

The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection



**An Action Guide for the Treatment of
Chronic Hepatitis C Infection:
Next Steps for Clinicians**

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Completed by:

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Introduction

About This Guide

Evidence from clinical research, which informs effectiveness reviews, provides a critical foundation for judgments that patients, clinicians, and health insurers must make about treatment choices and coverage policies. Yet that evidence is often not translated in a way that is helpful to inform health care decisions. This document is a companion policy guide designed to help patients, clinicians, and insurers make use of the results of a recent technology assessment entitled “[*The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection*](#)” developed by the Institute for Clinical and Economic Review (ICER) and faculty at University of California San Francisco. This report formed the basis for the deliberations and votes of the California Technology Assessment Forum (CTAF) Panel – an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy, who evaluate evidence and vote on the comparative clinical effectiveness and value of medical interventions. All CTAF Panel members meet strict conflict of interest policies.

CTAF held its public meeting on new treatments for hepatitis C on March 10, 2014 in San Francisco, California. A full report summarizing the discussion and votes taken is available on the [CTAF website](#). We have developed this Action Guide to provide a user-friendly overview of the CTAF findings and an associated list of specific evidence-based action steps that patients, clinicians, and insurers can take to improve patient outcomes and the overall value of treating hepatitis C. The content provided here is for informational purposes only, and it is not designed to replace professional medical advice.

A Note on CTAF Evidence Voting

Each public meeting of CTAF involves deliberation and voting on key questions on the comparative clinical effectiveness and value of the various diagnosis and treatment options discussed. When voting on economic impact, CTAF Panel members are not provided with prescribed thresholds or boundaries for how to interpret value. Rather, the CTAF Panel members are asked to assume the perspective of a state Medicaid program or a provider organization making resource allocation decisions within a relatively fixed budget.

Executive Summary

This assessment for the California Technology Assessment Forum (CTAF) evaluates the evidence on the comparative clinical effectiveness and value of two drugs recently approved by the FDA for the treatment of chronic hepatitis C: simeprevir and sofosbuvir. Chronic hepatitis C is a common infection that is a major cause of chronic liver disease, liver failure, and hepatocellular carcinoma, 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 gold standard of therapy for the treatment of chronic hepatitis C. Approximately half of patients with genotype 1, the most prevalent type of hepatitis C in the US, could expect with PR therapy to clear the virus from their bloodstream entirely and maintain a sustained virologic response (SVR) 24 weeks after the end of treatment. PR therapy can be difficult, however, as both interferon and ribavirin can produce bothersome side effects, and in some cases, dangerous levels of anemia, neutropenia, and/or thrombocytopenia.² The 2011 introduction of first generation direct-acting antiviral (DAA) protease inhibitors boceprevir (Victrelis®, Merck & Co.) and telaprevir (Incivek®, Vertex Pharmaceuticals, Inc.) resulted in substantially improved SVR rates in many patients when used with PR regimens. This improvement has come with new challenges, however, including significant additional side effects and drug-drug interactions as well as stringent dosing requirements and high pill burdens for patients.³

Novel DAA agents have been developed with the potential for simplified dosing, fewer side effects and drug-drug interactions, and in some patients, the promise of interferon- and/or ribavirin-free treatment, particularly for genotypes 2 and 3 (the other common genotypes in the US). These new agents include the recently-approved second generation protease inhibitor simeprevir (Olysio®, Janssen Products, LP) and polymerase inhibitor sofosbuvir (Sovaldi™, Gilead Sciences, Inc.), as well as several other agents that are currently in late-stage clinical trials. Uncertainties remain with these new agents, however, as data on treatment-related side effects and their performance in particular patient populations are still emerging in the published literature. In addition, the costs of treatment are likely to increase substantially, with the two new agents expected to cost approximately \$70,000 and \$170,000 per course of therapy, depending on the duration of therapy.^{4,5} Accordingly, the California Technology Assessment Forum has chosen to review the evidence on the comparative clinical effectiveness and comparative value of new DAA agents for chronic hepatitis C in relation to the existing standard of care in multiple patient populations.

