Health Evidence Review Commission's Value-based Benefits Subcommittee

August 8, 2014
1:30 PM

Meridian Park Hospital
Community Health Education Center, Room 117B & C
19300 SW 65th Avenue, Tualatin, OR 97062

Section 1.0

Call to Order

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE
August 8, 2014
1:30pm - 3:30pm
Meridian Park Room 117B&C
Community Health Education Center
Tualatin, OR 97062
All times are approximate

I.	**Call to Order, Roll Call, Approval of Minutes – Kevin Olson**	**1:30 PM**
II.	**Staff report –Ariel Smits, Cat Livingston, Darren Coffman**	**1:35 PM**
III.	**Previous Discussion Items** A. Hepatitis C treatment	**1:40 PM**
IV.	**Public comment**	**3:20 PM**
V.	**Adjournment**	**3:30 PM**

Value-based Benefits Subcommittee Recommendations Summary
For Presentation to:
Health Evidence Review Commission in June, 2014

For specific coding recommendations and guideline wording, please see the text of the 06/12/14 VbBS minutes.

CODE MOVEMENT

- Procedure codes for placement and removal of audient bone conductors were removed from two covered lines
- Physical therapy procedure codes were added to two covered gynecological lines for pelvic physical therapy
- Electroconvulsive therapy (ECT) procedure codes were added to the schizophrenia line
- Procedure codes for applied behavioral analysis for autism were added to the autism line

GUIDELINE CHANGES

- A new guideline regarding bone anchored hearing aids was adopted
- The guideline on treatment resistant depression was modified to remove reference to ECT and to change the title to reflect that the guideline only concerned repetitive transcranial stimulation
- A new guideline regarding use of ECT was adopted
- The bariatric surgery guideline was modified to clarify intent and update references to accrediting organizations
- The guideline for treatment of autism spectrum disorder was replaced with a new guideline on applied behavioral analysis

BIENNIAL REVIEW

- The audient bone conductor line (line 570) was deleted
- The autism spectrum disorder line was rescored from line 313 to approximately 199

VALUE-BASED BENEFITS SUBCOMMITTEE
Meridian Park Health
Community Health Education Center, Room 117B&C
Tualatin, OR
June 12, 2004
8:30 AM – 1:00 PM

Members Present: Lisa Dodson, MD, Chair; James Tyack, DMD; Susan Williams, MD; Mark Gibson; David Pollack, MD (via phone, left at 11:50 PM); Irene Croswell, RPh

Members Absent: Kevin Olson, MD, Vice-chair; Laura Ocker, LAc

Staff Present: Darren Coffman; Ariel Smits, MD, MPH; Cat Livingston, MD, MPH; Jason Gingerich; Dorothy Allen-Peck; Denise Taray, RN.

Also Attending: Jesse Little, OHA Actuarial Services Unit; Wally Shaffer, MD, DMAP; Brian Neiubuurt, OHA; Holly Jo Hodges, MD, Trillium Health; Henry Milzcuk MD, OHSU ENT (via phone); Jennifer Ratigan, Pacific University Audiology (via phone); Megan Bird, MD, Legacy; Maura Roche, Aubrey Harrison, and Danielle Askini, Basic Rights Oregon; Atif Zaman MD, OHSU Hepatology; Jose Cruz, RN; Andrew Wolfe; Karynn Fish, OHA; Cheryl Fletcher, Abbvie; Stephanie Heburn, PT; Stephanie Peters and Becca Reish, Oregon Physical Therapy Association; John Peterson and Michelle Bece, Gilliad; Shane Jackson and Tobi Rates, Autism Society of Oregon; Eric Larsson, Lovaas Institute; Becky Straus, ACLU of Oregon; Tom Culhane, Atrio Heatlhplan; Larren Sandt, Caring Ambassadors; Anne Murray, Bristol-Myers Squibb; Ashlen Strong, HealthShare of Oregon; Jenny Fischer, ORABA; Dianna Matthews, Johnson and Johnson; Black Wilson and Shane Gelcher, BMS; David Robertson, Providence Heatlh Plan; Shelley Kailey, Central Drugs; BJ Cavnor, 1-in-Four and Cascadia Project.

- **Roll Call/Minutes Approval/Staff Report**

The meeting was called to order at 8:40 am and roll was called. Minutes from the May, 2014 VbBS meeting were reviewed and approved with no corrections or changes.

> ACTION: HERC staff will post the approved minutes on the website as soon as possible.

Smits introduced Holly Jo Hodges, MD, who is a new VbBS member pending approval at the HERC's afternoon meeting. Dr. Hodges is a family physician who is the medical director of Trillium Healthcare in Eugene. She would be serving on the VbBS as the CCO/Medical Director member. Smits also noted that today is the last meeting for Lisa Dodson, MD. Her guidance as VbBS Chair has been exceptional and will be sorely missed.

Coffman noted that ICD-10 implementation is delayed until October 1, 2015; therefore there is no need to publish the biennial list in October 2014 anymore. The biennial list will instead be published January 1, 2015 to coincide with the CCO contract periods.

- **Topic: Audiant bone conductor biennial review**

  Discussion: Smits reviewed the summary document regarding deletion of the audient bone conductor line. Smits noted that there remains a line below the funding line for sensory conditions with no treatment necessary for any ENT/hearing technology which requires placement on a non-funded line. There was minimal discussion.

MOTION: To approve the proposed List changes as presented. CARRIES 6-0.

Actions:

1) Delete line 570 CONDUCTIVE HEARING LOSS Treatment: AUDIANT BONE CONDUCTORS from the Prioritized List
2) Remove CPT 69710 (Implantation or replacement of electromagnetic bone conduction hearing device in temporal bone) from line 427 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
3) Remove CPT 69711 (Removal or repair of electromagnetic bone conduction hearing device in temporal bone) from line 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
4) Add an entry regarding audient bone conductors to the new list of items reviewed by not placed on the Prioritized List. This new list will be reviewed at the August, 2014 VbBS meeting.

- **Topic: Unilateral hearing loss**

  Discussion: Smits reviewed the summary document regarding the coverage of unilateral vs. bilateral hearing loss. The subcommittee was comfortable with the evidence for treatment of unilateral hearing loss in children (language development improvement, school success improvement, etc.), but felt that the evidence for treatment in adults needed further review. Henry Milzcuk, MD, OHSU Pediatric Audiology, testified that adults with unilateral hearing loss have significant disability. They have problems with following conversations or speech in loud environments. He testified that treatment of unilateral hearing loss in children should be higher priority that treatment in adults, but that treatment in adults was also important. Gibson requested further information on the utilization of unilateral hearing loss treatment in adults—number of requests for treatment, treatment costs, etc. Jennifer Ratigan, audiologist from Pacific University, testified that the impact of treatment of unilateral hearing loss in adults depends on whether the hearing loss was long standing/congenital vs. sudden hearing loss in adulthood. Sudden unilateral hearing loss has impact on balance,

functionality, etc. The decision was to cover unilateral hearing loss in children, and to have staff further investigate coverage of unilateral hearing loss in adults.

Actions:

1) HERC staff will review the evidence of effectiveness of treatment of unilateral hearing loss in adults, both for adults with long term hearing loss and with sudden loss. Staff will work with the OHP health plans to determine the level of utilization of treatment of unilateral hearing loss in adults, and cost of such treatment. Staff will mock up possible lines with scoring for treatment of unilateral hearing loss in children and in adults, and compare this line scoring with current lines 317 and 450 (hearing loss medical treatment lines). This information will be brought back to the August VbBS meeting.

- **Topic: Bone anchored hearing aids**

Discussion: Smits reviewed the summary document regarding the coverage of bone anchored hearing aids (BAHA). Smits specified that the proposed new guideline does not address the treatment of children younger than age 5, or the use of technology such as SoftBand. Such treatment is still covered on the hearing loss lines. There was minimal discussion.

MOTION: To approve the new guideline as presented. CARRIES 6-0.

Actions:

1) A new guideline regarding BAHA was adopted as shown in Appendix A.

- **Topic: Physical therapy (PT) for urinary incontinence**

Discussion: Smits reviewed the summary document regarding the addition of PT procedure codes to two gynecology lines. Testimony was heard from two physical therapists, Stephanie Heburn and Becca Reisch from the Oregon Physical Therapy Association, who were present to answer questions. There was discussion about whether the guidelines in question should specify PT training type. The experts testified that PT providers need specialized training to provide pelvic PT; however, while certification of training in pelvic PT is available, such certification is not standardized or widely used. There was additional discussion about adding "pelvic" to the physical therapy requirement in the referenced guidelines, but the examples already in these guidelines were felt to be sufficient.

MOTION: To approve the staff recommendations as presented. CARRIES 6-0.

Actions:

1) Add the following PT services to line 471 UTERINE PROLAPSE; CYSTOCELE

a. 97001 Physical therapy evaluation
b. 97002 Physical therapy re-evaluation
c. 97110 Therapeutic procedure, 1 or more areas, each 15 minutes; therapeutic exercises to develop strength and endurance, range of motion and flexibility
d. 97140 Manual therapy techniques (eg, mobilization/ manipulation, manual lymphatic drainage, manual traction), 1 or more regions, each 15 minutes
e. 97530 Therapeutic activities, direct (one-on-one) patient contact (use of dynamic activities to improve functional performance), each 15 minutes

2) Add CPT 97140 and 97530 to line 459 URINARY INCONTINENCE
3) Add reference to line 471 to the Rehabilitation Guideline

- **Topic: Electroconvulsive therapy**

Discussion: Smits reviewed the summary document regarding the coverage of electroconvulsive therapy (ECT). There was discussion about the proposed addition of a clause stating that vagal nerve stimulation was not covered for treatment of depression. The committee felt that this clause would be better put in the new "excluded" list. Pollack requested that the new ECT guideline reference the DSM-V condition names (e.g. major depressive disorder rather than major depression).

MOTION: To approve the staff recommendations as amended. CARRIES 6-0.

Actions:
1) Modify GN 102 as shown in Appendix B
2) Add reference to vagal nerve stimulation (CPT 64568) to the new list of technology reviewed but not included on the Prioritized List
3) Add CPT 90870 (electroconvulsive therapy) to line 26 SCHIZOPHRENIC DISORDERS
4) Adopt a new guideline for ECT as shown in Appendix A

- **Topic: Applied behavior analysis for autism spectrum disorders**

Discussion: Livingston presented an issue summary discussing the process the evaluation of evidence has taken, from the direction of SB365, the Evidence-based Guidelines Subcommittee deliberations, and staff amendments regarding specific intensity and duration limits. Staff recommended being more description of the evidence base to help guide medical appropriateness and being less proscriptive about specific limits.

Dr. Eric Larsson, Director of the Lovaas Institute, presented for invited expert testimony. He stated the Association of Professional Behavior Analysts dispute some specific conclusions of the evaluation of evidence, and think studies are

misrepresented. They recommend that the evaluation of an individuals responsiveness to treatment is the best way to maximize value and that treatment intervals of 6 months allow establishment of baselines and progress. With the challenges of the parity rules, they feel that socially significant behavioral objectives should be evaluated and providers should be evaluated on their ability to improve outcomes with appropriate treatment planning.

There was a discussion about standardization of assessments. Larsson responded that standards of different providers are influenced by the level of funding that is available to them. Use of objective assessments does help, but there are many of them. Subcommittee members discussed that it would be very helpful for there to be a single assessment tool for all CCOs to use. Other states may be able to offer guidance about this. There is the challenge of identifying optimal tools amongst the many standardized tools. This may end up being a best practices consensus-type exercise rather than a current evidence-based pathway approach.

Public testimony was received from Jenny Fisher, representing the Oregon Association for Behavior Analysts. She recommends using existing codes in addition to adding temporary codes as they become available and to not delay the addition of ABA treatment for children and adolescents who need it. Additional public testimony was received by Tobi Rates, Executive Director of Autism Society of Oregon, who is also the parent of 2 children with ASD. She also requested ABA therapy be offered to autism spectrum disorder individuals as quickly as possible and is most concerned that children would potentially have to wait 6 months to get this therapy when early intervention is very important. They appreciate removal of duration and intensity limits. Rates expressed ongoing concern about the rating of evidence, particularly with regard to older patients.

With regard to the coding concerns, Coffman responded that current codes on the line would be inappropriate, as they refer to medication management and other non-related services. Nonspecific codes would have to be added to the line to comply with the request and the commission does not do that when more specific codes are available. The implementation delay specified in SB 365 was based on ICD-10 implementation, but because of the ICD-10 implementation delay, coding changes could be made to any upcoming List. The final decision on the go live date is up to OHA leadership.

Staff had presented a proposed rescoring of the autism line. Additionally, Coffman discussed Paul Terdal's submitted testimony on scoring changes. Coffman affirmed that the healthy life score of 5 was appropriate with precedent given that it is the highest score possible for a nonfatal condition. In terms of population effects, there can be dangerous or societal behaviors, and so the decision was to change this score from a 1 to a 2. The cost of this therapy was discussed, and while public testimony suggests it has a high offset to societal

costs, the medical costs continue to be significantly increased and the decision was made to change this from a 3 to a 1. Members affirmed that examining medical costs is consistent with the score of costs of other services on the Prioritized List. The new scoring would place the autism spectrum disorder line at approximately Line 199.

Actions:

1) Change treatment description of line: ~~CONSULTATION/MEDICATION MANAGEMENT/LIMITED BEHAVIORAL MODIFICATION~~ MEDICAL THERAPY/BEHAVIORAL MODIFICATION INCLUDING APPLIED BEHAVIOR ANALYSIS
2) Replace Guideline Note 75 with a new guideline as shown in Appendix B
3) Add CPT 0359T-0374T (adaptive behavior assessments and treatments) to line 313 AUTISM SPECTRUM DISORDERS
4) Recommend that EbGS review and revise their summary conclusions as time and meetings allows
5) Staff is directed to identify a pathway to determine the best standardized tools for assessment of ABA
6) Staff will bring the issue of a guideline for self-injurious behavior in non-autistic children back to a future meeting
7) Rescore the Autism Spectrum Disorders Line as follows (previous scoring in parenthesis):

    Category: 3 (3)
    HL: 5 (5)
    Suffering: 4 (4)
    Population effects: 2 (1)
    Vulnerable population: 0 (0)
    Tertiary prevention: N/A
    Effectiveness: 3 (2)
    Need for service: 0.7 (0.7)
    Net cost: 1 (3)
    Approximate new line placement: 199 (313)

- **Topic: Gender dysphoria**

Discussion: Smits introduced a summary of the evidence for the effectiveness of treatment of gender dysphoria in reducing depression, anxiety, suicide attempts, IV drug use and other high risk behavior. She reviewed expected numbers of patients who would request treatments for gender dysphoria in OHP, and the expected costs for such treatment. She reviewed staff recommendations to add cross-sex hormone therapy and sex reassignement surgery to the current gender dysphoria line, rather than creating a new surgical treatment line.

There was discussion about the evidence of effectiveness of treatments for gender dysphoria. There was discussion about whether outcomes were self-

reported. Smits noted that most older studies relied on self-reported outcomes, whereas most newer studies used validated tools to measure anxiety and depression symptoms.

Maura Roche, from Basic Rights Oregon, testified about her organization's concerns about proposed guideline wording which restricts sex reassignement surgery to patients 18 years and older. This concern was echoed by Danielle Askini from Basic Rights Oregon and Megan Bird, MD from Legacy Health Systems. There was discussion about committee member concerns about performing irreversible surgery on teens who are still undergoing brain development. Roche pointed out that the age of consent for medical procedures in Oregon is 15. Askini testified that teens are at higher risk for suicidality, and therefore should not have surgical treatments withheld if appropriate. The decision was to remove the age 18 requirement for surgery and replace with wording about patients must "have the capacity to make a fully informed decision and to give consent for treatment."

Roche, Askini, and Bird also expressed concern with the requirement to have "real life" experience living as the desired gender. Some persons who may not be able to easily physically pass as their desired gender face increased risk of discrimination, harassment, and violence. The experts felt that the requirement for 12 months of hormone therapy prior to surgery should provide an adequate waiting period. The experts suggested adding wording allowing a waiver of this requirement for certain patients. Committee members expressed concern with removing this requirement, given the irreversible nature of surgical therapies. Experts noted that very few patients expressed regrets about having surgical treatments (~1%), particularly when compared to the incidence of suicide attempts. Staff proposed adding a clause to this requirement stating that patients must live as their desired gender "unless a medical and a mental health professional both determine that this requirement is not safe for the patient." This was considered acceptable by the experts and committee members.

The scoring of the new line was briefly discussed. Askini expressed support for moving gender dysphoria to category 6, given the high risk of suicide and suicide attempts in this population, which are considerably higher than in major depression. Staff noted that they have received a comment that the Healthy Life score should be increased from 3 to 6, due to changing the category from 7 to 6. Completion of the re-scoring of the new gender dysphoria line with cross-sex hormone therapy and sex reassignment surgery was tabled until August.

