undominated
PR (48 weeks)	$ 85,229	$ 25,146	14.60	0.49	$ 51,314	ext. dominated
SOF + PR (12 weeks)	$ 117,673	$ 32,444	17.23	2.63	$ 12,320	ext. dominated
LDV/SOF (12/24 weeks	$ 122,913	$ 5,240	18.21	0.98	$ 5,348	undominated
SMV + SOF (12 weeks)	$ 169,445	$ 46,532	18.02	-0.19	$ (241,216)	abs. dominated
Tx exp, treat at F3, F4						
No Treatment	$ 60,082	$ -	14.11	0.00	$ -	undominated
PR (48 weeks)	$ 75,618	$ 15,535	14.24	0.14	$ 114,039	ext. dominated
SOF + PR (12 weeks)	$ 86,185	$ 10,568	16.37	2.13	$ 4,965	ext. dominated
LDV/SOF (12/24 weeks	$ 89,503	$ 3,318	17.23	0.86	$ 3,846	undominated
SMV + SOF (12 weeks)	$ 113,602	$ 24,099	17.10	-0.13	$ (187,341)	abs. dominated

Vs. PR			
	Cost	**Eff**	**ICER**
Tx naïve, treat all			
	$ (10,913)	-2.12	$ 5,141
	$ 23,302	1.85	$ 12,562
	$ 40,709	1.94	$ 20,970
	$ 40,990	1.55	$ 26,444
	$ 95,609	1.84	$ 51,834
	$ 121,834	0.84	$ 144,611
Tx Naive, treat at F3, F4			
	$ (664)	1.63	$ (407)
	$ 14,646	3.03	$ 4,830
	$ 20,042	2.80	$ 7,158
	$ 33,705	3.09	$ 10,894
	$ 51,130	2.99	$ 17,128
	$ 69,950	2.23	$ 31,428
Tx exp, treat all			
	$ (25,146)	-0.49	$ 51,314
	$ 32,444	2.63	$ 12,320
	$ 37,684	3.61	$ 10,429
	$ 84,216	3.42	$ 24,621
Tx exp, treat at F3, F4			
	$ (15,535)	-0.14	$ 114,039
	$ 10,568	2.13	$ 4,965
	$ 13,885	2.99	$ 4,642
	$ 37,984	2.86	$ 13,269

Vs. No Treatment		
Cost	**Eff**	**ICER**
$ 10,913	2.12	$ 5,141
$ 34,214	3.98	$ 8,602
$ 51,621	4.06	$ 12,702
$ 51,903	3.67	$ 14,132
$ 106,521	3.97	$ 26,850
$ 132,747	2.97	$ 44,769
$ 664	-1.63	$ (407)
$ 15,310	1.40	$ 10,917
$ 20,706	1.17	$ 17,693
$ 34,369	1.46	$ 23,472
$ 51,794	1.36	$ 38,212
$ 70,614	0.60	$ 118,457
$ 25,146	0.49	$ 51,314
$ 57,590	3.12	$ 18,437
$ 62,831	4.10	$ 15,311
$ 109,363	3.91	$ 27,966
$ 15,535	0.14	$ 114,039
$ 26,103	2.26	$ 11,526
$ 29,421	3.13	$ 9,407
$ 53,520	3.00	$ 17,847

Treat All vs. Treat at F3, F4		
ICER	**Eff**	**ICER**
Tx naïve, treat all		
$ 10,913	2.12	$ 5,141
$ 19,568	0.95	$ 20,695
$ 31,579	1.26	$ 24,982
$ 18,197	0.58	$ 31,436
$ 55,391	0.98	$ 56,399
$ 62,797	0.74	$ 84,926
Tx exp, treat all		
$ 9,611	0.35	$ 27,164
$ 31,487	0.86	$ 36,661
$ 33,410	0.98	$ 34,228
$ 55,843	0.91	$ 61,243

DR — Discontinuation Rate; Incr Net Cost — Incremental Net Cost; Eff — Effectiveness; Incr Eff — Incremental Effectiveness

Appendix G: Budgetary Impact Tables

Table G1. Clinical and Economic Impact of Alternative Treatment Regimens for Hepatitis C, per 1,000 Patients Treated (Treatment-naïve)

	Liver-Related Complications				HCV	*Costs (per patient, $)*		
Timeframe/Regimen	**Cirrhosis**	**Decompensation**	**HCC**	**Transplant**	**Death**	**Treatment**	**Other**	**Total**
Treatment-Naïve								
1 Year								
PR	5.6	3.0	1.5	0.0	5.4	$35,743	$1,549	$37,292
LDV/SOF 8/12	0.9	0.7	1.3	0.0	3.3	$78,095	$731	$78,826
Difference (LS-PR)	*(4.7)*	*(2.3)*	*(0.2)*	*0.0*	*(2.1)*	*$42,352*	*($818)*	*$41,534*
5 Years								
PR	29.4	16.0	10.6	0.3	32.1	$35,743	$6,136	$41,879
LDV/SOF 8/12	6.2	3.9	6.8	0.3	19.1	$78,095	$3,288	$81,383
Difference (LS-PR)	*(23.2)*	*(12.1)*	*(3.8)*	*0.0*	*(13.0)*	*$42,352*	*($2,848)*	*$39,504*
20 Years								
PR	104.2	56.9	41.0	4.2	226.6	$35,743	$21,236	$56,979
LDV/SOF 8/12	22.1	13.1	23.2	1.7	110.8	$78,095	$10,394	$88,489
Difference (LS-PR)	*(82.1)*	*(43.8)*	*(17.8)*	*(2.5)*	*(115.8)*	*$42,352*	*($10,842)*	*$31,510*