This assessment will address the following questions: 1) among patients with genotype 1, are treatment regimens incorporating simeprevir and sofosbuvir equivalent or superior to the previous standard of care: pegylated interferon plus ribavirin and one of the first generation protease inhibitors telaprevir or boceprevir; 2) among patients with genotypes 2 and 3, is the combination of sofosbuvir and ribavirin equivalent or superior to the previous standard of care, pegylated

interferon plus ribavirin; and 3) among interferon-ineligible or intolerant patients, is the combination of sofosbuvir plus ribavirin or sofosbuvir plus simeprevir equivalent or superior to no treatment. 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.

Methods

The lack of head-to-head trials makes it difficult to assess the relative efficacy of the different drug regimens. In order to assess the relative efficacy of various treatment options, we performed a network meta-analysis, a form of indirect comparison that synthesizes direct and indirect evidence in a network of clinical trials to compare multiple interventions for the same indication. Network meta-analysis allows for indirect comparisons between therapies as long as they have the same type of control group (often placebo) in randomized trials.

To examine the potential clinical and economic impact of the introduction of sofosbuvir and simeprevir in California, we also developed a cohort model that assessed these effects over time horizons of one year, five years, and 20 years. Our model examined outcomes in different hypothetical cohorts of chronic hepatitis C patients organized by genotype, prior treatment status (i.e., treatment-naïve versus treatment-experienced), and eligibility for interferon therapy. Within each of these strata, outcomes and costs were assessed for a cohort of 1,000 hypothetical patients, age 60 years. We focused on genotypes 1, 2, and 3, as these represent over 97% of the hepatitis C population in the US.

Results

Genotype 1

Table ES1 on the next page summarizes the key benefits and harms for the treatment options for genotype 1. Among treatment-naïve patients, the first generation protease inhibitors increase the SVR at 12 weeks (SVR12) from the 40% range with PR to the 70% range. However, a large number of pills have to be taken about every 8 hours, and there are burdensome new side effects. These include a marked increase in anemia, with nearly 50% of patients taking telaprevir requiring erythropoietin stimulating agents for a median of 15 weeks during the course of treatment. Also common were nausea for both boceprevir and telaprevir, 20% more patients experiencing taste disturbance for boceprevir, and 20% more patients experiencing generalized pruritus with telaprevir. The drugs also have a large number of important drug interactions. Despite these problems, triple therapy with one of the two first generation protease inhibitors and PR was considered the standard of care for treatment of genotype 1 until the approval of simeprevir and sofosbuvir.

Table ES1. Summary of Benefits and Harms for Genotype 1 by Prior Treatment Status and Interferon Eligibility.

| Treatment Approach (weeks) | SVR12 (Percent) | Treatment Burden | Adverse effects | Interferon -ineligible |
|------------------------------|---------------------------|---------------------------------|--|------------------------|
| Genotype 1 | | | | |
| <i>Treatment-naïve</i> | | | | |
| PR (48) | 47 | 48 weeks with weekly injections | Fatigue (50-60%), fever (40-45%), anemia ($\leq 30\%$) | No |
| BOC(24) + PR(48) | 73 | Add Q8 pills | Anemia ($\leq 50\%$), more nausea and dysgeusia, drug interactions | No |
| TVR(12) + PR(48) | 74 | Add Q8 pills | Anemia ($\leq 50\%$), more nausea and pruritus, drug interactions | No |
| SMV(12) + PR(24-48)* | 84 | Add 1 pill to PR | No increase in anemia | No |
| SOF(12) + PR(12) | 83 | Add 1 pill to PR Fewer weeks | No increase in anemia | No |
| SMV(12) + SOF(12) | No data (Likely >90) | No P, maybe no R | Not reported yet | Maybe |
| <i>Treatment-experienced</i> | | | | |
| PR (48) | 22 | 48 weeks with weekly injections | Fatigue (50-60%), fever (40-45%), anemia (up to 30%) | No |
| BOC(24) + PR(48) | 64 | Add Q8 pills | Anemia ($\leq 50\%$), more nausea and dysgeusia, drug interactions | No |
| TVR(12) + PR(48) | 70 | Add Q8 pills | Anemia ($\leq 50\%$), more nausea and pruritus, drug interactions | No |
| SMV(12) + PR(24-48)* | 70 | Add 1 pill to PR | No increase in anemia | No |
| SOF(12) + PR(12) | No data (FDA estimate 71) | Add 1 pill to PR Fewer weeks | No increase in anemia | Maybe |
| SMV(12) + SOF(12) | 90 | No P, maybe no R | Not reported yet | Yes |