There was extensive discussion of the proposed guideline for gender dysphoria, including the suggested changes to the requirements for an age limit and a requirement for "real life" experience prior to surgery. There was considerable discussion about the mental health assessment required prior to surgery. Pollack requested the addition of wording that the assessment be done by mental health professionals "with experience in working with patients with gender

dysphoria." There was also discussion about requiring this assessment to address the relevance and urgency of the requested procedure(s). Bird noted that pages 26 and 27 of the WPATH guideline outline what should be done in the mental health assessment. Askini stated that she felt that adding such wording to the guideline was too detailed and redundant to WPATH requirements, which are followed by most professionals in the field. Committee members expressed concern that such major surgery should be authorized without specifying what the mental health evaluation should provide.

General consensus was reached that cross-sex hormone therapy and sex reassignment surgery should be added to the gender dysphoria line. The surgical codes required to be added to this line were not discussed. The scoring of the line was tabled. Staff will work on refining the gender dysphoria guideline, and will send out to committee members for comments and input prior to the packet being sent out.

Actions:

1) HERC staff will work with experts to revise the proposed guideline regarding gender dysphoria. This guideline will be sent to the VbBS members via email prior to the next meeting for feedback.
2) Discussion of adding cross-sex hormone therapy and sex reassignment surgery to the gender dysphoria line and rescoring this line was tabled to the August VbBS meeting

- **Topic: Bariatric surgery guideline clarification**

Discussion: Smits introduced a summary of suggested modifications to clarify the bariatric surgery guideline. There was some discussion about eliminating the requirement for Centers of Excellence, as CMS has removed this requirement. The group decided to continue to require COE at this time.

MOTION: To approve the modified guideline as presented. CARRIES 5-0.

Actions:

1) The bariatric surgery guideline was modified as shown in Appendix B

- **Topic: Rehabilitation guideline clarifications**

Discussion: Smits summarized concerns that have been brought to HERC staff by the OHP Medical Directors regarding proposed changes to the rehabilitation guideline approved in May, 2014. Holly Jo Hodges testified that the medical directors are requesting guidance on the number of PT/OT visits that should be approved for a given condition and how to monitor whether the patient is improving with therapy. Staff noted that it was beyond the capability of the HERC

and HERC staff to determine the number of visits that should be authorized for various individual conditions, given the vast amount of literature that would need to be reviewed. Additionally, there is very poor evidence for the effectiveness of PT/OT for most conditions. Staff noted that the cost of PT/OT with the current guideline restriction in place (unlimited care for 3 months, then 2 visits a year for adults) was approximately $2 PMPM.

HERC staff was directed to propose guideline revisions that include a total number of visits allowed per year (for all conditions), such as 30 visits per year, with additional visits allowed in case of significant change in status, such as surgery, new major diagnosis, or major developmental change. Staff was directed to send this proposed guideline to the medical directors for comment at their July meeting.

Actions:
1) Tabled for further discussion in August, 2014

- **Topic: Lymphedema guideline**

Discussion: Smits briefly introduced a summary of suggested changes to the lymphedema guideline. The recommended changes referenced the rehabilitation guideline, which are still being discussed. Staff requested that this topic be brought back in August to be discussed after the rehabilitation guideline.

Actions:
1) Tabled for further discussion in August, 2014

- **Topic: Treatment of hepatitis C**

Discussion: Livingston presented an issue summary. Dr. Atif Zaman, a hepatologist at OHSU provided expert input. He testified that due to the side effects of interferon, none of his patients are interested in interferon treatment. He argued that the focus should be on who needs treatment now versus who can wait. He is having meetings with CareOregon and other payors to try to come up with appropriate limitations. As the new treatments emerge, ongoing decisions will have to be made about prioritizing appropriate candidates for treatment.

He answered questions about the progression of the disease and encouraged coverage of patients with stage 3 or stage 4 fibrosis. However, by the time someone reaches stage 4, they will need monitoring for liver cancer every 6 months. It was reiterated that most patients will never progress to cirrhosis.

Advocates argued that treating would result in fewer liver transplants and thus be cost-saving. However, it was clarified the limiting factor of liver transplantation is

the waitlist for available donor organs. Therefore if liver transplants due to complications of hepatitis C, those organs will still be used to treat other patients, which will not result in a true cost savings to the system, but will provide additional health benefits to the population

Public testimony was received from Larren Sandt representing Caring Ambassadors. A conflict of interest of unrestricted funding grants from pharmaceutical companies was disclosed. She recommended coverage. There are active studies being done about real world outcomes. Next, BJ Cavenaugh, Cascade AIDS project testified. He also disclosed a conflict of interest that his organization receives unrestricted funding from pharmaceutical companies. He argued it was important to treat, especially those with HIV, because of their higher rate of comorbidities and poorer health outcomes.

Subcommittee members discussed the problem that the budget is a zero sum game. Paying for hepatitis C trugs will take away from other health care services, or if more money is allocated, then either taxes would need to go up or cuts would be made to such areas as education or public safety. The concern was stated that as long as health plans keep paying for it, the drug companies are going to continue charging these increasingly high prices.

It was agreed that the prioritized list gives Oregon a unique opportunity to base coverage on value. Several members suggested that Oregon attempt to negotiate with manufacturers based on the value to the state.

Testimony was received by Ashlen Strong, JD, MPH of Health Share of Oregon. She stated if they treated hepatitis C with the newer drugs, it would cost them 68 million dollars compared to a 72 million dollar total drug budget. It would entirely wipe out the pharmaceutical budget for their CCO. They also have 60,000 new members since January.

Health Share offered a consensus recommendation to convene 2 panels:

1) The first to include clinical experts (including hepatology, infectious disease) to develop prescribing criteria to ensure patients who need the drug right now can get it
2) The second comprised of health economists to determine the price at which Sovaldi is sustainable and value-based for OHP

She stated that health care organizations have been charged with the goal of improving the proposition of health care. It was stated it is time to ask pharmaceutical companies to step up the plate.

The question was asked by subcommittee members why CCOs can't negotiate price. The answer was, without competition, the company doesn't have to negotiate the price.

Health Share has calculated that the total cost to fly someone to Egypt, cover their stay and physician visits and the cost of the drug is about $3,000, compared to $84,000 for the drug treatment alone in the U.S.

Subcommittee members expressed interest in knowing more about the net costs of treatment and a possibility of a health economic analysis.

Actions:

1) Staff will bring back this issue to the August meeting for more discussion
2) Staff will obtain information about a proposal for a health economic analysis
3) Staff will confer with the P&T Committee about community standard discussions

- **Public Comment:**
  No additional public comment was received

- **Issues for next meeting:**
  1) Unilateral vs bilateral hearing loss coverage in adults
  2) Gender dysphoria
  3) Hepatitis C treatments
  4) Self-injurious behavior guideline
  5) Standardized tools for ABA assessment
  6) Rehabilitation guideline
  7) Lymphedema guideline
  8) Botulinum toxin therapy for various indications
  9) Electronic tumor treatment fields
  10) New list of items reviewed but not included in the Prioritized List

- **Next meeting:**
  Meridian Park Health Education Center, Tualatin, OR Room 117B&C

- **Adjournment:**
  The meeting was adjourned at 1:20 PM.

Appendix A

New Guideline for implementation on 10/1/14

GUIDELINE NOTE XXX, BONE ANCHORED HEARING AIDS

Lines 317, 450

Bone anchored hearing aids (BAHA, CPT 69714, 69715) are included on these lines when the following criteria are met:

1) The patient is age 5 years or older
2) Treatment is for unilateral severe to profound hearing loss when the contralateral ear has normal hearing
3) Traditional air amplification hearing aids and contralateral routing of signal (CROS) hearing aid systems are not indicated or have been tried and are found to be not effective.
4) Implantation is unilateral.

Use of BAHA for treatment of tinnitus is not covered.

GUIDELINE NOTE XXX, ELECTROCONVULSIVE THERAPY (ECT)

Line 7,26,29

Electroconvulsive therapy (ECT; CPT 90870) is included on these lines for the treatment of major depressive disorder, bipolar disorder, schizophrenic disorder, or schizoaffective disorder when one or more of the following conditions are present:

1) Acute suicidality with high risk of acting out suicidal thoughts
2) Psychotic features
3) Rapidly deteriorating physical status due to complications from the depression, such as poor oral intake
4) Catatonia
5) History of poor response to multiple adequate trails of medications and/or combination treatments, or the patient is unable or unwilling to comply with or tolerate side effects of available medications, or has a co-morbid medical condition that prevents the use of available medications
6) History of good response to ECT during an earlier episode of the illness
7) The patient is pregnant and has severe mania or depression, and the risks of providing no treatment outweigh the risks of providing ECT

The frequency and number of treatments need to be determined by the severity of illness and by the relative benefits and risks of ECT treatment. During the course of ECT, it is important to monitor therapeutic responses and adverse effects of treatment. Continuation treatment of patients who have responded to ECT consists of treatment with antidepressant medications and/or a tapering schedule of ECT treatments. Continuation treatment reduces the risk of relapse and should be offered to all patients who respond to ECT. Continuation ECT treatments should be tapered and discontinued as the patient's clinical condition allows. Maintenance treatment with ECT is indicated to prevent recurrence of depression in patients whose remission of symptoms cannot be maintained with pharmacologic antidepressant treatment.

Appendix B

Modified guidelines

For implementation on 10/1/14

GUIDELINE NOTE 102, ~~NON-PHARMACOLOGIC INTERVENTIONS FOR TREATMENT-RESISTANT DEPRESSION~~ REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

Line 7

Repetitive transcranial magnetic stimulation (CPT 90867-90868) ~~and electroconvulsive therapy (CPT 90870) are~~ is covered only after failure of at least two antidepressants.

GUIDELINE NOTE 8, BARIATRIC SURGERY

Lines 30,594

Bariatric surgery ~~for obesity~~ is included ~~on Line 30 TYPE II DIABETES MELLITUS, and Line 594 OBESITY (ADULT BMI ≥ 30, CHILDHOOD BMI ≥ 95 PERCENTILE)~~ under the following criteria:

A) Age ≥ 18
B) The patient has
   1) a BMI ≥ 35 with co-morbid type II diabetes for inclusion on Line 30 TYPE II DIABETES MELLITUS; OR
   2) BMI >=35 with at least one significant co-morbidity other than type II diabetes (e.g., obstructive sleep apnea, hyperlipidemia, hypertension) or BMI >= 40 without a significant co-morbidity for inclusion on Line 594 OBESITY (ADULT BMI ≥ 30, CHILDHOOD BMI ≥ 95 PERCENTILE)

   ~~For inclusion on Line 30: BMI ≥ 35 with co-morbid type II diabetes. For inclusion on Line 594: BMI >=35 with at least one significant co-morbidity other than type II diabetes (e.g., obstructive sleep apnea, hyperlipidemia, hypertension) or BMI >= 40 without a significant co-morbidity.~~
C) No prior history of Roux-en-Y gastric bypass or laparoscopic adjustable gastric banding, unless they resulted in failure due to complications of the original surgery.
D) Participate in the following four evaluations and meet criteria as described.
   1) Psychosocial evaluation: (Conducted by a licensed mental health professional)
      a) Evaluation to assess potential compliance with post-operative requirements.
      b) Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of nicotine or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within one month of the surgery to confirm abstinence from nicotine and illicit drugs.
      c) No mental or behavioral disorder that may interfere with postoperative outcomes[1].

Appendix B

d) Patient with previous psychiatric illness must be stable for at least 6 months.

2) Medical evaluation: (Conducted by OHP primary care provider)
   a) Pre-operative physical condition and mortality risk assessed with patient found to be an appropriate candidate.
   b) Optimize medical control of diabetes, hypertension, or other co-morbid conditions.
   c) Female patient not currently pregnant with no plans for pregnancy for at least 2 years post-surgery. Contraception methods reviewed with patient agreement to use effective contraception through 2nd year post-surgery.
3) Surgical evaluation: (Conducted by a licensed bariatric surgeon associated with program[2])
   a) Patient found to be an appropriate candidate for surgery at initial evaluation and throughout period leading to surgery while continuously enrolled on OHP.
   b) Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure[3] and understands the many potential complications of the surgery (including death) and the realistic expectations of post-surgical outcomes.
4) Dietician evaluation: (Conducted by licensed dietician)
   a) Evaluation of adequacy of prior dietary efforts to lose weight. If no or inadequate prior dietary effort to lose weight, must undergo six-month medically supervised weight reduction program.
   b) Counseling in dietary lifestyle changes

E) Participate in additional evaluations:
   1) Post-surgical attention to lifestyle, an exercise program and dietary changes and understands the need for post-surgical follow-up with all applicable professionals (e.g. nutritionist, psychologist/psychiatrist, exercise physiologist or physical therapist, support group participation, regularly scheduled physician follow-up visits).

[1] Many patients (>50%) have depression as a co-morbid diagnosis that, if treated, would not preclude their participation in the bariatric surgery program.

[2] All surgical services must be provided by a program with current certification by the ~~American College of Surgeons (ACS) or the American Society for Metabolic and Bariatric Surgery (ASMBS),~~ Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) or in active pursuit of such certification with all of the following: a dedicated, comprehensive, multidisciplinary, pathway-directed bariatric program in place; hospital to have performed bariatrics > 1 year and > 25 cases the previous 12 months; trained and credentialed bariatric surgeon performing at least 50 cases in past 24 months; qualified bariatric call coverage 24/7/365;appropriate bariatric-grade equipment in outpatient and inpatient facilities; appropriate medical specialty services to complement surgeons' care for patients; and quality improvement program with prospective documentation of surgical outcomes. If the program is still pursuing MBSAQIP ~~ACS or ASMBS~~ certification, it must also restrict care to lower-risk OHP patients including: age < 65 years; BMI < 70; no major elective revisional surgery; and, no extreme medical comorbidities (such as wheel-chair bound, severe cardiopulmonary compromise, or other excessive risk). All programs must agree to yearly submission of outcomes data to Division of Medicaid Assistance Programs (DMAP).

[3] Only Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding and sleeve gastrectomy are approved for inclusion.

[4] ~~The patient must meet criteria #1, #2, and #3, and be referred by the OHP primary care provider as a medically appropriate candidate, to be approved for evaluation at a qualified bariatric surgery program~~.

Appendix B

Implementation date to be determined by OHA Leadership

GUIDELINE NOTE 75, APPLIED BEHAVIOR ANALYSIS FOR AUTISM SPECTRUM DISORDER

Line 313

Applied behavioral analysis (ABA), including early intensive behavioral intervention (EIBI), represented by CPT codes 0359T-0374T, is included on line 313 for the treatment of autism spectrum disorders.

ABA services are provided in addition to any rehabilitative services (e.g. physical therapy, occupational therapy, speech therapy) included in guideline note 6, REHABILITATIVE THERAPIES that are indicated for other acute qualifying conditions.

Individuals ages 1-12

Intensive interventions

Specifically, EIBI (for example, UCLA/Lovaas or Early Start Denver Model), is included on this line.

For a child initiating EIBI therapy, EIBI is included for up to six months. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives (objectives should be achieved as a result of the EIBI, over and beyond gains that would be expected to arise from maturation alone) using a standardized, multimodal assessment, no more frequently than every six months. Examples of such assessments include Vineland, IQ tests (Mullen, WPPSI, WISC-R), language measures, behavioral checklists (CBCL, ABC), and autistic symptoms measures (SRS).

The evidence does not lead to a direct determination of optimal intensity. Studies of EIBI ranged from 15-40 hours per week. Through Oregon's Senate Bill 365, other payers are mandated to cover a minimum of 25 hours per week of ABA. There is no evidence that increasing intensity of therapy yields improves outcomes. Studies for these interventions had a duration from less than one year up to 3 years.

Less intensive ABA-based interventions

If EIBI is not indicated, has been completed, or there is not sufficient progress toward multidimensional goals, then less intensive ABA-based interventions (such as parent training, play/interaction based interventions, and joint attention interventions) are included on this line to address core symptoms of autism and/or specific problem areas. Initial coverage is provided for six months. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives, with demonstration of medical appropriateness and/or emergence of new problem behaviors.

Appendix B

Effective interventions from the research literature had lower intensity than EIBI, usually a few hours per week to a maximum of 16 hours per week, divided into daily, twice-daily or weekly sessions, over a period of several months.

Parent/caregiver involvement

Parent/caregiver involvement and training is recommended as a component of treatment.

Individuals ages 13 and older

Intensive ABA is not included on this line.