HCC: Hepatocellular carcinoma; HCV: hepatitis C virus; LS-PR: difference between LDV/SOF and PR therapy

Table G2. Clinical and Economic Impact of Alternative Treatment Regimens for Hepatitis C, per 1,000 Patients Treated (Treatment-experienced)

	Liver-Related Complications				HCV	*Costs (per patient, $)*		
Timeframe/Regimen	**Cirrhosis**	**Decompensation**	**HCC**	**Transplant**	**Death**	**Treatment**	**Other**	**Total**
Treatment-Experienced								
1 Year								
PR	11.2	5.6	2.8	0.0	5.5	$32,044	$1,963	$34,007
LDV/SOF 12/24	0.6	0.1	0.8	0.0	3.7	$107,838	$563	$108,401
Difference (LS-PR)	*(10.6)*	*(5.5)*	*(2.0)*	*0.0*	*(1.8)*	*$75,794*	*($1,400)*	*$74,394*
5 Years								
PR	55.2	29.0	16.6	0.7	47.2	$32,044	$8,731	$40,775
LDV/SOF 12/24	5.5	1.5	6.4	0.2	17.4	$107,838	$3,153	$110,991
Difference (LS-PR)	*(49.7)*	*(27.5)*	*(10.2)*	*(0.5)*	*(29.8)*	*$75,794*	*($5,578)*	*$70,216*
20 Years								
PR	183.7	104.0	61.5	7.3	332.4	$32,044	$31,743	$63,787
LDV/SOF 12/24	19.2	6.8	22.1	0.9	102.6	$107,838	$9,536	$117,374
Difference (LS-PR)	*(164.5)*	*(97.2)*	*(39.4)*	*(6.4)*	*(229.8)*	*$75,794*	*($22,207)*	*$53,587*

HCC: Hepatocellular carcinoma; HCV: hepatitis C virus; LS-PR: difference between LDV/SOF and PR therapy

Table G3. Budget Impact of New Treatment Regimens for Chronic Hepatitis C in the Medi-Cal/Department of Corrections Population in California

	All Patients				*Fibrosis Level 3-4 Only*			
Analysis Step	**Genotype 1**	**Genotype 2**	**Genotype 3**	**Total**	**Genotype 1**	**Genotype 2**	**Genotype 3**	**Total**
(1) HCV Prevalence	65,100	14,880	11,160	91,140	16,926	3,869	2,902	23,696
(2) # Treated (50%)	32,550	7,440	5,580	45,570	8,463	1,934	1,451	11,848
(3) Interferon Eligibility								
Eligible (60%)	19,530	4,464	3,348	27,342	5,078	1,161	870	7,109
Ineligible (40%)	13,020	2,976	2,232	18,228	3,385	774	580	4,739
(4) Current Total Expenditures (All Care)				$ 56,456,400,000				$ 56,456,400,000
PMPM				$ 611				$ 611
(5) Increase in HCV Treatment Costs*								
Total $	$ 1,607,150,391	$ 544,712,160	$ 900,556,200	$ 3,052,418,751	$ 417,859,102	$ 141,625,162	$ 234,144,612	$ 793,628,875
PMPM	$ 17.39	$ 5.90	$ 9.75	$ 33.03	$ 4.52	$ 1.53	$ 2.53	$ 8.59
% Change	3%	1%	2%	5%	1%	0%	0%	1%
(6) Cost Offsets from New HCV Treatments								
5 Years	$ (111,363,315)	$ (85,121,040)	$ (57,496,320)	$ (253,980,675)	$ (28,954,462)	$ (22,131,470)	$ (14,949,043)	$ (66,034,976)
20 Years	$ (430,592,558)	$ (475,244,880)	$ (321,017,400)	$ (1,226,854,838)	$ (111,954,065)	$ (123,563,669)	$ (83,464,524)	$ (318,982,258)
(7) Total Net Budgetary Impact								
5 Years	$ 1,495,787,076	$ 459,591,120	$ 843,059,880	$ 2,798,438,076	$ 388,904,640	$ 119,493,691	$ 219,195,569	$ 727,593,900
% Change	3%	1%	1%	5%	1%	0%	0%	1%
20 Years	$ 1,176,557,834	$ 69,467,280	$ 579,538,800	$ 1,825,563,914	$ 305,905,037	$ 18,061,493	$ 150,680,088	$ 474,646,618
% Change	2%	0%	1%	3%	1%	0%	0%	1%

*Based on average treatment cost for ledipasvir+sofosbuvir (genotype 1, for 8, 12, or 24 weeks) and sofosbuvir+ribavirin (genotypes 2 and 3, for 12 and 24 weeks respectively)

PMPM: Per-member per-month; HCV: hepatitis C virus