Abbreviations: Q8 = taken every 8 hours; P = pegylated interferon; R = ribavirin

* Excluding patients with the Q80K mutation (approximately 10-15% of genotype 1 patients)

Among patients without the Q80k polymorphism, simeprevir appears to significantly improve the SVR12 compared with triple therapy. Additional benefits of simeprevir are reductions in the incidence of anemia and the pill burden for patients: simeprevir requires only one pill per day. It should be noted, however, that there are no published data from head-to-head trials of simeprevir and either of the first generation protease inhibitors, nor are there data on the impact of treatment on important long term patient outcomes such as the incidence of cirrhosis, liver decompensation, hepatocellular carcinoma, transplant, or death. Adverse events (AEs) specifically associated with simeprevir include pruritus, photosensitivity-induced rashes, and hyperbilirubinemia, but these are generally not severe and are easily managed.

Sofosbuvir plus PR also appears to cause less anemia and certainly represents a lower pill burden than standard triple therapy. It also requires only 12 weeks of PR rather than the 24 to 48 weeks

with the first generation protease inhibitors. Simeprevir plus PR in patients without the Q80K polymorphism and sofosbuvir plus PR appear to have very similar SVR12 rates for genotype 1 patients who are treatment-naïve or treatment-experienced. Most of the data for sofosbuvir, however, come from uncontrolled studies. Because of the shorter course of PR, sofosbuvir + PR has fewer severe/life-threatening (grade 3 and 4) AEs and fewer patients discontinuing treatment due to AEs, with no consistent pattern of an increase in AEs other than anemia (23% versus 14% for PR). As with simeprevir, this combination cannot be used in patients who are interferon-ineligible, and there are no long-term outcome data.

The preliminary data on simeprevir plus sofosbuvir (an off-label use not indicated by the FDA) with or without ribavirin come from uncontrolled trials and should be considered preliminary at this point but are nonetheless encouraging. The available data for treatment-experienced patients shows SVR12 rates averaging 90%; the SVR12 of treatment-naïve patients should be even better. This regimen is interferon-free, so can be used in interferon-ineligible patients. Since it is interferon-free (and perhaps ribavirin-free), simeprevir plus sofosbuvir should have markedly lower adverse event rates than regimens including PR.

Genotype 2

The story is more straightforward for genotype 2 (see Table ES2 on the next page). The combination of sofosbuvir plus ribavirin is superior in clinical effectiveness to prior standard treatment options. Among treatment-naïve patients, there was a large increase in SVR12 seen in the randomized FISSION trial and supported by the non-randomized VALENCE trial. The SVR12 for treatment-experienced patients was 86% and 90% in the two uncontrolled studies, but it was high enough to assume at least non-inferiority to PR therapy. The sofosbuvir-based regimen is interferon-free, which decreases grade 3 and 4 AEs, markedly decreases patients discontinuing therapy because of AEs, and reduces interferon-associated AEs such as fatigue, fever, myalgias, and headaches. Sofosbuvir therapy does not come with an increase in the anemia seen with the first generation protease inhibitors – in fact the incidence of anemia was lower in the sofosbuvir arms of the trials. The treatment course is also half as long (12 versus 24 weeks). Since the sofosbuvir-based regimen is interferon-free, the benefits should be even greater in those genotype 2 patients who are treatment-naïve but ineligible for interferon because of psychiatric or other co-morbidities. In the POSITRON trial, the SVR12 was 93% compared to 0% for treatment-naïve patients and 76% versus 0% for treatment-experienced patients.