Targeted ABA-based behavioral interventions to address problem behaviors, are included on this line. The quality of evidence is insufficient to support these interventions in this population. However, due to strong caregiver values and preferences and the potential for avoiding suffering and expense in dealing with unmanageable behaviors, targeted interventions may be reasonable. Behaviors eligible for coverage include those which place the member at risk for harm or create significant daily issues related to care, education, or other important functions. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives, with demonstration of medical appropriateness and/or emergence of new problem behaviors.

Very low quality evidence is available to illustrate needed intensity and duration of intervention. In the single-subject research design literature, frequency and duration of interventions were highly variable, with session duration ranging from 30 seconds to 3 hours, number of sessions ranging from a total of three to 8 times a day, and duration ranging from 1 to 20 weeks. These interventions were often conducted in inpatient or residential settings and studies often included patients with intellectual disabilities, some of which were not diagnosed with autism.

Parent/caregiver involvement and training is encouraged.

Section 2.0

Previously Discussed Items

Treatment of Hepatitis C with Newer Agents

Question: As new treatment options have emerged for Hepatitis C, what guideline adjustments need to be made?

Question source: Medical Directors from CCOs

Issue: The CCO Medical Directors have expressed many concerns about the hepatitis C drugs which have recently become available and the population impact of the tremendous cost that this represents to the plans. These concerns are reiterated through national media and professional discussions, and the Medicaid Evidence-based Decisions project collaboration of 12 states. The CCO Medical Directors have asked HERC to evaluate the prioritization of hepatitis C treatments as well as coverage criteria. The HERC last looked at Hepatitis C treatment and guidelines in 1999.

Comments from one medical director:

> "By one calculation, if we took all the dollars we currently spend on Pharmacy in Oregon in Medicaid and dedicated them solely to Hep C, we would only be able to treat 25% of the currently diagnosed Hep C population… with no money left for anything else. If this is even close to true, the consequences are enormous. I believe someone said that California Medicaid plans have said they will not cover the drug until there is some way to pay for it."

At the national level discussions abound:

- National economists are discussing this being a "tipping point" for pharmaceutical pricing. Concern that this will set the bar on pricing of these types of drugs, and if allowed to proceed, lead to even higher pricing.
- Challenges for states and purchasers of healthcare to afford the new treatment options.
- Discussions of how drug prices could be better negotiated, issues of transparency of pricing
- Discussions of whether to cover the new treatments
- Discussions of potentially significantly limiting coverage

Costs:

- About 5,600 OHP clients are known to have hepatitis C; there are likely more than 13,000 additional clients who do not know they are infected
- The new drug sofosbuvir is $1,000 a pill.
- Expected costs to OHP (FFS +CCO) = $168 million over the next 12 months (assuming only treating those with stage 3 and 4 disease which is approximately 30% of the hep C population)
- Costs to all state programs are estimated to be approximately $250 million, with current P&T restrictions in place

VbBS process so far and interim updates

The first discussion including the review of evidence occurred at the June VbBS meeting. Expert testimony from Atif Zaman and public testimony was heard.

The Pharmacy and Therapeutics Committee has updated and revised its PA criteria for the treatment of hepatitis C, following a drug review and after considering the "community standard" that was developed and submitted by a group of Oregon hepatologists. At their July 31, 2014 meeting, the P&T committee finalized their PA criteria, incorporating "community standard" language, and adopted a "readiness to refer assessment" with the goal of having primary care physicians discuss a variety of issues related to readiness to treat with their patients.

Since that meeting, CCO Medical directors shared that if hepatitis C treatment with low value agents is prioritized below the line, there may be significant numbers of requests using the comorbidity rule, and there is concern that patients who may be approved through this process should be good candidates.

Clinical background from MED 2014:

> "Hepatitis C is estimated to affect between 1% and 2% of the US population. Although up to one quarter of those infected can clear the virus spontaneously, in those remaining infected it can progress over the span of 10 to 30 years or more to cirrhosis, liver failure, HCC and death. The genotype HCV-1 accounts for about three-quarters of cases in the US.

Table 1. Progression of Hepatitis C Virus Infection (CDC 2014)

Condition	Percentage of Patients Who Develop Condition
Chronic HCV infection	75% to 85%
Chronic liver disease	60% to 70%
Cirrhosis over 20 to 30 years	5% to 20%
Death from cirrhosis or liver cancer	1% to 5%

Table 2. Standard of Care Treatment Regimens (US Department of Veterans Affairs 2013)

Genotype	Treatment	Approximate SVR24 Rate
HCV-1	Double therapy PEG-IFN alfa-2a or alfa-2b weekly + RBV daily for up to 48 weeks	45%
	Triple therapy PEG-INF alfa-2a OR alfa-2b weekly + RBV daily for up to 48 weeks depending on treatment response and either BOC or TVR. BOC is added during weeks 8 to 32 depending on treatment response and TVR is given with PEG-INF and RBV during first 12 weeks of treatment.	65% to 70%
HCV-2	PEG-INF weekly + RBV daily for up to 24 weeks	75%
HCV-3	PEG-INF weekly + RBV daily for up to 24 weeks	75%

Current List Placement:

Line: **205**
Condition: CHRONIC HEPATITIS; VIRAL HEPATITIS (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-9: 070.0-070.1,070.20-070.9,571.40-571.49,571.8-571.9,573.0
CPT: 96150-96154,98966-98969,99051,99060,99070,99078,99201-99239,99281-99360, 99366,99374,99375,99379-99412,99429-99449,99471-99476,99487-99496,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463

Line: **333**
Condition: CIRRHOSIS OF LIVER OR BILIARY TRACT; BUDD-CHIARI SYNDROME; HEPATIC VEIN THROMBOSIS; INTRAHEPATIC VASCULAR MALFORMATIONS; CAROLI'S DISEASE (See Coding Specification Below) (See Guideline Note 76)
Treatment: LIVER TRANSPLANT, LIVER-KIDNEY TRANSPLANT
ICD-9: 277.03,453.0,571.2,571.5-571.6,573.5,751.62,774.4,777.8,996.82,V59.6
CPT: 47133-47147,50300,50323-50365,76776,86825-86835,96150-96154

Liver-kidney transplant only covered for a documented diagnosis of Caroli's disease (751.62).

Line:	**340**
Condition:	CANCER OF LIVER (See Guideline Notes 7,11,12,33,64,65,76,78)
Treatment:	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-9:	155.0,155.2,197.7,235.3,284.11,V10.07,V58.0,V58.11
CPT:	32553,36260-36262,37243,37617,43274-43277,47120-47130,47370,47371,47380-47382,47562,47600-47620,47711,47712,48150,49411,77014,77261-77295,77300-77327,77331-77370,77402-77417,77424-77432,77469,77470,79005-79440,96150-96154,96405,96406,96420-96450,96542-96571,98966-98969,99051,99060,99070,99078,99201-99239,99281-99360,99366,99374,99375,99379-99412,99429-99449,99471-99476,99487-99496,99605-99607
HCPCS:	G0396,G0397,G0406-G0408,G0425-G0427,G0463,S9537

Line:	**360**
Condition:	ALCOHOLIC FATTY LIVER OR ALCOHOLIC HEPATITIS, CIRRHOSIS OF LIVER (See Guideline Notes 64,65,76,77)
Treatment:	MEDICAL THERAPY
ICD-9:	571.0-571.3,571.5-571.6,572.2-572.3,572.8,573.8
CPT:	37182,37183,96150-96154,97802-97804,98966-98969,99051,99060,99070,99078,99201-99239,99281-99360,99366,99374,99375,99379-99412,99429-99449,99471-99476,99487-99496,99605-99607
HCPCS:	G0396,G0397,G0406-G0408,G0425-G0427,G0463

Line:	**644**
Condition:	OTHER VIRAL INFECTIONS, EXCLUDING PNEUMONIA DUE TO RESPIRATORY SYNCYTIAL VIRUS IN PERSONS UNDER AGE 3 (See Guideline Notes 61,64,65)
Treatment:	MEDICAL THERAPY
ICD-9:	051.01-051.02,052.0-052.9,055.0-055.2,055.71-055.9,056.79-056.9,057.0-057.9,058.10-058.12,059.00-059.9,072.0-072.3,072.71-072.9,074.0-074.1,074.20-074.8,078.0,078.2,078.4-078.7,078.81-078.89,079.0-079.4,079.50-079.6,079.83-079.99,480.0-480.9
CPT:	98966-98969,99051,99060,99070,99078,99201-99239,99281-99360,99366,99374,99375,99379-99412,99429-99449,99471-99476,99487-99496,99605-99607
HCPCS:	G0396,G0397,G0406-G0408,G0425-G0427,G0463

Evidence Review

MED, 2014

1. Rapid evidence review for the Medicaid Evidence based Decisions project, a collaboration of 13 states
2. 10 studies in 7 articles – majority non-comparative, 9 with a high risk of bias. 2 were comparative of sofosbuvir for HCV-2 and HCV-3 infection (neither comparing against standard treatment). No comparative studies for HCV-1.
3. Results of published studies:

FDA Approved Treatment Regimens and Response Rates					
Genotype	**Treatment**	**SVR12**	**Relapse**	**# of Studies (Study name)**	**Study N**
HCV-1	SOF+PEG+RBV 12 w	89%	4% to 8.6%	2 (NEUTRINO, ATOMIC)	379
	SOF+RBV 24 w	68%	28%	1 (Osinusi, NIH Study)	60
HCV-2	SOF+RBV 12 w	82% to 95%	5% to 18%	4 (FISSION, FUSION, POSITRON, VALENCE)	1051
HCV-3	SOF+RBV 24 w	84%	14%	1 (VALENCE)	250

MED, 2014 (Cont'd)

4. Potential concerns about the evidence
    a. Relapse rate may be substantial ranging from 5% to 28%, even among patients who are fully treated with these regimens.
    b. Adverse effects not well studied
5. Patient exclusion criteria from published sofosbuvir trials
    a. Age less than 18 years
    b. HIV or HBV co-infection
    c. Significant alcohol or drug use within the past 12 months
    d. Excessive current alcohol use
    e. Significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, significant renal disease (estimated glomerular filtration rate less than 60mL/min)
6. <u>Conclusions: Based on the usual standards of comparative effectiveness research, currently available studies do not provide sufficient evidence for the routine use of sofosbuvir-containing regimens for the treatment of Hepatitis C infection.</u>
7. If coverage is chosen, potential criteria to guide the use of sofosbuvir that are consistent with current published studies are listed below with several factors to consider.
    a. Limit use to genotypes 2 and 3, until comparative trials available for genotype 1.
    b. Do not use sofosbuvir as monotherapy.
    c. Limit use to patients who failed or did not tolerate current standard of care regimens or in whom PEG is contraindicated.

d. Confirm degree of liver fibrosis or cirrhosis prior to authorizing treatment.
e. Treat only patients at greatest risk of progressing to cirrhosis (e.g., Metavir fibrosis stage greater than or equal to 2 and additional factors increasing risk of progression to cirrhosis [e.g., hepatic steatosis, men, older, elevated serum alanine transaminase, greater hepatic inflammation]).
f. Consider use for patients with HIV or HBV co-infection or those post-liver transplant carefully until comparative trials are available.
g. Exclude use in patients with alcohol or drug use within the past year, significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, renal disease (estimated glomerular filtration rate less than 60mL/min).
h. Ensure that patients who start therapy are closely tracked to optimize full treatment and follow-up, including prevention of re-infection.

Cost-Effectiveness

ICER, 2014

1. Comparative clinical effectiveness and value of sofosbuvir and simeprevir
    a. Technology assessment
    b. The costs for initial treatment regimens including sofosbuvir or simeprevir: $88,000 to > $175,000 per patient. Estimate for CA that replacing current care with simeprevir and sofosbuvir-based regimens would raise drug expenditures by $22-33 billion in a single year
    c. Incremental cost required to achieve one additional SVR with newer treatment regimens is greater than $300,000.
    d. Roundtable discussion, with the following policy implications:
        i. Despite having voted that the evidence is adequate to demonstrate the superior clinical effectiveness of the new drugs in most patient subpopulations, the CTAF Panel emphasized in discussion that serious limitations in the evidence base remain.
        ii. For most patient subpopulations, the CTAF Panel found the new drug treatments for hepatitis C to represent a "low value" due to the magnitude of the potential impact on health care budgets of treating large numbers of patients with these high-priced drug regimens.
        iii. 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.
        iv. In recognition of limitations of the clinical infrastructure for initiating treatment among a very large patient population,

patients, physicians, and payers should work together to encourage informed, shared decision-making about whether patients need to initiate treatment immediately or whether they are well enough to postpone treatment.

v. Given the limited number of experienced treating clinicians, the balance of risks and benefits for immediate treatment of patients without significant liver damage, and the financial impact of current high prices, it is reasonable to consider prioritization of treatment by level of liver fibrosis.
vi. 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 developing prior authorization criteria that
    1. require patient commitment to and compliance with the treatment regimen,
    2. utilize "futility rules" that define when a lack of early response should lead to discontinuation of treatment, and
    3. require that prescriptions of simeprevir and sofosbuvir be written by specialist physicians with experience treating patients with hepatitis C.
vii. Although there is very little evidence regarding the off-label use of simeprevir and sofosbuvir in combination to treat interferon-ineligible genotype 1 patients, payers may wish to consider covering these drugs on a limited basis for certain patients needing immediate treatment.
viii. Specialty society clinical guidelines should be developed using best practices**,** including ratings of strength of evidence, transparency regarding the role of various organizations involved in guideline development, and full transparency regarding potential conflicts of interest of individual guideline committee members, with limits on the proportion of committee members who receive direct or indirect financial support from manufacturers.
ix. Further evidence should be generated to evaluate more fully the comparative clinical effectiveness and value of these new treatment regimens for patients with hepatitis C.

NICE

NICE has released a statement saying that they will not pay for the new expensive drugs until there is a further economic analysis and price discussions.

Guidelines

American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) Hepatitis C Guidance (AASLD 2014)

1. Only guideline on treatment
2. Methodologic quality: Poor
    a. Multiple conflicts of interest. Unclear how these were addressed.
3. Includes 27 recommended treatment regimens based on HCV genotype, prior treatment, and co-morbid conditions and nine alternative treatment regimens. All 27 recommended regimens include sofosbuvir except in patients with severe renal impairment.
4. It was published without key sections (coming soon) on:
    • In whom and when to initiate treatment;
    • Monitoring patients who are on or have completed therapy

Recommendations and considerations by others

Veterans Administration

Table 2. Considerations for Selecting Chronic HCV-Infected Patients for Treatment

Liver Disease Category	Considerations	Evidence Grade
No cirrhosis	Consider waiting until better treatments are available. Future treatments are likely to have fewer side effects, shorter duration, higher efficacy, and lower pill burden.	B-III
Compensated cirrhosis	Treatment is recommended for appropriate patients with compensated cirrhosis. Refer to Table 13, "Diagnosis of Compensated Cirrhosis for the Purpose of Identifying Treatment Candidates," for guidance on diagnosis of cirrhosis.	B-III
Decompensated cirrhosis, defined by one of the following: CTP score ≥7, ascites, hepatic encephalopathy, variceal bleeding or jaundice	Treatment options are limited and the risk versus benefits of treatment must be carefully considered. Consult a specialist with experience in management of HCV.	A-II
Hepatocellular carcinoma (HCC)	Consider treatment for patients in whom HCC treatment is potentially curative, including selected patients on the liver transplant list.	A-II
Post-transplant recipients with cirrhosis	Risk versus benefits of treatment must be carefully considered. Consult a specialist with experience in management of HCV.	A-II
Patients with serious extra-hepatic manifestations of HCV	Patients with serious extra-hepatic manifestations of HCV, such as leukocytoclastic vasculitis, membranoproliferative glomerulonephritis, or symptomatic cryoglobulinemia despite mild liver disease should receive treatment as soon as possible. Consult a specialist with experience in management of HCV.	A-III

CTP = Child-Turcotte-Pugh

Input from Oregon metro area hepatologists

David Labby of Health Share of Oregon worked with a group of hepatologists self-identified as the Hepatitis C Clinical Advisory Group who developed a "community standard" for treatment. They decided to prioritize the group whom they deemed the most urgent to treat. In the face of a lack of evidence and limited numbers of people who may be able to be treated, they came to a consensus on those groups they felt were most likely to benefit.

Participants included clinicians specializing in hepatology in the Portland metropolitan area: Atif Zaman and Ken Ingram (OHSU); Ken Flora, Kent Benner, Adrian Davies, Jeremy Holden (Oregon Clinic); Brian Willis, Jennifer Urquhart, Jason Snider (Kaiser Permanente).

These guidelines are based on agents and evidence available as of July 2014. They will be reviewed and updated when new agents and new evidence are available over the next 6-12 months.

HCV patients who need treatment with Sovaldi in next 6-12 months in order to avoid poorer outcomes if treatment is delayed include:

1. Patients with the extrahepaitic manifestations of hepatitis C infection listed below who have formal documentation from a relevant specialist that their condition is HCV related.
    a. Vasculitis
    b. Glomerulonephritis
    c. Cryoglobulinemia
    d. Lymphoma

2. HIV/HCV co-infected patients with cirrhosis (Stage 4 disease).

3. HCV infection in the transplant setting (approval needs to be cleared by the OHSU Liver Transplant Program)
    a. Listed patients who it is essential to eradicate the virus in order to realistically prevent a transplant or it is critical to prevent recurrent HCV infection post-transplant
    b. Post-transplant patients with Stage 4 fibrosis
    c. Post-transplant patients with fibrosing cholestatic hepatitis due to HCV infection

4. Cirrhotic (Stage 4) patients without ongoing progressive decompensation
    a. MELD between 8-11
    b. MELD>11 patients if cleared for treatment by the HCV Advisory Panel

5. Other scenarios not included can be brought to the Advisory Group on a case by case basis.

6. In all cases, expected survival from non-HCV associated morbidity should be >5 years.

Oregon Pharmacy & Therapeutics Committee

- The State's Pharmacy &Therapeutics (P&T) Committee has developed prior authorization criteria to restrict coverage of the new drugs to those fee-for-service OHP clients who have hepatitis C with advanced liver disease. They incorporated criteria based on their drug class review and also on the community standard guideline.
- Requirements include:
    - Advanced liver disease (stage 4 fibrosis) or proof of cirrhosis without ongoing decompensation and expected survival from other morbidity of > 5 years
    - Prescription by or in consultation with a hepatologist or gastroenterologist with experience in Hepatitis C
    - Patients either need to have:
        - Extrahepatic manifestations of hepatitis C, including
            - Vasculitis
            - Glomerulonephritis
            - Cryoglobulinemia
            - Lymphoma
        - HIV/HCV coinfection
        - Be pre/post liver transplant
    - Have screening performed by primary care clinicians about discussions that should happen as part of the referral process in the "Readiness to Refer Assessment"
    - Exclusions for a marijuana use, alcohol abuse or IV drug use in the prior 6 months, or significant renal impairment

Summary

Hepatitis C is a very slowly progressive disease. Most patients who have it will never progress to cirrhosis. While the new treatment options of these new DAAs are being put forth as having great promise in treating this disease, there is still insufficient evidence to support use of these therapies and the potential cost to OHP is extraordinary.

The MED report discussed the evidence available as well as making some potential suggestions for limitations on coverage.

The metro Portland area community "Hepatitis C Clinical Advisory Group" developed a list of individuals whom they felt would be the most urgent to treat based on likelihood of disease progression.

A combination of the "community standard" recommendations and the available evidence have been developed into Prior Authorization criteria by the Pharmacy & Therapeutics Committee.

CCO Medical Directors have continued to support language in the Prioritized List discussing what type of candidates are the most appropriate to undergo treatment in terms of their likelihood of success.

HERC Staff Recommendations:

Based on the existing evidence as summarized in the May 2014 MED report, and the low value of these new DAA agents HERC staff recommends the following:

1. Add the hepatitis C ICD-9 and ICD-10 codes to Line 644, OTHER VIRAL INFECTIONS, EXCLUDING PNEUMONIA DUE TO RESPIRATORY SYNCYTIAL VIRUS IN PERSONS UNDER AGE 3

ICD-9 Code	Description
070.44	Chronic hepatitis C with hepatic coma
070.49	Other specified viral hepatitis with hepatic coma
070.51	Acute hepatitis C without mention of hepatic coma
070.54	Chronic hepatitis C without mention of hepatic coma
070.59	Other specified viral hepatitis without mention of hepatic coma
070.6	Unspecified viral hepatitis with hepatic coma
070.70	Unspecified viral hepatitis C without hepatic coma
070.71	Unspecified viral hepatitis C with hepatic coma
070.9	Unspecified viral hepatitis without mention of hepatic coma
571.40	Chronic hepatitis, unspecified
571.41	Chronic persistent hepatitis
571.49	Other chronic hepatitis
571.8	Other chronic nonalcoholic liver disease
571.9	Unspecified chronic liver disease without mention of alcohol
571.5	Cirrhosis of liver without mention of alcohol

ICD-10 Code	Description
B18.2	Chronic viral hepatitis C
B18.8	Other chronic viral hepatitis

B18.9	Chronic viral hepatitis, unspecified
B19.0	Unspecified viral hepatitis with hepatic coma
B19.20	Unspecified viral hepatitis C without hepatic coma
B19.21	Unspecified viral hepatitis C with hepatic coma
B19.9	Unspecified viral hepatitis without hepatic coma
K73.0	Chronic persistent hepatitis, not elsewhere classified
K73.1	Chronic lobular hepatitis, not elsewhere classified
K73.2	Chronic active hepatitis, not elsewhere classified

K73.8	Other chronic hepatitis, not elsewhere classified
K73.9	Chronic hepatitis, unspecified
K74.0	Hepatic fibrosis
K74.1	Hepatic sclerosis
K74.2	Hepatic fibrosis with hepatic sclerosis
K74.60	Unspecified cirrhosis of liver
K74.69	Other cirrhosis of liver

2. Add a guideline:

GUIDELINE NOTE XXX, HEPATITIS C TREATMENT

Lines 205, 333, 340, 360, 644

Pharmacotherapy for hepatitis C is included on Lines 205 and 360 only when using prescription drugs receiving FDA approval for the treatment of hepatitis C prior to 2012, otherwise pharmacotherapy for hepatitis C is included on Line 644.

For these newer pharmacotherapies (2012 and after), patients must meet criteria for treatment as defined by the Pharmacy and Therapeutics Committee according to OAR 410-121-0040 as found in Prior Authorization Approval Criteria Guide relating to the treatment of hepatitis C available at http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/pa-criteria.pdf. Treatment under the comorbid rule should only be considered with comorbidities described in the Pharmacy and Therapeutics Committee criteria.

Furthermore, candidates for the use of oral direct acting antivirals that obtained FDA approval during or after 2012 (CHOOSE SOME OR ALL):

A. MUST ALSO:
    1. Demonstrate early responsiveness to treatment for treatment to be continued
    2. Be determined to be appropriate candidates for treatment based on demonstrated ability to comply with treatment and demonstrate ongoing compliance

3. Have appropriate control of unrelated comorbid disease (e.g. psychosis, relapsed major depression, uncontrolled hypertension)
4. Be closely tracked to optimize full treatment and follow-up, including prevention of re-infection.

B. MUST NOT:
1. Have had previous treatment with an oral direct acting antiviral that was FDA approved after 2012
2. Be using sofosbuvir or simeprevir as monotherapy
3. Have had alcohol or drug use within the past 6 OR 12 months
4. Have decompensated liver disease
5. Have severe comorbidities that may affect the long-term utility of therapy

3. Revisit hepatitis C treatments in early 2015 once the new winter DERP report has been completed, the NICE report is finalized, and additional economic analyses have been released.

Sofosbuvir for the Treatment of Hepatitis C and Evaluation of the 2014 American Association for the Study of Liver Diseases Treatment Guidelines

May 2014

Center for Evidence-based Policy

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About the Center for Evidence-based Policy

The Center for Evidence-based Policy (Center) is recognized as a national leader in evidence-based decision making and policy design. The Center understands the needs of policymakers and supports public organizations by providing reliable information to guide decisions, maximize existing resources, improve health outcomes, and reduce unnecessary costs. The Center specializes in ensuring diverse and relevant perspectives are considered, and appropriate resources are leveraged to strategically address complex policy issues with high-quality evidence and collaboration. The Center is based at Oregon Health & Science University in Portland, Oregon.

Suggested citation:

Leof, A., Gerrity, M., Thielke, A., & King, V. (2014). *Sofosbuvir for the treatment of hepatitis C and evaluation of the 2014 American Association for the Study of Liver Diseases treatment guidelines.* Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.

Table of Contents

List of Tables and Appendices

Introduction

Chronic Hepatitis C virus (HCV) infection is a slowly progressive condition affecting between 2.7 million and 5.2 million United States (US) citizens (Chak 2011; Denniston 2014). Hepatitis C infection is associated with an increased risk of cirrhosis, liver failure, and hepatocellular carcinoma, and is the most common condition leading to liver transplant. Over a 20- to 30-year period, 5% to 20% of infected patients will develop cirrhosis and 1% to 5% will die of cirrhosis or liver cancer (Center for Disease Control and Prevention [CDC] 2010).

For HCV infected patients who develop liver disease, the most recently recommended standard of care is a combination of pegylated interferon therapy (PEG) and ribavirin (RBV), and, for patients with genotype 1 HCV infection, one of the protease inhibitors boceprevir (Victrelis™) or telaprevir (Incivek™). The standard interferon-based treatment regimens result in 45% to 75% of patients having no detectable virus at 24 weeks post treatment with results varying based on patient characteristics (US Department of Veterans Affairs 2013). These regimens can take up to a year to complete, place a high burden on patients requiring weekly injections and complicated dosing schedules, and are associated with significant side effects leading patients to discontinue treatment. The ideal treatment for HCV would be highly effective, easy to take, have a low side effect profile, have a low patient burden, and be affordable.

Pharmaceutical companies have invested significant resources in finding alternative treatment regimens that would improve rates of sustained viral response while reducing patient burden for patients infected with HCV. More than 30 direct-acting anti-viral agents (DAAs) designed to treat HCV have entered clinical trials since 2011 (Tice 2014). In 2013, two new DAAs were approved: sofosbuvir (Sovaldi™) and simeprevir (Olysio™). At least two more DAAs are expected to be approved in 2014, including faldaprevir and daclatasvir. Gilead is also seeking approval for multi-drug combination pills including sofosbuvir and AbbVie recently reported positive results from its investigational oral regimen (AbbVie 2014).

Of the recently developed DAAs, sofosbuvir has drawn the most attention because it is the first new DAA the US Food and Drug Administration (FDA) approved for the treatment of HCV genotypes 1 to 4 (including an interferon free regimen for genotypes 2 and 3). In addition, many reports of the initial sofosbuvir trials suggest that 80% to 90% of patients will not have detectable virus 12 weeks after completing treatment. In January 2014, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) released treatment guidance for hepatitis C and recommended sofosbuvir for all patients except those with severe renal impairment.

With the recent FDA approval of sofosbuvir, clinicians and purchasers will need to decide whether to include sofosbuvir in their treatment protocols for HCV infection. This report

evaluates the evidence about the effectiveness and harms of sofosbuvir treatment for HCV, evaluates the AASLD guideline, and provides a compilation of the evidence to guide decisions on who and when to treat. With the approval of new HCV treatments and more drug approval applications currently at the FDA, it is clear that this is a rapidly evolving clinical and policy topic. Center for Evidence-based Policy staff will continue to place updated material on the Medicaid Evidence-based Decisions (MED) Project Clearinghouse website and will consider this report for updating as new evidence emerges.

Background

Clinical Overview

Between 2.7 million and 5.2 million Americans are infected with the HCV virus (Chak 2011; Denniston 2014). Prevalence of the HCV infection is greater in Medicaid and non-insured populations than in commercially insured groups, with one Florida study showing the Medicaid infection rate to be twice that of the commercially insured populations (663 per 100,000 beneficiaries compared to 302 per 100,000 over ten years) (Levin 2012). Because the early stages of the disease are often asymptomatic, up to half of infected individuals are unaware of their status. In June 2013, the United States Preventive Services Task Force (USPSTF) recommended that individuals at high risk of infection (intravenous drug users, individuals who received blood transfusions before 1992) and all adults born between 1945 and 1965 be screened for HCV (USPSTF 2013).

Progression of HCV is generally slow and varies significantly by individual. Approximately 15% to 25% of people infected with HCV will clear the virus during the acute stage without treatment. Seventy-five to 85% of infected individuals will develop a chronic HCV infection, and 60% to 70% of patients with chronic infection will develop chronic liver disease. Over 20 to 30 years, 5% to 20% of infected patients will develop cirrhosis and 1% to 5% will die of cirrhosis or liver cancer (CDC 2010).

Table 1. Progression of Hepatitis C Virus Infection (CDC 2014)

Condition	Percentage of Patients Who Develop Condition
Chronic HCV infection	75% to 85%
Chronic liver disease	60% to 70%
Cirrhosis over 20 to 30 years	5% to 20%
Death from cirrhosis or liver cancer	1% to 5%

Accelerated progression of the disease is associated with male gender, greater age, duration of the disease, steatosis, obesity, human immunodeficiency virus infection (HIV), hepatitis B infection (HBV), immunosupression following solid organ transplant, insulin resistance and type

2 diabetes, and significant alcohol consumption (European Association for the Study of the Liver [EASL] 2013; Ghany 2009; Louie 2012). It is also important to note that neither spontaneous clearance nor successful treatment confers immunity and that reinfection can occur (Grebely 2012).

Common comorbid conditions with HCV infection include metabolic syndrome (approximately 27% of infected people), dyslipidemia (16% to 21%), peripheral vascular disease (19%), HIV (4%), and diabetes (5% to 15%) (Levin 2012). In a commercially insured population, alcohol and drug abuse were more common in HCV-infected patients than non-infected controls, with 7% versus less than 1% having an alcohol problem and 15% versus 3% abusing illegal drugs (Louie 2012).

There are six major genotypes of the HCV virus. Genotype 1 (HCV-1) is the most common form found in the US population accounting for approximately 73% of cases. Genotype 1 is further distinguished by subtypes 1a (HCV-1a) (39% of patients) and 1b (HCV-1b) (29%). Genotype 2 (HCV-2) is found in approximately 14% of US patients, genotype 3 (HCV-3) in 8%, a mixed-genotype in 4%, and genotypes 4 through 6 (HCV-4, -5, -6) in less than 1% of patients (Blatt 2000). Patients with genotype 1 have had a poorer response to treatment than patients with genotype 2 or 3, and subtype 1a has a poorer response than subtype 1b.

In addition, people have a gene that is related to Hepatitis C virus infection called the IL28B gene. The IL28B genotype can be of CC, CT or TT type. Patients with IL28B genotype CC are significantly more likely to clear the virus spontaneously and to respond to HCV treatment than patients with types CT or TT (EASL 2013).

Treatment

The goal of HCV treatment is to decrease the risk of virus-related conditions such as cirrhosis, hepatocellular carcinoma (HCC), decompensated liver disease, liver transplant, or death from other liver-related causes. Because of the slow progression of the disease, clinical trials have not evaluated these patient-important conditions as trial outcomes. Instead, a surrogate endpoint of sustained virologic response (SVR) has been used to measure success of treatment. The SVR is defined as undetectable HCV-ribonucleic acid (RNA) levels. The standard measure of treatment success has been SVR at 24 weeks post treatment (SVR24).

Several long term studies of patients with chronic HCV infection have shown an association between achieving SVR24 and patient-important clinical outcomes. In a systematic review by the Agency for Healthcare Research and Quality (AHRQ), Chou (2012) found a moderate strength of evidence that achievement of SVR24 post treatment was associated with lower risks of all-cause mortality, liver-related mortality, and HCC with hazard ratios ranging from 0.10 to 0.71. Chou (2012) also reviewed nine poor-quality studies that found a low strength of evidence

that achieving SVR24 was associated with improvement in generic and disease-specific quality of life. Two additional studies were published since the AHRQ systematic review and corroborate its findings. Van der Meer (2012) found that among patients with HCV and advanced fibrosis or cirrhosis (Ishak scores between four and six) achievement of SVR24 was significantly associated with reduced mortality. The ten-year cumulative all-cause mortality rate in the 192 patients who achieved SVR24 was 8.9% (95% CI, 3.3% to 14.5%) compared to 26% (95% CI, 20.2% to 28.4%) ($p<0.001$) in the 338 patients who failed to achieve SVR24. A 2014 observational study of a VA population found that out of 128,769 patients infected with HCV, the 5180 patients (4%) who were able to achieve an undetectable viral load with interferon-based treatment had a 45% reduction in the risk of death (hazard ratio [HR] 0.55, 95% CI 0.47 to 0.64) and a 27% reduction in the composite clinical endpoint (HR 0.73, 95% CI 0.66 to 0.82) of newly diagnosed cirrhosis, HCC, or a liver-related hospitalization (McCombs 2014).