Table ES2. Summary of Benefits and Harms for Genotype 2 by Prior Treatment Status and Interferon Eligibility.

| Treatment Approach (weeks) | SVR12 (Percent) | Treatment Burden | Adverse effects | Interferon-ineligible |
|------------------------------|-----------------|---------------------------------|--|-----------------------|
| Genotype 2 | | | | |
| <i>Treatment-naïve</i> | | | | |
| PR (24) | 78 | 24 weeks with weekly injections | Fatigue (50-60%), fever (40-45%), anemia (up to 30%) | No |
| SOF(12) + R(12) | 97 | Shorter, no P | Less fatigue, less anemia | Yes |
| <i>Treatment-experienced</i> | | | | |
| PR (24) | No data | 24 weeks with weekly injections | Fatigue (50-60%), fever (40-45%), anemia (up to 30%) | No |
| SOF(12) + R(12) | 88 | Shorter, no P | Less fatigue, less anemia | Yes |

Abbreviations: P = pegylated interferon; R = ribavirin

Genotype 3

The story is more complex for genotype 3 (see Table ES3 on the next page). For interferon-eligible patients, the existing randomized trial data do not demonstrate the superiority of sofosbuvir + PR to PR alone. Among treatment-naïve patients in the genotype 3 subgroup of the randomized phase 3 FISSION trial, 12 weeks of sofosbuvir plus ribavirin had a lower SVR12 than 24 weeks of PR (56% versus 62%). The SVR12 of the same regimen in the genotype 3 subgroup of the POSITRON study was similarly low at 61%. Given the poor outcomes at 12 weeks, the uncontrolled VALENCE study examined longer treatment courses, and the SVR consistently increased with increasing lengths of therapy to 16 and 24 weeks (56% to 93%). Similarly, the VALENCE study also showed that the SVR for treatment-experienced patients increased from 12 weeks (30%) to 16 weeks (62%) to 24 weeks (77%). These results should be confirmed in a second trial, but they formed the basis for the FDA approved regimen of 24 weeks of sofosbuvir for patients with genotype 3. The FDA approval also took into account that the sofosbuvir-based regimen is interferon-free, which decreases grade 3 and 4 AEs, markedly decreases patients discontinuing therapy because of AEs, and reduces interferon-associated AEs such as fatigue, fever, myalgias, and headaches. The treatment course is the same length as PR but without the injections and side effects of interferon. Since the sofosbuvir-based regimen is interferon-free, the benefits should be even greater in those genotype 3 patients who are treatment-naïve but ineligible for interferon because of psychiatric or other co-morbidities. In the POSITRON trial, the SVR12 was 61% compared to 0% for treatment-naïve patients and 76% versus 0% for treatment-experienced patients.

Table ES3. Summary of Benefits and Harms for Genotype 3 by Prior Treatment Status and Interferon Eligibility.

| Treatment Approach (weeks) | SVR12 (Percent) | Treatment Burden | Adverse effects | Interferon-ineligible |
|------------------------------|-----------------|---------------------------------|--|-----------------------|
| Genotype 3 | | | | |
| <i>Treatment-naïve</i> | | | | |
| PR (24) | 62 | 24 weeks with weekly injections | Fatigue (50-60%), fever (40-45%), anemia (up to 30%) | No |
| SOF(24) + R(24) | 93 | Shorter, no P | Less fatigue, less anemia | Yes |
| <i>Treatment-experienced</i> | | | | |
| PR (24) | No data | 24 weeks with weekly injections | Fatigue (50-60%), fever (40-45%), anemia (up to 30%) | No |
| SOF(24) + R(24) | 77 | Shorter, no P | Less fatigue, less anemia | Yes |

Abbreviations: P = pegylated interferon; R = ribavirin

Model Results Evaluating Clinical and Economic Outcomes of Hepatitis C Treatment Scenarios

Consistent with the findings of our systematic review and network meta-analysis, our model demonstrates that therapeutic regimens containing simeprevir or sofosbuvir have the potential to substantially increase the number of patients achieving SVR relative to previous therapeutic options, and sofosbuvir also provides the first effective interferon-free option for patients ineligible or intolerant to interferon.

For many patient subpopulations, however, the benefits of sofosbuvir and simeprevir come at a substantially increased cost. The costs for initial treatment regimens including sofosbuvir or simeprevir are expected to range from a low of approximately \$88,000 to a high exceeding \$175,000 per patient, depending on the drugs selected and the duration of initial treatment. Many patients who are treated with an initial course and who fail to achieve a prolonged SVR would likely be retreated, adding further to the estimated treatment costs over a one-year time frame.