The FDA recently accepted SVR at 12 weeks post treatment (SVR12) as an endpoint for FDA drug approval (FDA 2013a). This decision is based on a 2013 analysis of data from 13,599 adults (11,730 with genotype 1) treated with double (PEG+RBV) or triple therapy (PEG+RBV+PI) in phase II or III drug development trials. The analysis found an association between SVR12 and SVR24 as measured by a positive predictive value (PPV) of 98%. (Chen 2013). However, there is uncertainty about this result due to uncertainty about how the authors accounted for missing data. Although the authors state that they imputed missing data for some analyses, the data used to calculate their main measure of concordance (positive and negative predictive values) did not employ imputed values. The authors state that "missing viral load data were not used in calculating the tabularized relations between SVR24 and SVR12 or SVR4." There were 1,536 patients excluded with missing data. Ten-thousand one hundred-ninety-four (10,194/11,730 or 87%) genotype 1 patients were included in the analysis. If the 1,536 missing patients were added back into the calculations for PPV making assumptions about the best case scenario (all patients with missing data achieved SVR24) and worst case scenario (all patients with missing data did not achieve SVR24), the range of potential values for the PPV is 77% to 99%., meaning that of a hundred patients, between one and 23 patients who achieved SVR12 will not achieve SVR24. In addition, these calculations are based on trial populations who generally have favorable treatment characteristics and may not reflect patient populations likely to be treated under Medicaid programs.

In contrast to Chen's findings (2013), Thorlund (2014) performed a meta-analysis of randomized controlled trials that treated HCV genotype 1 patients with PEG and RBV. Thorlund found that SVR12 was 5% to 6% higher than SVR24 in these studies (2014). It may be that the association between SVR12 and SVR24 could vary depending on treatment regimen and concordance measures for one treatment cannot be extrapolated from data gathered from other regimens

(Thorlund 2014). If this is true, the lack of data on both SVR12 and SVR24 for the new DAAs precludes certainty about long term effectiveness of these drugs.

The sofosbuvir trial protocols registered in the ClinicalTrials.gov database include SVR24 as a secondary outcome, yet only two of these studies, ELECTRON (Gane 2013) and the NIH-funded study (Osinusi 2013), reported SVR24 data. Thorlund (2014) has called upon researchers in clinical trials to report both SVR12 and SVR24 "to allow for complete transparency and clarity in […] interpretation" (p. 49).

Standard Treatment Regimens

Since the early 2000s, standard treatment for HCV infection has been a combination of pegylated interferon (PEG-INF) in a weekly injection (either PEG-INF alfa-2a or alfa-2b) and ribavirin (RBV) daily (double therapy). In 2011, the FDA approved the protease inhibitors boceprevir (BOC) or telaprevir (TVR) in addition to PEG-INF and RBV to treat genotype 1 (triple therapy). Standard treatment protocols by genotype and the estimated SVR24 rates from treatment are described in Table 2 below.

Table 2. Standard of Care Treatment Regimens (US Department of Veterans Affairs 2013)

Genotype	Treatment	Approximate SVR24 Rate
HCV-1	Double therapy PEG-IFN alfa-2a or alfa-2b weekly + RBV daily for up to 48 weeks	45%
	Triple therapy PEG-INF alfa-2a OR alfa-2b weekly + RBV daily for up to 48 weeks depending on treatment response and either BOC or TVR. BOC is added during weeks 8 to 32 depending on treatment response and TVR is given with PEG-INF and RBV during first 12 weeks of treatment.	65% to 70%
HCV-2	PEG-INF weekly + RBV daily for up to 24 weeks	75%
HCV-3	PEG-INF weekly + RBV daily for up to 24 weeks	75%

Treatment effectiveness for HCV with double or triple therapy varies based on patient characteristics. Patients with genotype 1 are significantly less likely to achieve SVR24 than patients with genotypes 2 or 3. Patients with high pre-treatment viral loads (HCV-RNA greater than 600,000 IU/mL) are also less likely to achieve SVR. Other factors associated with lower response to treatment include male sex, older age, being African American, obesity, diabetes, reduced alanine aminotransferase (ALT) levels, bridging fibrosis or cirrhosis, and a CT or TT polymorphism on the IL28B gene. In patients with genotype 1 treated with PEG-INF and RBV,

SVR24 rates ranged from 69% in patients with the CC genotype, to 33% with CT, and 27% with TT (Ghany 2011). Differences in response rates by race may be related to African Americans being less likely to have the favorable CC polymorphism on the IL28B gene (Chou 2012; Ghany 2011).

Issues with Standard Treatment

Interferon-based treatments have high rates of side effects that affect quality of life. Patients report significant fatigue, headache and flu-like symptoms as well as neuropsychiatric symptoms such as depression. The Veteran's Administration reports that approximately 10% of patients discontinue interferon-based treatment due to side effects (VA 2013). Interferon and RBV are also associated with anemia, neutropenia, thrombocytopenia, ophthalmologic disorders, thyroid dysfunction, and sarcoidosis.

Triple therapy with BOC or TVR involves a high burden on patients as the dosing schedule is complicated with multiple doses during the day and all medication must be consumed with fat. There are also significant drug-drug interactions with BOC and TVR (Ghany 2011). Adverse events associated with these drugs include increased hematological complications (BOC) and increased risk of anemia and severe rash (TVR) that may lead to discontinuation of treatment (Chou 2012).

Deciding to Initiate Treatment

In contrast to conditions where there is rapid progression and an immediate need for treatment (e.g., acute leukemia or serious bacterial infections), hepatitis C is a slowly progressing disease. Fifteen to 25% of infected persons clear the infection spontaneously. For those with ongoing infection, it is a disease where clinicians and patients have the option of delaying or forgoing treatment. Because of the slow progression of the disease as well as the moderate success rates and the side effects of current treatments, many patients have refused interferon-based treatments. Some physicians have also been recommending that patients wait until new treatment regimens are approved by the FDA. Earlier guidelines by the AASLD recommended that patients be monitored and treated if they show signs of liver involvement. Indications include a liver biopsy showing significant fibrosis (bridging or higher), compensated liver disease (defined as total serum bilirubin less than 1.5 g/dL; international normalized ratio [INR] of 1.5; serum albumin greater than 3.4, platelet count of 75,000 mm and no evidence of hepatic decompensation) and acceptable hematological and biochemical indices (hemoglobin 13 g/dL for men and 12 g/dL for women; neutrophil court of 1500/mm^3, serum creatinine less than 1.5 mg/dL). Interferon treatment is contraindicated for patients with uncontrolled major depression, solid organ transplant, untreated thyroid disease, severe comorbid health conditions (e.g., hypertension, heart failure, coronary heart disease, diabetes, chronic obstructive pulmonary disease), or known hypersensitivity to medications (Ghany 2009).

Sofosbuvir (Solvadi™)

Sofosbuvir (SOF), manufactured by Gilead Sciences, is a nucleotide analog NS5B polymerase inhibitor. In December 2013, the FDA approved SOF 400mg in a once daily pill for the treatment of hepatitis C genotypes 1, 2, 3 and 4, in combination with RBV and, for genotype 1, PEG-INF. The approval specifically includes patients who have the most urgent need for treatment due to advanced disease and increased risk of death including those with HCC, those awaiting liver transplantation, and patients with HIV-1 co-infection. Sofosbuvir is not approved for patients with severe renal impairment (estimated glomerular filtration rate less than or equal to 30 mL/min/1.73m^2) or end stage renal disease. The FDA approved sofosbuvir under a priority review process that allowed use of SVR12 as a study endpoint. Approved treatment regimens are described in Table 3 below.

Table 3. FDA Approved Sofosbuvir Treatment Regimens (FDA 2013b)

Patient Genotype	Treatment Regimen	Duration[1]
HCV-1 or -4	PEG-INF weekly + RBV + SOF daily	12 weeks
HCV-1	For interferon-ineligible: RBV + SOF	24 weeks
HCV-2	RBV + SOF	12 weeks
HCV-3	RBV + SOF	24 weeks

[1]All medications are taken for the full duration.

The FDA approved label for Sofosbuvir does not identify any adverse reactions besides those that commonly occur with RBV treatment (fatigue and headache) or PEG-INF (fatigue, headache, nausea, insomnia, and anemia).

Sofosbuvir has attracted attention because of its potential improvement over previous standard of care. For genotypes 2 and 3, SOF plus RBV provides an interferon-free, all oral regimen with shorter duration. For genotype 1, SOF provides an alternative to BOC and TVR with their higher pill burden and side effect profile; it provides a shorter treatment period; and, for interferon-ineligible patients, it offers an alternative treatment protocol. Studies report SVR12 rates of 80% to 90% in patients treated with sofosbuvir regimens, and low rates of serious adverse events. If, indeed, the clinical research evidence supports these claims, the new SOF regimens would be a tremendous step forward for patients with HCV.

Gilead Science has set the wholesale acquisition cost of sofosbuvir at $1,000 per tablet in the U.S. With daily dosing, the cost of a course of treatment with sofosbuvir will range from $84,000 for 12 weeks to $168,000 for 24 weeks of treatment (Robison 2013). This price does not include the drug cost of RBV and/or PEG-INF in regimens that include those drugs. These costs also do not account for the medical care needed before, during and after treatment, or further treatment in the case of treatment failure or relapse.

Key Questions

This report will address the following key questions:

1. What is the evidence for the efficacy of sofosbuvir in treating hepatitis C?
2. What is the evidence for harms of sofosbuvir treatment?
3. Is there any evidence of subgroup differences in efficacy and harms (e.g., genotype, race, comorbidity)?
4. Are there studies in the research pipeline that will add significantly to the knowledge of sofosbuvir's effectiveness and harms?
5. What polices have private payers set around sofosbuvir coverage?
6. What is the quality and reliability of the AASLD treatment guideline?
7. What does the evidence say about whom to treat and when to treat?

Methods

Search Strategy

The FDA's website was searched for the summary review of evidence and the approved label for sofosbuvir. The website clinicaltrials.gov was searched with the term "sofosbuvir" and all studies were reviewed for their design, treatment population, interventions and outcomes. Completed studies were reviewed to identify publications. A MEDLINE search was conducted with the search term "sofosbuvir" and all studies examining efficacy and harms of sofosbuvir were included regardless of design. Editorials, letters, and commentaries were excluded. Studies were also initially excluded if they were unpublished or presented in abstracts or slides since details about study design and patient characteristics were not available. However, after peer review comments were received additional studies available in abstract form only and unpublished studies from the information submitted by the manufacturer for FDA review were included. Due to insufficient information within these documents, formal methodological quality assessment was not performed on abstracts or unpublished trials.

The search for relevant clinical practice guidelines included the following sources: UK National Institute for Health and Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), USPSTF, Institute for Clinical Systems Improvement (ICSI), and Australian Government National Health and Medical Research Council (NHMRC), Veterans Affairs guidelines, and gastroenterology and hepatology professional organizations.

Quality and Applicability Assessment

All identified published studies were included for review. Three reviewers rated the quality (risk of bias or internal validity) of each study as well as criteria to assess the risk for biased inferences from study results (external validity or applicability) due to factors such as inappropriate comparator or outcome for the key questions raised in this report. Several

studies presented in abstracts and slides were later summarized, based on requests from external reviewers, but were not quality rated.

A checklist was adapted from those used by the National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guideline Network (SIGN), Drug Effectiveness Review Project (DERP) for risk of bias (internal validity). Reviewers used a checklist based on criteria proposed by Montori (2004) to address potential biases in inferences made from study results for questions posed in this report (external validity). Finally, conflicts of interest and study funding were noted. Disagreements were resolved by discussion and studies received an overall quality rating that incorporated both risk of bias related to study results and applicability of study results to questions in this report (Appendix D).

Table 4. Critical Appraisal and Summary Judgment

Author, Year (Trial)	How well was the study done to minimize bias in study design? (Good, Fair, Poor)	How well did the study respond to the PICO of this report? (Good, Fair, Poor)	Overall Study Quality (Good Fair, Poor)
Gane, 2013 (ELECTRON)	Poor	Poor	Poor
Jacobson, 2013a (Study 1) (POSITRON)	Poor	Poor	Poor
Jacobson, 2013a (Study 2) (FUSION)	Poor	Poor	Poor
Kowdley, 2013 (ATOMIC)	Poor	Poor	Poor
Lawitz, 2013 (Lancet)	Poor	Poor	Poor
Lawitz, 2013 (NEJM) (Study 1) (NEUTRINO)	Poor	Poor	Poor
Lawitz, 2013 (NEJM) (Study 2) (FISSION)	Poor	Poor	Poor
Osinusi, 2013 (Study 1)	Poor	Poor	Poor
Osinusi, 2013 (Study 2)	Poor	Fair	Poor
Rodriguez-Torres, 2013	Poor	Poor	Poor

Two raters independently rated the quality of the guidelines using a checklist adapted Appraisal of Guidelines Research & Evaluation (AGREE) instrument. Disagreements were resolved by discussion. For guidelines to be considered evidence-based, the following criteria had to be

met: systematic search for studies; study selection criteria clearly described; quality of individual studies and overall strength of evidence assessed; methods for formulating recommendation clearly described; benefits/side effects/risks considered; explicit link between evidence and recommendations; external review; funding source and member conflict of interest managed so as not to influence recommendations.

Peer Review

The draft report was peer reviewed by four experts representing the fields of pharmacology, hepatology, primary care, clinical epidemiology and health policy. Potential reviewers were asked to declare any significant financial or intellectual conflicts of interest. None of the experts who completed the standardized peer review form reported conflicts of interest. A table of de-identified peer reviewer comments along with their disposition was developed and a final version of this report prepared by the authors.

Findings

Seven publications addressing the effectiveness and harms of sofosbuvir (Gane 2013; Jacobson 2013a; Kowdley 2013; Lawitz 2013a; Lawitz 2013b; Osinusi 2013; Rodriguez-Torres 2013) were identified. These seven publications described ten studies, with three articles (Jacobson 2013a, Lawitz 2013b, and Osinusi 2013) describing two studies each. In addition, three studies cited in the FDA review which have not been published were reviewed and data from these trials was included in the appendices where appropriate (Mishra 2013). Three abstracts presented at two conferences on the unpublished COSMOS trial of a sofosbuvir and simeprevir treatment regimen were also reviewed and are described below (Jacobson 2013b; Lawitz 2014; Sulkowski 2014). .

Full study descriptions are offered in Appendix C titled Evidence Table. The evidence table gives detailed information about each study, including design, sample size, inclusion and exclusion criteria, patient characteristics, the drug regimen and comparator employed, the primary outcomes reported and study limitations. In addition, Appendix A presents response and relapse rates by study and Appendix B breaks down study populations by important characteristics (i.e., HCV genotype, prior treatment experience, proportion of male and Caucasian subjects in study, and proportion of subjects with cirrhosis or bridging fibrosis). A table summarizing the findings from the detailed critical appraisal assessment conducted on each of these studies is presented in Appendix D. This report identified 53 studies registered on clinicaltrials.gov, of which 15 were marked as completed. Of the 15 trials marked as completed, only four trials had results posted on clinicaltrials.gov.

The only guideline that addressed the use of sofosbuvir is the 2014 AASLD publication.

Treatment Effectiveness

Overview – Published Studies

Of the ten published studies, there was one placebo controlled trial (Jacobson 2013a, POSITRON) and one study that compared SOF + weight-based RBV to PEG + low dose RBV 3 (Lawitz 2013b, FISSION). Both of these studies included patients with HCV genotypes 2 and 3. All other studies were designed to refine drug dose, drug combination or duration of treatment. Nine studies enrolled patients with HCV-1 (total n=889), five included those with HCV-2 or HCV-3 (total n=1060) and two studies also included patients with HCV-4, -5, or -6 (total n=41).

Studies tended to include populations with favorable prognostic factors. About 10% of total enrolled populations were African or African American. Slightly over 13% had cirrhosis. No subjects with concurrent hepatitis B or HIV infections were included among the published studies. However, one study of HCV/HIV co-infected patients (Mishra 2013, PHOTON-1) was included in the FDA review and available details of the study are described below.

All studies were rated as having a high risk of bias. No study was judged to have good applicability, and only the National Institutes of Health (NIH) sponsored study by Osinusi (2013) was rated as having fair applicability. The overall summary judgment for each of the published studies yielded a rating of poor. Only one of 10 published studies used a comparator that would answer the key clinical question raised in this report – do the new sofosbuvir drug regimens have better clinical outcomes and fewer harms than the current standard of care? In other words, do the sofosbuvir trials compare the current treatment (see Table 2) to the newly recommended sofosbuvir regimens (see Table 3)? These nine published studies, as well as the three unpublished trials included in the FDA review, were single arm non-comparative studies, placebo controlled, or dose or duration varying studies that did not have a meaningful comparator. The outcomes of these studies (e.g., SVR12, SVR24, harms) may be strongly influenced by the characteristics of the patients in the studies, many of whom had characteristics associated with better outcomes (e.g., Caucasian, , lower viral load at baseline, no active or excessive alcohol use, low rates of cirrhosis, other comorbid conditions such as cardiac disease). The one study which did compare the sofosbuvir regimen to the standard PEG and RBV treatment used a low dose of RBV (800mg) rather than weight-based RBV (1000 to 12000 mg depending on weight) which is the current standard of care. Neither this comparator nor the placebo controlled trial were appropriate study designs for answering the questions raised by this report.

No study of sofosbuvir in HCV-1 populations compared the drug to current standard of care, which is triple therapy including PEG-INF + RBV with boceprevir or telaprevir. Most studies were open label and all but one (Osinusi 2013) were funded and controlled by the drug's manufacturer. Most study arms included few patients, especially among subgroups of particular interest to public payers. Duration of follow-up was limited with no study reporting primary

outcomes at more than 24 weeks after the end of treatment. Most studies were multi-centered, and eight studies enrolled 10 or fewer patients per site. None of these studies reported results by study center.

Response rates tended to vary by the underlying prognostic factors of the population (i.e., genotype, presence of cirrhosis, prior treatment status), sample size and study characteristics. Response rates from the published studies, using SVR12 as the outcome measure, ranged from 10% to 89% for patients with HCV-1, 82% to 95% for HCV-2, and 30% to 84% for patients with HCV-3 (Appendix A and B). Few studies reported SVR24, and among the eight study arms reporting both SVR12 and SVR24, the differences in these response rates ranged from 0% to 7%.

Not all studies reported relapse rates and those that did used various measures of "relapse." Relapse is defined as a patient achieving HCV RNA < lower limit of quantitation (LLOQ) or the lower limit of detection (LLOD) at the last measurement on treatment but subsequently having a HCV RNA ≥ LLOQ or LLOD post treatment. The FDA analysis (Mishra 2013) as well as the FISSION, NEUTRINIO, POSITRON, and FUSION studies (Lawitz 2013b; Jacobson 2013a) all defined the LLOQ as < 25 IU/mL. The ELECTRON study (Gane 2013) used a measure of LLOD of < 15 IU/mL while the NIH study (Osinusi) measured both LLOQ and LLOD, but the thresholds varied based on the assay used. Osinusi specified that when using the Abbot Molecular assay, the LLOQ should be < 12 IU/mL and the LLOD < 3 IU/mL, but when using the COBAS TaqMan assay, LLOQ < 43 IU/mL and LLOD < 12 IU/mL. The FDA review (Mishra 2013) did not specify which assay was used to determine LLOQ, but Gane (2013), Jacobson (2013a), and Lawitz (2013) all used the COBAS TaqMan assay.

In those studies that did report relapse rates, some reported only on the basis of per-protocol analysis (patients completing treatment only) and did not account for losses to follow-up. Relapse rates ranged from 5% in treatment naïve genotype 2 patients treated with SOF + RBV for 12 weeks, (FISSION, Lawitz 2013b; POSITRON, Jacobson 2013a) to 90% in treatment experienced genotype 1 patients treated with the interferon-free SOF + RBV 12 week regimen (Gane 2013). For the FDA approved treatment regimens, relapse rates were 4% to 8.6% for genotype 1 patients treated with SOF + PEG + RBV for 12 weeks (Lawitz 2013a; Lawitz 2013b) and 28% for genotype 1 patients treated with the interferon free SOF + RBV for 24 weeks (Osinusi 2013). For genotype 2 patients treated with SOF + RBV for 12 weeks, relapse rates ranged from 5% to 18% (Jacobson 2013a; Lawitz 2013b) and for genotype 3 patients treated with SOF + RBV for 24 weeks, the relapse rates was 14% (Mishra 2013).

Overview – Unpublished Studies Included in FDA Review

Three additional unpublished studies were identified. These three studies, VALENCE, PHOTON-1 and an unnamed trial in pre-transplant patients, were all on-going trials at the time of FDA review but were included in the FDA's efficacy and safety assessment.

The original protocol for VALENCE was as a placebo controlled trial of SOF + RBV for 12 weeks in patients with HCV genotypes 2 or 3. Early results, primarily from the FUSION trial, however, indicated that SVR12 rates in genotype 3 patients improved with longer duration of treatment, and so the protocol for VALENCE was redesigned to treat all genotype 2 patients with SOF + RBV for 12 weeks, and offer genotype 3 patients SOF + RBV for 24 weeks. The SVR12 rate for genotype 3 patients in the trial who took 12 weeks of treatment was 56%, which increased to 93% with 24 weeks of treatment. The relapse rate decreased from 40% to 5%. The VALENCE trial led the FDA to approve a genotype 3 treatment regimen of SOF + RBV for 24 weeks (Mishra 2013).

The PHOTON-1 trial was an on-going, three arm trial of SOF + RBV therapy in patients co-infected with HIV. The first arm included treatment naïve patients with genotype 2 or 3 who received 12 weeks of therapy. The SVR12 rate for the genotype 2 patients was 88% (23/26) and 67% (28/42) for genotype 3. The second arm included treatment experienced patients with genotypes 2 and 3, and they received 24 weeks of treatment. The SVR12 rates were 93% for genotype 2 (14/15) and 92% (12/13) for genotype 3. The third arm included treatment naïve genotype 1 patients who received SOF + RBV for 24 weeks, and the SVR12 response was 76% (87/114). Genotype 1a responded better with 82% achieving SVR12 (74/90) compared to genotype 1b where only 54% (13/24) achieved SVR12 (Mishra 2013).

The FDA also included data from an unnamed, on-going, open-label trial evaluating whether administering SOF + RBV to pre-transplant patients would prevent HCV recurrence post-transplant (trial number P7977-2025). The trial reported incomplete data on a total of 61 patients (Mishra 2013). The preliminary results are presented in Appendix C.

All three of these unpublished trials were incomplete at the time of FDA review and had not been published in a peer reviewed publication as of April 2014. Available details of the trials are included in report charts and tables, but the studies were not quality assessed or reviewed due to lack of information.

Summary of Evidence on FDA Approved Treatment Regimens

Of the 11 studies identified which evaluated sofosbuvir treatment in general populations (ten published studies and the unpublished VALENCE trial, excluding the HIV and pre-transplant studies), only six studies tested one of the four FDA approved treatment regimens. These studies are summarized in Table 5 below.

Table 5. FDA Approved Treatment Regimens and Response Rates

FDA Approved Treatment Regimens and Response Rates					
Genotype	**Treatment**	**SVR12**	**Relapse**	**# of Studies (Study name)**	**Study N**
HCV-1	SOF+PEG+RBV 12 w	89%	4% to 8.6%	2 (NEUTRINO, ATOMIC)	379
	SOF+RBV 24 w	68%	28%	1 (Osinusi, NIH Study)	60
HCV-2	SOF+RBV 12 w	82% to 95%	5% to 18%	4 (FISSION, FUSION, POSITRON, VALENCE)	1051
HCV-3	SOF+RBV 24 w	84%	14%	1 (VALENCE)	250

Note that for both genotype 3 and the interferon-free regimen for genotype 1, the evidence base consists of one study and the total number of patients with reported data is 60 (for genotype 1 patients treated with the interferon-free regimen) and 250 (genotype 3 regimen). The evidence for the genotype 1 SOF + PEG + RBV 12-week treatment is primarily based on the NEUTRINO study which tested the regimen on a total of 327 patients. Fifty-two additional patients also received that treatment regimen in the ATOMIC study that evaluated duration ranges. The genotype 2 regimen has the most documented evidence with the SOF + RBV 12-week treatment being tested on 1051 patients in four trials, and the SVR12 rate varied from 82% to 95%.

Adverse Events

The FDA compiled reports of adverse events from four trials (FISSION, FUSION, NEUTRINO, POSITRON) compiling a data-set of 1305 patients treated with sofosbuvir and RBV, with or without PEG, or placebo. There were no treatment-related deaths reported.

Approximately 78% of patients receiving placebo, 88% of patients on SOF + RBV treatment and 95% of patients receiving PEG + SOF + RBV reported a side effect from treatment. The most common side effects were fatigue, anemia, nausea, rash, headache, insomnia, and pain (Mishra, 2013, p. 115).

Discontinuation of therapy due to adverse events was relatively low in these studies. In the combined safety analysis, the FDA reported withdrawal rates of approximately 1.4% in patients receiving SOF + RBV for 12 weeks (eight out of 566 patients). This compares to 4.2% of patients receiving placebo (three out of 71 patients), 1.5% of patients receiving SOF + PEG + RBV for 12 weeks (five out of 327 patients), and 10.7% of patients on PEG + RBV alone (26 out of 243 patients) (Mishra 2013, p. 109).

Fifty-one treatment-emergent, serious adverse events (SAE) occurred in 34 patients (2.6%). The events by treatment regimen are summarized in Table 6 below.

Table 6. Total Number of Patients with Serious Adverse Events

Regimen	Placebo 12 wks	SOF+RBV 12 wks	SOF+RBV 16 wks	PEG+SOF+RBV 12 wks	PEG+RBV 24 wks
N	71	566	98	327	243
Number of pts w/ SAE	2 (2.8%)	22 (3.9%)	3 (3.1%)	4 (1.2%)	3 (1.2%)
Number of SAEs	3	31	3	8	6
SAES (# of events)	Pancreatitis (1); bile duct stone (1); bronchitis (1);	Anemia (1); abdominal pain (1); non-cardiac chest pain (1); pyrexia (2); chest pain (1); drug withdrawal syndrome (1); edema peripheral (1); portal vein thrombosis (1); allergy to arthropod sting (1); hypersensitivity (1); cellulitis (2); abdominal abscess (1); osteomyelitis chronic (1); urinary tract infection (1); overdose (1); spinal compression fracture (1); fall (1); injury (1);	Non-cardiac chest pain (1); overdose (1); suicide attempt (1);	Anemia (1); leukopenia (1); abdominal pain (1); non-cardiac chest pain (1); pyrexia (1); cryoglobulinaemia (1); spinal compression fracture (1); laryngeal cancer	Atrioventricular block (1); infection (1); clavicle fracture (1); rib fracture (1); breast cancer in situ (1); pneumothrorax (1)

Regimen	Placebo 12 wks	SOF+RBV 12 wks	SOF+RBV 16 wks	PEG+SOF+RBV 12 wks	PEG+RBV 24 wks
		road traffic accident (1); toxicity to various agents (1); upper limb fracture (1); hypoglycemia (1); hepatic neoplasm malignant (3); basal cell carcinoma (1); abnormal behavior (1); COPD (1); eczema (1)			

Adapted from Mishra 2013, p.101.

The other studies reviewed reported similar high rates of mild to moderate side effects such as fatigue, nausea and headache. No significant patterns in serious adverse events were noted.

In assessing the risk of adverse events, it is important to note that the studies on sofosbuvir were small, included populations that were healthier than the general hepatitis C population, were of short duration and had limited follow-up. In many of the studies, the manufacturer was responsible for recording and reporting adverse events. In general, reporting of adverse events is often incomplete and discrepancies between clinical trial reports and publications are common (Hartung 2014). All of these factors would lead to a bias in under-representing the true nature of adverse events.

Long range studies and expanded use may reveal a different harms profile as adverse events associated with new medications often appear only after general clinical use (Prasad 2013). When the protease inhibitors BOC and TVR were approved, studies showed 9% to 14% of patients experienced serious side effects. Post approval studies in Europe found the rate of serious adverse events to be significantly higher, with 38% of patients treated with boceprevir experiencing an adverse event and 48.6% of those receiving telaprevir developing a serious side effect (Hezode 2012).

While the studies reviewed here do not report significant adverse events associated with sofosbuvir treatment, larger and longer term studies would be needed to accurately describe the drug's harms profile.

Subgroup Differences in Effectiveness and Harms

The 11 studies reviewed did not report effectiveness or harms data separately for many relevant subgroups (e.g., by race, gender, IL28B genotype). These studies did suggest that sofosbuvir treatment regimens are similar to interferon-based treatment regimens in that the treatment is more effective in patients with genotype 2 and 3 than in patients with genotype 1, patients with genotype 2 do better than patients with genotype 3, patients with the IL28B CC genotype fare better, and patients without cirrhosis are more likely to achieve SVR12 than those with cirrhosis.

Additional Studies

Due to the rapidly changing environment and information surrounding treatment options for HCV, several peer reviewers suggested including the COSMOS study which tests a treatment regimen of both simeprevir and sofosbuvir for HCV genotype 1 patients. The study remains unpublished.

COSMOS [Sofosbuvir (Sovaldi™) and Simeprevir (Olysio™)]

Simeprevir (Olysio™) is a NS3/4A protease inhibitor jointly developed by Janssen R&D and Medivir AB. In October 2013, the FDA approved simeprevir for the treatment of HCV genotype 1 patients in combination with PEG and RBV.

In November 2013, preliminary results from the COSMOS trial were presented at the annual meeting of the American Association for the Study of Liver Diseases (AASLD). The COSMOS trial includes 167 patients divided into two cohorts each with four study arms and treats these HCV genotype 1 patients with 400 mg SOF and 150 mg SMV with or without weight-based ribavirin for 12 or 24 weeks. The2013 AASLD presentation reported data for the 80 patients in Cohort 1 who were all non-responders to prior treatment with PEG and RBV and who had Metavir fibrosis scores of F0 to F2. The preliminary results were published in *Hepatology* in December 2013 (Jacobson 2013b).

In April of 2014, during the European Association for the Study of the Liver (EASL) conference, two additional presentations on COSMOS trial data were made with the abstracts published on the conference website. The first abstract (Sulkowski 2014) was presented as a “subgroup analysis” of COSMOS, but essentially repackaged the data previously presented at the 2013 AASLD conference which was published in *Hepatology* (Jacobson 2013b). The data is from Cohort 1 (HCV genotype 1 patients with prior non-response to therapy) but the EASL presentation excludes “five patients withdrawn for non-virologic failure” and thus the reported SVR12 rates increase significantly in one treatment group (SMV + SOF + RBV for 24 w, see Table 7 below). The second abstract (Lawitz 2014) reported SVR12 results from Cohort 2 patients who

were either treatment naïve or prior null responders with Metavir scores of F3 to F4. The SVR12 results are summarized in Table 7 below.

Table 7. COSMOS Trial – SVR12 Results

COSMOS SVR12 Results Presented at AASLD and EASL Conferences					
Cohort	**Citation**	**SOF + SMV 12 weeks**	**SOF+SMV+RBV 12 weeks**	**SOF + SMV 24 weeks**	**SOF+SMV+RBV 24 weeks**
1	AASLD 2013 (Jacobson 2013b)	92.9% (13/14)	96.3% (26/27)	100% (14/14)	79.2% (19/24)
	EASL 2014 (Sulkowski 2014)	92.9% (13/14)	96.3% (26/27)	100% (13/13)	90.5% (19/21)
2	EASL 2014 (Lawitz 2014)	92.9% (13/14)	92.6% (25/27)	100% (16/16)	93.3% (28/30)

Adverse events (AEs) occurred in approximately 77% of individuals in both cohorts. For Cohort 1, Jacobson (2013b) reported that four patients (2.4%) discontinued treatment due to AEs while Sulkowski (2014) reported two discontinuations due to AEs. For Cohort 2, Lawitz (2014) reported two discontinuations (2.3%). Jacobson (2013b) reported three serious AEs (1.8%) in Cohort 1; however, Sulkowski (2014) reported no serious AEs. Lawitz (2014) reported four serious AEs but did not provide details.

The abstracts do not present sufficient information to assess adverse events fully or to judge study quality.

No other published studies on the SOF and SMV combination treatment have been identified. In total, there is data on this treatment regimen in 58 genotype 1 patients, 28 of whom had a 12-week course of treatment and 30 who received the drugs for 24 weeks.

Drug Research Pipeline

As of March 7, 2014, there were 53 studies registered on clinicaltrials.gov that include the drug sofosbuvir. The majority of the studies are similar to the studies reviewed in this report in that they compare different doses of sofosbuvir or vary duration of treatment in defined populations. No registered studies compare a sofosbuvir-based regimen with current standard of care (e.g., interferon based double or triple therapy). All but four of the studies are sponsored by sofosbuvir's manufacturer, Gilead Science, and the other trials are sponsored by Bristol Myers (three trials combining sofosbuvir and daclatasvir) and the University of Florida with Vertex Pharmaceuticals (sofosbuvir combined with telaprevir).

Twenty-two of the registered studies test regimens that combine sofosbuvir with other new DAAs. Most significantly, the manufacturer has registered 15 trials of a sofosbuvir/ledipasvir fixed dose combination (FDC) pill with or without ribavirin in all genotypes. These trials do not include interferon. The manufacturer has also registered four trials combining sofosbuvir treatment with unnamed drugs identified as GS-9669, GS-9938, and GS-5816.

Several trials address specific populations, including HIV co-infection (one completed study, not yet published and two studies in progress), patients with renal insufficiency, pre and post-liver transplant, and cirrhosis. No trials examine sofosbuvir, interferon and ribavirin in genotype 1 patients who have previously failed treatment. There are four trials that administer the sofosbuvir/ledipasvir FDC with or without ribavirin to genotype 1 patients who have failed treatment. Those trials are scheduled for completion between July and December 2014.