For many comparisons with the previous standard of care, we estimate that the incremental cost required to achieve one additional SVR with newer treatment regimens is greater than \$300,000. While the “cost per additional SVR” is not a common measure of cost-effectiveness in the literature, the costs per SVR generated in this analysis are generally higher than those previously published for telaprevir versus PR (\$189,000),⁸ alternative regimens of PR versus standard PR therapy (\$17,000-\$24,000),⁹ and even highly active antiretroviral therapy in HIV patients (\$1,000-\$79,000).¹⁰

The clinical advantages of newer treatment regimens would therefore come with a substantial potential impact on health care budgets should a large number of patients be treated. As estimated by our model, we anticipate the average increase in treatment costs to be approximately \$70,000 per patient for the newer agents. For example, in an employer-sponsored group health plan with 1 million enrollees, with an assumed underlying infection rate of 1.7%, there would be approximately 17,000 patients in this population infected with hepatitis C. If even 50% of this population comes forward for treatment, the immediate one-year budget impact for the plan would be estimated to be nearly \$600 million, or approximately \$50 on a per member, per month basis. It would be impossible for this magnitude of immediate increased spending to be accommodated within the budgets established by current health care premium structures, provider risk-sharing contracts, and patient co-payments.

Using an estimate that 50% of infected individuals in California would know of their infection and would be considered for treatment, we estimate that replacing current care with simeprevir and sofosbuvir-based regimens would raise drug expenditures by \$22 billion in a single year. We looked for potential cost offsets to drug treatment resulting from downstream reductions in liver-related complications that would be expected with successful treatment of hepatitis C infection. For every 1,000 patients treated, our model estimated that switching from previous standard treatments to the most effective new regimens in all patients would prevent 18 liver-related events over five years and 70 events over 20 years. At a 5-year time horizon, however, cost offsets would still be estimated to represent less than 10-20% of upfront treatment costs. Even at a 20-year horizon, if all patients infected with hepatitis C are treated with the new regimens, the cost offset will only cover approximately three-quarters of initial drug costs.

The budget impact and cost offset figures change substantially under our second treatment scenario in which only patients with advanced liver fibrosis are started on the new treatment regimens, with other patients treated with existing pre-DAA regimens. Treating this smaller group of patients is estimated to result in an increase in initial drug expenditures of \$7 billion in the first year for the population of California, one-third of the extra amount needed to treat all infected patients. Costs saved by reducing liver-related complications in this subgroup would total only 17% of added drug costs at five years, but at 20 years, estimated cost offsets would produce a net savings to the statewide health care system of approximately \$1 billion.

We must emphasize several important limitations of our budget impact analyses. First, while there were sufficient data to perform a network meta-analysis for patients with genotype 1 infection, estimates could not be generated for all stratifications of interest for the model, and we could not even attempt quantitative synthesis for patients with genotypes 2 or 3. We therefore often had to resort to basing the input to the model on point estimates from individual studies, which in some cases involved small numbers of patients. Our results are therefore quite sensitive to the estimates of drug effectiveness and should be viewed with caution.

In addition, as described previously, we modeled only the immediate clinical effects of treatment as well as the potential downstream benefits of preventing liver-related complications. While we presented pooled rates of discontinuation due to adverse events from available clinical trial data, we assumed equally across all drug regimens that all patients completed their course of therapy and were fully compliant while doing so. This assumption likely does not adequately reflect the benefits of better adherence to newer regimens with shortened courses of interferon or no interferon at all.

For the 20-year time horizon analyses of clinical and economic outcomes, we did not try to include estimates of the impact of competing risks of morbidity and mortality for patients as they neared 80 years of age. If we had attempted to model these competing risks, the estimates of liver-related complications and resulting potential cost offsets would have been lower, serving to make the budget impact of newer regimens even more unfavorable.

We estimated the costs of medication using published wholesale acquisition costs or average wholesale prices.⁷ Of note, however, telaprevir costs have increased substantially over the past 1.5 years, even as its use has declined to near zero.⁶ We chose to model telaprevir costs using estimates from the time period in which it was considered the previous standard of care for triple therapy (\$4,920 per week) rather than using a more current, and what we believe to be artificially-inflated, price.

Finally, our analyses did not consider other possible benefits to patients from greater treatment success, such as improved quality of life and reduced absenteeism from work or school. Full analysis of all potential outcomes and costs of these new treatment options will only be possible through additional data collection and/or the development of complex simulation models that approximate the natural history of hepatitis C and its treatment.