In summary, there are no studies registered in clinicaltrials.gov which compare sofosbuvir-based treatment to the current standard of care, there is no forthcoming evidence on sofosbuvir, interferon, and ribavirin treatment in genotype 1 patients who have failed previous treatment, and there are no registered studies being conducted by any parties other than pharmaceutical companies.

Private Payer Policies

A review of Center core policy sources and references from the California Technology Assessment Forum draft report (Tice 2014) identified six private payer policies on sofosbuvir: Aetna, Anthem/Express Scripts, Caremark/CVS, Cigna, HealthNet, and Humana. Copies of these policies are included in Appendix E. Four of the policies cover sofosbuvir for all FDA approved indications, although three payers require evidence of compensated liver disease and Humana requires that patients with genotype 1 have previously failed treatment with triple therapy or have documented contraindications to interferon therapy. Cigna has published a prior authorization form but does not have coverage criteria publicly available. The private payer policies are summarized in Table 8 below.

Table 8. Private Payer Policies

Payer	Prior Authorization	Approved for all FDA Indications	Notes
Aetna	Yes	Yes	Allows for simeprevir and sofosbuvir combination treatment for genotype 1 PEG ineligible or non-responder
CareMark	Yes	Yes	Excludes ESRD, decompensated cirrhosis, post liver transplant, or significant or unstable cardiac disease

Payer	Prior Authorization	Approved for all FDA Indications	Notes
Cigna	Yes	Unclear	PA form requests information but does not list approval criteria
Anthem/Express Scripts	Yes	Yes	Requires compensated liver disease including cirrhosis
Health Net	Unclear	Yes	Requires liver biopsy showing fibrosis Metavir score ≥ 2 or Ishak score ≥ 3 Policy states that treatment is not authorized for "treatment regimen that patient who has failed therapy with an NS3/4A protease inhibitor (e.g., boceprevir, simeprevir, telaprevir)." Not authorized for post-liver transplant Explicitly excludes simeprevir and sofosbuvir combination treatment
Humana	Yes	No	Requires compensated liver disease Genotype 1 without HIV or HCC requires prior treatment failure with PI triple therapy Approved for all other FDA indications

Abbreviations: ESRD – end-stage renal disease; HIV – human immunodeficiency virus; HCC – hepatocellular carcinoma; PA – prior authorization; PI – protease inhibitors

Note: Private payer policies state coverage subject to individual member benefit contracts.

Guideline Assessment

The only identified guideline addressing the use of sofosbuvir is published by the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) Hepatitis C Guidance (AASLD 2014). The AASLD/IDSA Hepatitis C Guidance was published in January 2014 and includes 27 recommended treatment regimens based on HCV genotype, prior treatment, and co-morbid conditions and nine alternative treatment regimens. All 27 recommended regimens include sofosbuvir except in patients with severe renal impairment.

When the guideline was published, the authors noted that three sections would be "coming soon":

- In whom and when to initiate treatment;
- Monitoring patients who are on or have completed therapy; and

- Management of acute HCV infection.

As of May 1, 2014, the additional sections had not been published. The guideline is available on a dedicated website: http://www.hcvguidelines.org.

The overall methodologic quality of the guidance was poor (see Table 9 below). Two areas raised the greatest concern. First, there were no assessments of risk of bias (quality) for individual studies or the overall strength of the evidence cited for each recommendation. The published studies cited in the AASLD/IDSA Guidance as supporting the efficacy of sofosbuvir are described in other sections of this report. As noted above, all of the 10 published studies (Gane 2013; Jacobson 2013a; Kowdley 2013; Lawitz 2013a; Lawitz 2013b; Rodriguez-Torres 2013; Osinusi 2013) were given a poor quality summary rating. Second, there is substantial risk of conflict of interest influencing the recommendations from both individual panel members and funding source. For example, four of the five panel chairs had financial relationships with Gilead Science, as did 15 of the 21 panel members. Although members were given the "opportunity" to divest and recuse themselves from discussions or be recused by the chair, there was no description of when or how this occurred. More important, the International Antiviral Society-USA (IAS-USA) was the collaborating partner for development of the guidance. It was "responsible for providing expertise and managing the [p]anel and the [g]uidance development process", and one of the five panel chairs was from this society. Funding for the IAS-USA is primarily from the pharmaceutical industry including Gilead Science.

Table 9. AASLD/IDSA Hepatitis C Guidance Quality Assessment*

Category	Rating
Primary Criteria	
Rigor of development: Evidence	Poor
Rigor of development: Recommendations	Poor
Editorial independence	Poor
Secondary Criteria	
Scope and purpose	Fair
Stakeholder involvement	Fair
Clarity and presentation	Fair
Applicability	Poor
Overall rating	**Poor**

*Checklist adapted Appraisal of Guidelines Research & Evaluation (AGREE) instrument. Each category rated as good, fair or poor by two raters who were consistent in all ratings. To be considered evidence-based, none of the primary criteria should receive a poor rating.

In summary, the ASSLD/IDSA Guidance was found to be of poor methodological quality as its findings were based on poor quality evidence and the authors and sponsors of the guidance had multiple and significant conflicts of interest.

Who to Treat and When to Treat

The primary goal of treating patients with chronic HCV infection is to prevent long-term complications including cirrhosis (compensated and decompensated), HCC, and mortality. Hepatitis C is a slowly progressive disease and current treatments have significant side effects making it difficult to determine who to treat and when (Davis 2010). The AASLD and others suggest using the following guiding principle in selecting patients for treatment – *antiviral treatment should be considered in patients who are at greatest risk of progressing to cirrhosis or serious hepatic complications from HCV (e.g., decompensated cirrhosis, HCC, death) or extra hepatic complications such as cryoglobunimia* (AASLD 2009; SIGN 2013; Veterans Health Administration Pharmacy Benefits Management 2014). Ongoing trials involving new direct acting agents may clarify treatment choices in the next one to two years.

In general, patients at greatest risk of progressing to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis as defined by Metavir fibrosis stage 2 or greater (portal fibrosis with few septa – see Table 10 below). In fact, the current AASLD-IDSA Guidance (AASLD 2014) states that "it may be advisable to delay treatment for some patients with documented early fibrosis state (F 0 to 2), because waiting for future highly effective, pangenotypic, DAA combinations in INF-free regimens may be prudent" (p.31). Other risk factors for progression are listed in Table 11 and mirror the factors predicting response to treatment (Table 12) (AASLD 2009; Chou 2012; Freeman 2001; Thein 2008; Yee 2012). These factors may play an additional role in identifying patients most likely to benefit from treatment. Patients with compensated cirrhosis (total serum bilirubin less than 1.5 g/dL, INR less than or equal to 1.5, serum albumin greater than 3.4 g/dL, platelet count greater than or equal to 75,000/mm^2, no evidence of ascites or hepatic encephalopathy) are at risk of progressing to decompensation, HCC, or death.

Table 10. Metavir Fibrosis Scores

Score	Description
F0	No fibrosis
F1	Portal fibrosis without septa
F2	Portal fibrosis with few septa
F3	Numerous septa without cirrhosis
F4	Cirrhosis

Table 11. Risk Factors for Progression of Hepatic Fibrosis

Risk Factor for Progression of Hepatic Fibrosis
Detectable HCV RNA
Hepatic fibrosis greater than stage 1*
Male sex
Obesity
Hepatic steatosis
Heavy alcohol use
Advanced age
Elevated serum alanine transaminase
Greater hepatic inflammation

*Metavir fibrosis score 1: portal fibrosis without septa formation

Table 12. Factors Predicting Response to Treatment for HCV

Major Predictors
Viral genotype other than genotype 1
Pretreatment viral load less than 600,000
Other Predictors
Female sex
Age less than 40 years
Non-Black race
Absence of bridging fibrosis or cirrhosis on liver biopsy
Body weight less than or equal to 75 kg
Absence of insulin resistance or metabolic syndrome
Elevated alanine aminotransferase (ALT) levels (3x higher than the upper limit of normal)
IL28B genotypes CC

Once the decision is made to treat patients with antiviral agents, the next step is to consider who to treat with the current standard treatment and who to treat with regimens containing sofosbuvir. The recent AASLD/IDSA guidance on simeprevir and sofosbuvir (AASLD/IDSA 2014) and other organizations (Veterans Health Administration Pharmacy Benefits 2014) *recommend against using sofosbuvir as monotherapy*.

The inclusion and exclusion criteria from published studies (Gane 2013; Jacobson 2013a; Kowdley 2013; Lawitz 2013a; Lawitz 2013b; Osinusi 2013; Rodriguez-Torres 2013) may be useful in selecting patients who are more likely to have response rates closer to those reported in these studies. It is important to note that of the 10 currently published studies and the three trials added in FDA review, only two are comparative (Jacobson [NEJM] 2013a, Lawitz [NEJM]

2013). These two studies only enrolled *patients with genotype 2 and 3*. Table 13 lists the exclusion criteria from the published trials. Six of the 10 studies excluded patients with cirrhosis. The presence or absence of cirrhosis was usually based on liver biopsy within three years of trial entry, and liver biopsy is currently the standard for confirming degree of fibrosis (Bain 2004; Imbert-Bismut 2001; Parkes 2006). In the four studies including patients with cirrhosis, 15% to 35% percent of patients had cirrhosis, and none had decompensated cirrhosis (Jacobson [NEJM] 2013a; Lawitz [NEJM] 2013).

Table 13. Patient Exclusion Criteria from Published Sofosbuvir Trials

Exclusion Criteria
Age less than 18 years
HIV or HBV co-infection
Significant alcohol or drug use within the past 12 months
Excessive current alcohol use
Significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, significant renal disease (estimated glomerular filtration rate less than 60mL/min)

Treatment Summary

Although the evidence base to support use of sofosbuvir presently is poor, some clinicians, policymakers and payers may wish to develop interim treatment and coverage criteria. Potential criteria to guide the use of sofosbuvir that are consistent with current published studies are listed below with several factors to consider.

- Limit use to genotypes 2 and 3, until comparative trials available for genotype 1.
- Do not use sofosbuvir as monotherapy.
- Limit use to patients who failed or did not tolerate current standard of care regimens or in whom PEG is contraindicated.
- Confirm degree of liver fibrosis or cirrhosis prior to authorizing treatment.
- Treat only patients at greatest risk of progressing to cirrhosis (e.g., Metavir fibrosis stage greater than or equal to 2 and additional factors increasing risk of progression to cirrhosis [e.g., hepatic steatosis, men, older, elevated serum alanine transaminase, greater hepatic inflammation]).
- Consider use for patients with HIV or HBV co-infection or those post-liver transplant carefully until comparative trials are available.
- Exclude use in patients with alcohol or drug use within the past year, significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, renal disease (estimated glomerular filtration rate less than 60mL/min).

- Ensure that patients who start therapy are closely tracked to optimize full treatment and follow-up, including prevention of re-infection.

Overall Summary

Hepatitis C is estimated to affect between 1% and 2% of the US population. Although up to one-quarter of those infected can clear the virus spontaneously, in those remaining infected it can progress over the span of 10 to 30 years or more to cirrhosis, liver failure, HCC and death. The genotype HCV-1 accounts for about three-quarters of cases in the US. The current standard of care for HCV-1 involves treatment with PEG, RBV and a protease inhibitor (boceprevir and telapravir are approved for this indication in the US) and treatment of HCV-2 and HCV-3 involves use of PEG and RBV only. These interferon-based regimens have success rates of 40% to 80%, depending of the underlying characteristics of the patient being treated, including factors such as genotype, progression of liver disease, adherence to therapy, and presence of other comorbidities.

Current therapy options present substantial treatment burdens to patients ranging from side effects of drugs and complicated dosing schedules. Treatment options for HCV have been changing quickly since 2011 when protease inhibitors were first approved in the US. In December 2013, the FDA approved two new agents, sofosbuvir and simeprevir, under expedited "breakthrough" status designation which allowed the use of an intermediate trial endpoint (SVR12 instead of the previously required SVR24). There are at least two more DAAs expected to be approved in 2014 and there are other newer drugs in the development pipeline.

Although improved treatments for HCV are certainly desirable, the long course of disease progression also makes it incumbent upon policymakers and clinicians to make sure that treatments will be effective. Most currently infected patients have time available to wait for conclusive data on the effectiveness and harm profile of sofosbuvir or other new drugs before deciding on an optimal treatment regimen.

This rapid evidence review located 10 studies published in seven articles, although the majority of them were non-comparative studies and all but one was at high risk of bias. There were two comparative studies of sofosbuvir treatment for HCV-2 and HCV-3 infection, but no published comparative studies for the treatment of HCV-1. Based on the usual standards of comparative effectiveness research, currently available studies do not provide sufficient evidence for the routine use of sofosbuvir-containing regimens for the treatment of Hepatitis C infection. While initial, uncontrolled, response rates appear to be relatively high among carefully selected populations, response rates in "real world" populations are likely to be lower. Furthermore, there is evidence that relapse rates may be substantial, ranging from 5% to 28% even among patients who are fully treated with these regimens. Similarly, adverse effects have not been

studied in large numbers of patients and among those with substantial other risk factors for harms. When the first two protease inhibitors began to be used in clinical practice, the risks of adverse events approximately tripled and there could be a similar concern with these even newer drugs as they are used in widespread clinical practice.

The recently published HCV treatment guideline published by AASLD and IDSA is of poor methodologic quality and does not adhere to international or US standards for guideline development. In addition, guideline authors had substantial and multiple conflicts of interest.

Due to the lack of the usual requirement of well-designed comparative studies for approval to guide treatment and purchasing studies there is not clear evidence that this drug should be used to treat

While awaiting full disclosure of existing research and the production of more and better evidence on sofosbuvir, policymakers may decide to not allow use of or to allow very limited use of this drug. If limited use is contemplated this report details factors to consider, such as limitation to use in carefully selected HCV-2 and -3 infected individuals who are at great risk of shortly progressing to cirrhosis, and only as part of a regimen including RBV. Policymakers, clinicians and patients should remain aware of upcoming drug research and carefully examine the quality of new research as it is made available.

In addition, the evidence gaps highlighted in this review may offer an opportunity for policymakers and clinicians to advocate for improved research and to contribute to a better evidence base for decision-making. Policymakers might consider the following activities:

- Require transparency about the research. Patients, clinicians and policymakers need adequate information available in order to make good decision about the safety, effectiveness and place in treatment of sofosbuvir. True patient-centeredness requires the availability of all existing data in order for considered decisions to be made that respect patient autonomy. Public stewardship requires those same kind of data to make sure that patients are helped more than harmed and that the overall value of the treatment is worthwhile. As an example, most studies of sofosbuvir include SVR24 as a secondary outcome measure, but this information is not included in many publications. Policymakers can encourage the FDA and ask the manufacturer directly to release this data.
- Policymakers can ask the NIH to fund and the FDA to demand truly comparative studies on this and other newer drugs for Hepatitis C. Current trials do not answer the question of which therapy is best for which patient at which point in time during the disease course. Studies of these drugs should include populations that approximate the

characteristics of publically insured patients including race, stage of disease, prior treatment history, comorbid medical and behavioral health conditions.

- State policymakers may wish to cover sofosbuvir and other newer agents with the requirement of evidence development. Relatively simple data collection efforts may yield evidence more applicable to publically insured populations more rapidly than industry or federally funded research might. For example, if a state simply required submission of SVR24 as a condition of coverage, real world data on this important outcome could be obtained in less than a year.