CTAF Public Meeting – Voting Results and Policy Issues

During a March 10, 2014 public meeting, the CTAF Panel deliberated and voted on key questions related to the comparative clinical effectiveness and comparative value of new treatments for hepatitis C. The key questions addressed the most important issues in applying the evidence to support clinical practice and medical policy decisions. Following its deliberation on the evidence and subsequent voting, the CTAF Panel engaged in a moderated discussion with a Policy Roundtable composed of clinical experts in liver disease, a patient advocate, payer representatives, and a representative from a manufacturer of one of the new drugs, all of whom were asked at the

meeting to disclose any conflicts of interest. This discussion was distilled into nine specific recommendations. The key themes are summarized below:

1. Even though the CTAF panel voted that the new drugs are likely superior in terms of clinical effectiveness for most patients and offer clinical benefits beyond current treatments, serious limitations in the evidence base remain. Further evidence is needed to more fully evaluate the comparative clinical effectiveness and value of these new treatments.
2. A majority of the CTAF Panel rated the new treatments as “low value” compared with older drugs due to the magnitude of the potential impact on health care budgets of treating large numbers of patients with these high-priced drug regimens. Because the financial impact of using these new drugs to treat all eligible patients with hepatitis C is untenable, policy makers should seek avenues to achieve reductions in the effective price of these medications.
3. Panel members and outside experts nearly all agreed that for both clinical and cost reasons, not every patient with hepatitis C needs to be immediately treated with the new drugs. Patients and providers should discuss the timing of treatment. Given the circumstances, it is reasonable to consider prioritizing treatment with the new drugs for patients who need urgent treatment and have advanced fibrosis or cirrhosis.
4. Additional policy measures to increase the likelihood of clinical benefit from treatment while reducing the financial impact should be considered. Payers seeking to achieve these goals should consider use of prior authorization criteria that a) require patient commitment, b) utilize “futility rules” that define when a lack of early response should lead to discontinuation of treatment, and c) require that the new drugs be prescribed by specialists with experience treating patients with hepatitis C.

Action Steps for Clinicians

If you are a clinician treating patients with hepatitis C, the following action steps may help you ensure that patient care is coordinated and incorporates the best available evidence.

- 1. Engage patients in discussions to determine whether immediate treatment is warranted given that most infected patients will not develop cirrhosis or end stage liver disease, more interferon-free treatment regimens will be available over the next 12-24 months, and current treatments are extremely expensive.**

Most patients with chronic hepatitis C infection do not progress to severe liver dysfunction over the course of their lifetimes. The majority of patients with hepatitis C are completely asymptomatic, including in the early stages of cirrhosis. Although overt symptoms of liver dysfunction are not an appropriate way to monitor for the onset of liver damage, many patients with hepatitis C, especially those diagnosed through broad screening efforts, will not need immediate treatment. They should, however, be evaluated thoroughly and monitored closely to assess for worsening liver function. Although the idea of postponing treatment will not come naturally to many patients, it is an option that physicians and patients should discuss given:

- a) The current limited number of clinicians with significant experience caring for patients undergoing treatment for hepatitis C,
- b) The promise of additional options for interferon-free regimens in the near future, and
- c) The uncertain balance of risks and benefits of immediate treatment for patients who show no current signs of liver dysfunction.

Informed patients and clinicians together should decide whether to initiate or postpone treatment taking these and other considerations, including patient values, into account.

- 2. Advocate for and use high-quality evidence-based guidelines to guide treatment decisions.**

Guidelines for the treatment of hepatitis C should be developed using best practices, including ratings of the strength of evidence, clarity about the role of various organizations involved in developing the guidelines, and complete openness about potential conflicts of interest of individual guideline committee members. This will allow patients, physicians, and other stakeholders to fully believe that key clinical guidelines are objective and can be trusted. The Institute of Medicine (IOM), an independent organization of scientists that analyzes available data and provides advice on medical issues, recommends that chairs of guideline committees should have no conflicts of interest if possible, and that the entire group developing the guidelines should also be free of ties

to industry; if that is not possible, then at least half of the members should meet this criterion.

Links to the two best known clinical guidelines are shown below. The guideline from the Department of Veterans Affairs was developed using a process that meets more IOM criteria, and its guideline committee members had no ties to the drug industry.

1) US Department of Veterans Affairs (VA)

<http://www.hepatitis.va.gov/provider/guidelines/2014hcv/index.asp>

The April 2014 VA guidelines document provides a detailed algorithmic approach to assist in clinical decision-making on HCV treatment considerations based on specific patient characteristics including genotype, treatment history, presence of cirrhosis, and interferon eligibility. They include a discussion of when patients can be considered for deferred treatment, methods for documenting the level of liver fibrosis/identifying treatment candidates based on liver disease stage, and specific criteria for patients who are interferon ineligible or intolerant. The guidelines will be revised periodically as new treatments become approved, additional trial results are published, and data from real-world practice become available.

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

<http://www.hcvguidelines.org>

On January 29, 2014, the AASLD, IDSA, and IAS-USA published online guidelines for the treatment of chronic hepatitis C. These guidelines will be continuously updated online.

3. Consider prioritizing treatment by level of liver fibrosis.

Treating all eligible patients with hepatitis C with the new drug regimens is not clinically required nor is it feasible given constraints on clinical infrastructure and financial resources. Under these circumstances, it is reasonable to consider prioritizing treatment with the new drugs for patients who have advanced fibrosis or cirrhosis. The use of the drugs in patients with decompensated cirrhosis is not yet well studied and should be done only under the guidance of experts. While noting that symptoms of liver dysfunction alone are an unreliable means of assessing hepatic fibrosis, the clinical experts on a CTAF Policy Roundtable¹ indicated that patients with advanced fibrosis and cirrhosis (METAVIR scores of F3-F4), those who have liver cancer and are awaiting

¹ The Policy Roundtable at the March 10, 2014 CTAF meeting was composed of clinical experts in liver disease, a patient advocate, payer representatives, and a representative from a manufacturer of one of the new drugs, all of whom were asked at the meeting to disclose any conflicts of interest.

transplant, and those who are post-liver transplant have the greatest chance of benefiting from immediate treatment. Ideally, it would be desirable to treat all patients with hepatitis C to prevent progressive fibrosis. However, the clinical trial data are still new, and outcomes in the “real-world” are not yet available. Immediate treatment is not necessary in most cases, and allowing drugs to be further studied may be a better strategy for those patients who have little or mild fibrosis. If cost necessitates that not all patients be treated immediately, then using the level of liver fibrosis as a basis for patient selection offers the greatest likelihood of long-term clinical benefits while moderating the short-term financial impact on the health care system.

4. Seek patient commitment to compliance with the treatment regimen.

In discussions with patients for whom treatment with one of the new regimens is an option, consider initiating treatment contingent upon a documented patient commitment to the planned course of treatment, including anticipated blood tests and office visits during and after treatment. Because the new treatments for hepatitis C have fewer side effects, it is expected that fewer patients will discontinue treatment. However, given the high cost of initial treatment, the risk that poor adherence would lead to the development of resistant viral strains, and the additional cost if a patient stops treatment and then starts again with a new treatment course, patient commitment to compliance with treatment is crucial.

5. Specialists in treating patients with hepatitis C should partner with primary care physicians to establish clear mechanisms for coordinating care, including specifying what tests should be performed in primary care prior to patient referral to specialty care.

Most patients with hepatitis C will be diagnosed by a primary care clinician, but the decision-making around whether to initiate treatment, and if so with which treatment regimen, still benefits from the involvement of a clinician with a significant level of expertise. This may change in the future if, as expected, drug regimens for all genotypes are fully interferon-free and become even simpler to administer and monitor. For now, however, given the large numbers of patients who may soon be identified with hepatitis C infection through enhanced screening efforts, primary care clinicians should partner with specialists to clarify the best way to coordinate care for these patients. For example, if formal referral will be made, it will be helpful if primary care clinicians order a series of baseline tests on liver function, including the hepatitis C viral load, prior to referring the patient. Provider groups should start working now on internal guidelines for initial laboratory testing and other mechanisms to coordinate the care between primary care and specialty care.

Suggestions for pretreatment assessments may be found at the link below:

US Department of Veterans Affairs (VA):

<http://www.hepatitis.va.gov/provider/guidelines/2012HCV-pretreatment-assessments.asp>

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