Appendix A. Treatment Response and Relapse Rates by Genotype and Specialized Studies

Genotype	Treatment	Response	Relapse[1]	Study
Treatment Response and Relapse Rates by Genotype				
Genotype 1	SOF + PEG + RBV 12 w	SVR12: 89% (260/291)	8.6% (28/326)[2]	NEUTRINO, Lawitz 2013, (NEJM)
	Interferon-free regimens			
	SOF + RBV 12 w (tx exp)	SVR12: 10% (1/10) SVR24: 10% (1/10)	90% (9/10)	ELECTRON, Gane 2013
	SOF + RBV 12 w (tx naïve)	SVR12: 84% (21/25) SVR24: 84% (21/25)	16% (4/25)	
	SOF + RBV 24 w	SVR12: 68% (17/25) SVR24: 68% (17/25)	28% (7/25)	NIH study, Osinusi 2013
	SOF + low-dose RBV (600mg) 24 w	SVR12: 48% (12/25) SVR24: 48% (12/25)	40% (10/25)	
Genotype 2	SOF + RBV 12 w	SVR12: 95% (69/73)	5% (4/73)	FISSION, Lawitz 2013, (NEJM)
		SVR12: 82% (33/39)	18% (7/39)	FUSION, Jacobson 2013a (NEJM)
		SVR12: 93% (101/109)	5% (5/107)	POSITRON, Jacobson 2013a (NEJM)
		SVR12: 93% (68/73)	7% (5/73)	VALENCE, Mishra (FDA) 2013 ***Unpublished study***
	SOF + RBV 16 w	SVR12: 89% (31/35)	11% (4/35)	FUSION, Jacobson 2013a

Genotype	Treatment	Response	Relapse[1]	Study
				(NEJM)
Genotype 3	SOF + RBV 12 w	SVR12: 56% (102/183)	40% (72/179)	FISSION, Lawitz 2013, (NEJM)
		SVR12: 30% (19/64)	66% (42/64)	FUSION, Jacobson 2013a (NEJM)
		SVR12: 61% (60/98)	38% (37/98)	POSITRON, Jacobson 2013a (NEJM)
	SOF + RBV 16 w	SVR12: 62% (39/63))	38% (24/63)	FUSION, Jacobson 2013a (NEJM)
	SOF + RBV 24 w	SVR12: 84% (210/250)	14% (34/249)	VALENCE, Mishra (FDA) 2013 ***Unpublished study***
Genotype 4	SOF + PEG + RBV 12 w	SVR12: 96% (27/28)	*Relapse rates were not separately reported by genotype. Overall relapse rate in study 8.6% (28/326)*	NEUTRINO, Lawitz 2013, (NEJM)
Treatment Response and Relapse Rates for HCV/HIV Co-infected Patients				
Genotype 1 (tx naïve)	SOF + RBV 24 w (***interferon free regimen***)	SVR12: 76% (87/114)	22% (25/113)	PHOTON-1, Mishra (FDA) 2013 ***Unpublished study***
Genotype 2	SOF + RBV 12 w (tx naïve)	SVR12: 88% (23/26)	18% (12/67) (combines genotype 2/3)	
	SOF + RBV 24 w (tx exp)	SVR12: 93% (14/15)	7% (2/28) (combines genotype 2/3)	
Genotype 3	SOF + RBV 12 w (tx naïve)	SVR12: 67% (28/42)	18% (12/67) combines	

Genotype	Treatment	Response	Relapse[1]	Study
			genotype 2/3)	
	SOF + RBV 24 w (tx exp)	SVR12: 92% (12/13)	7% (2/28) (combines genotype 2/3)	
Treatment Response Sofosbuvir + Simeprevir Combination Study				
Genotype 1 **Cohort 1 (null response prior tx (PEG+RBV)** **Metavir score = F0-F2)**	SOF + SMV 12 w	SVR 12: 93% (13/14)	Relapse was unevenly reported in the abstracts Jacobson (2013b) reported that "3 pts in the C1/C2 12 w groups (± RBV) and 1 pt in the C1 24 w (+RBV) group" relapsed. Sulkowski (2014) reported that 3 pts in cohort 1 relapsed (tx regimen not specified) Lawitz (2014) reported that 3 pts relapsed in cohort 2 (tx regimen not specified)	COSMOS Jacobson 2013b Hepatology ***Published abstract only*** Sulkowski 2014 ***Conference presentation; excluded 5 pts included in Jacobson (2013b)***
	SOF + SMV + RBV 12 w	SVR12: 96% (26/27)		
	SOF + SMV 24 w	SVR12: 100% (14/14)		
	SOF + SMV + RBV 24 w	**SVR12: 79% (19/24)[3]**		
Genotype 1 **Cohort 2 – (null response to prior tx or tx naïve with Metavir Score F3-F4)**	SOF + SMV 12 w	SVR12: 92.9% (13/14)		Lawitz 2014 ***Conference presentation***
	SOF + SMV + RBV 12 w	SVR12: 92.9% (13/14)		
	SOF + SMV 24 w	SVR12: 92.9% (13/14)		
	SOF + SMV + RBV 24 w	SVR12: 92.9% (13/14)		

Abbreviations: Exp – experienced; NEJM – New England Journal of Medicine; NR – not reported; PEG – pegylated interferon therapy; RBV – ribavirin; unless otherwise specified, RBV refers to weight-based ribavirin, e.g. 1000 mg for weight < 75 kg and 1200 mg for weight ≥ 75 kg daily; SOF – sofosbuvir 400 mg daily; SMV – simeprevir 150 mg daily; SVR – sustained virologic response; tx – treatment; w – weeks

Notes

[1]Relapse is defined as a patient achieving HCV RNA < lower limit of quantitation (LLOQ) at the last measurement on treatment but subsequently having a HCV RNA ≥ LLOQ post treatment

[2]Relapse rate includes data on the 35 pts with HCV 4-6 as data was not separated out.

[3]A subsequent abstract presented at the April, 2014 European Association for the Study of the Liver (EASL) conference excluded "five patients withdrawn for non-virologic failure" and reported an SVR12 rate for this group of 90.5% (19/21) (Sulkowski 2014). No other SVR12 rates changed after excluding the patients.

Appendix B. Study Population Characteristics

Author, Year (Trial)	Study Design	HCV-1, Tx Naïve (n)	HCV-1, Prior Tx (n)	HCV-2 Tx Naïve (n)	HCV 2 , Prior Interferon Tx (n)	HCV-3, Tx Naïve (n)	HCV-3, Prior Interferon Tx (n)	HCV-2, Tx w/ Interferon Not an Option (n)	HCV-3, Tx w/ Interferon Not an Option (n)	HCV-4, 5 or 6 (n)	Male (n, %)	Caucasian (n, %)	C: Cirrhosis (n, %) F: Bridging fibrosis (n, %)
Gane, 2013 (ELECTRON)	Open label Largely a PEG regimen range study for HCV-2,3 and PEG sparing for HCV-1	25	10	18	---	42	---	---	---	---	58 (61%)	74 (78%)	---
Jacobson, 2013a (Study 1) (POSITRON)	Placebo control RCT INF tx contraindicated, unacceptable or prior discontinuation due to unacceptable AEs 12w SOF + RBV vs placebo	---	---	---	---	---	---	143	135	---	151 (54%)	254 (91%)	C: 68 (34%)
Jacobson, 2013a (Study 2) (FUSION)	Active control RCT No prior response to prior INF containing regimen Duration ranging study	---	---0	---	68	---	127	---	---	---	140 (70%)	174 (87%)	C: 44 (16%)

Author, Year (Trial)	Study Design	HCV-1, Tx Naïve (n)	HCV-1, Prior Tx (n)	HCV-2 Tx Naïve (n)	HCV 2 , Prior Interferon Tx (n)	HCV-3, Tx Naïve (n)	HCV-3, Prior Interferon Tx (n)	HCV-2, Tx w/ Interferon Not an Option (n)	HCV-3, Tx w/ Interferon Not an Option (n)	HCV-4, 5 or 6 (n)	Male (n, %)	Caucasian (n, %)	C: Cirrhosis (n, %) F: Bridging fibrosis (n, %)
Kowdley, 2013 (ATOMIC)	Open label RCT (Cohorts A and C) Duration ranging 12 vs 24w PEG + RBV	207	---	---	---	---	---	---	---	---	141 (68%)	[% black] 18 (9%)	F: 47 (14%)
Kowdley, 2013 (ATOMIC)	Open label NRS (Cohort B of ATOMIC with addition of NR HCV-4, 6 pts)	109	---	---	---	---	---	---	---	16	73 (58%)	[% black] 17 (14%)	See above: 23 of 47 pts with BF were in this group
Lawitz, 2013a (Lancet)	Dose finding placebo control RCT for HCV-1 and additional single group for HCV-2, 3; all tx naïve and non-cirrhotic	121	---	---	---	---	---	---	---	---	73 (60%)	97 (80%)	F: 5 (4%)
Lawitz, 2013a (Lancet)	Additional single group study with HCV-2,3	---	---	15	---	10	---	---	---	---	16 (64%)	20 (80%)	F: 0%
Lawitz, 201b3 (Study 1) (NEJM)	Open label, single group, tx naïve, predominantly HCV-1	291	---	---	---	---	---	---	---	35	209 (64%)	257 (79%)	C: 54 (17%)

Author, Year (Trial)	Study Design	HCV-1, Tx Naïve (n)	HCV-1, Prior Tx (n)	HCV-2 Tx Naïve (n)	HCV 2 , Prior Interferon Tx (n)	HCV-3, Tx Naïve (n)	HCV-3, Prior Interferon Tx (n)	HCV-2, Tx w/ Interferon Not an Option (n)	HCV-3, Tx w/ Interferon Not an Option (n)	HCV-4, 5 or 6 (n)	Male (n, %)	Caucasian (n, %)	C: Cirrhosis (n, %) F: Bridging fibrosis (n, %)
(NEUTRINO)													
Lawitz, 2013b (Study 2) (NEJM) (FISSION)	Open label non-inferiority RCT; tx naïve HCV-2, 3; 12w SOF + RBV vs PEG + RBV	3	---	137	---	359	---	---	---	---	327 (66%)	435 (88%)	100 (20%)
Osinusi, 2013 (Study 1)	Proof of concept(n=10) with HCV-1 and unfavorable tx characteristics	10	---	---	---	---	---	---	---	---	4 (40%)	1 (10%)	F: [Knodell HAI fibrosis score 3 to 4] 1 (10%)
Osinusi, 2013 (Study 2)	Open label RCT with HCV-1 and unfavorable tx characteristics	50	---	---	---	---	---	---	---	---	33 (66%)	7 (14%)	F: [Knodell HAI fibrosis score 3 to 4] 13 (26%)
Rodriguez-Torres, 2013	Blinded RCT; tx naïve with HCV-1; dose ranging	63	---	---	---	---	---	---	---	---	43 (68%)	57 (90%)	F: 4 (6 %)

Author, Year (Trial)	Study Design	HCV-1, Tx Naïve (n)	HCV-1, Prior Tx (n)	HCV-2 Tx Naïve (n)	HCV 2 , Prior Interferon Tx (n)	HCV-3, Tx Naïve (n)	HCV-3, Prior Interferon Tx (n)	HCV-2, Tx w/ Interferon Not an Option (n)	HCV-3, Tx w/ Interferon Not an Option (n)	HCV-4, 5 or 6 (n)	Male (n, %)	Caucasian (n, %)	C: Cirrhosis (n, %) F: Bridging fibrosis (n, %)
Unpublished Trial Included in FDA Review													
FDA (Mishra 2013) VALENCE	Open label trial; tx naïve with HCV 2 or 3 SOF + RBV for 12 w (HCV-2) SOF + RBV for 24 w (HCV 3)	---	---	91	---	317	---	---	---	---	250 (60%)	393 (94%)	C: 88 (21%)
TOTALS (from above trials)	n/a	879	16	261	68	728	127	143	135	51	n/a	n/a	n/a
Unpublished Trial Included in FDA Review on HCV and HIV Coinfected Patients													
FDA (Mishra 2013) PHOTON-1	Open label dose ranging study in patients **with HIV-1 diagnosis** Total n = Tx naïve HCV 2-3: SOF + RBV 12 w	114	---	26	24	42	17	---	---	---	185 (83%)	153 (69%)	C: 22 (10%)

Author, Year (Trial)	Study Design	HCV-1, Tx Naïve (n)	HCV-1, Prior Tx (n)	HCV-2 Tx Naïve (n)	HCV 2 , Prior Interferon Tx (n)	HCV-3, Tx Naïve (n)	HCV-3, Prior Interferon Tx (n)	HCV-2, Tx w/ Interferon Not an Option (n)	HCV-3, Tx w/ Interferon Not an Option (n)	HCV-4, 5 or 6 (n)	Male (n, %)	Caucasian (n, %)	C: Cirrhosis (n, %) F: Bridging fibrosis (n, %)
	Tx experienced HCV 2-3 or HCV 1 SOF + RBV 24 w												

Abbreviations: AEs – adverse events; HAI – histology activity index; HCV – hepatitis C virus; INT – interferon; n/a – not applicable; NR – not reported; NRS – not reported study; PEG – pegylated interferon therapy; RBV – ribavirin; unless otherwise specified, RBV refers to weight-based ribavirin, e.g. 1000 mg for weight < 75 kg and 1200 mg for weight ≥ 75 kg daily; RCT – randomized controlled trial; SOF – sofosbuvir 400 mg daily; tx – treatment; w – weeks

Appendix C. Evidence Tables

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
Gane, 2013	Open label Largely a PEG regimen range study for HCV-2, 3 and PEG sparing for HCV-1 N=95 *Group 1* n=10 *Group 2* n=9 *Group 3* n=10 *Group 4* n=11 *Group 5* n=10 *Group 6*	Inclusion • Age ≥ 19 • HCV RNA > 50,000 IU/mL • For groups 1 to 6, HCV-2 or 3 and tx naïve • For group 7, HCV-1, prior tx failure • For group 8, HCV-1, tx naïve Exclusion • Cirrhosis • HIV or HBV positive	*Group 1; Group 2; Group 3; Group 4; Group 5; Group 6; Group 7; Group 8* Male n (%) 8 (80) 5 (56) 5 (50) 9 (82) 4 (40) 5 (50) 7 (70) 15 (60) Race n (%) *White* 7 (70) 4 (44) 8 (80) 9 (82) 4 (40) 5 (50) 9 (90) 20 (80)	Intervention 8 arm trial, all pts rec'd SOF in different regimen Groups 1 to 6, all HCV-2 or 3 and tx naïve *Group 1* SOF 400 mg/d + weight based RBV/d for 12w *Group 2* SOF 400 mg/d + RBV for 12w + PEG 180µg/w for 4w *Group 3* SOF 400 mg/d + RBV for 12w + PEG 180µg/w	Outcomes • SVR 24 • Adverse events Findings **SVR 24** n (%, 95%CI) *Group 1* 10 (100, 69 to 100) *Group 2* 9 (100, 66 to 100) *Group 3* 10 (100, 69 to 100) *Group 4* 11 (100, 72 to 100) *Group 5* 6 (60, 26 to 88) *Group 6* 9 (90, 66 to 100)	Gilead sponsored, analyzed data and prepared final version of report Not a controlled trial as all pts rec'd SOF. 4 groups (2 HCV-2/3 and 2 HCV-1) did not also get PEG Small sample size, not designed to statistically test outcomes Race is reported only as percentage

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	n=10 *Group 7* n=10 *Group 8* n=25		<u>Age</u> <u>mean (range)</u> 47 (36 to 53) 48 (29 to 66) 49 (30 to 62) 46 (37 to 57) 43 (22 to 58) 39 (19 to 54) 48 (30 to 58) 49 (22 to 69) <u>BMI</u> <u>mean (range)</u> 28 (24 to 36) 26 (21 to 32) 25 (18 to 33) 24 (21 to 28) 26 (18 to 39) 25 (21 to 35) 28 (20 to 36) 26 (19 to 38) <u>HCV RNA log_{10}IU/mL</u> <u>mean (range)</u> 6.7 (5.7 to 7.1) 6.6 (5.6 to 7.4)	for 8w *Group 4* SOF 400 mg/d + RBV for 12w + PEG 180µg/w for 12w *Group 5* SOF 400 mg/d for 12w *Group 6* SOF 400 mg/d + RBV + PEG for 8w *Group 7* HCV-1 with prior tx failure SOF 400 mg/d + RBV for 12w *Group 8* HCV-1 tx naïve SOF 400 mg/d + RBV for 12w	*Group 7* 1 (10, 0 to 45) *Group 8* 21 (84, 64 to 96) **Adverse events** n (%) *Grade 3 anemia* 17 (17.9%) *Grade 3 or 4 lymphopenia* 4 (4.2%) *Grade 3 or 4 neutropenia* 12 (12.6%) *Grade 3 leukopenia* 5 (5.3%) Authors state reduced hemoglobin levels more common in pts receiving PEG than those w/o,	white with no further details

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			6.5 (5.5 to 7.2) 6.5 (5.2 to 7.3) 5.9 (4.6 to 7.4) 6.0 (4.3 to 7.3) 7.0 (5.6 to 7.5) 6.2 (4.4 to 7.2) <u>HCV-2 (Groups 1 to 6) n (%)</u> 4 (40) 3 (33) 4 (40) 4 (36) 3 (30) 0 <u>HCV-3 (Groups 1 to 6) n (%)</u> 6 (60) 6 (67) 6 (60) 7 (64) 7 (70) 10 (100)	<u>Follow-up</u> 24w post tx	but no statistical analysis	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			HCV-1a (Groups 7 to 8) n (%) 9 (90) 22 (88) HCV-1b (Groups 7 to 8) n (%) 1 (10) 3 (12) IL28B genotype n (%) *CC* 5 (50) 4 (44) 4 (40) 4 (36) 2 (20) 3 (30) 2 (20) 11 (44) *CT* 4 (40) 4 (44) 4 (40) 5 (45) 6 (60)			

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			6 (60) 5 (50) 12 (18) *TT* 1 (10) 1 (11) 2 (20) 2 (18) 2 (20) 1 (10) 3 (30) 2 (8) <u>Loss to follow-up</u> 1 pt, group 6			
Jacobson , 2013a (study 1) POSITRON study	Placebo control RCT Interferon tx contraindicated, unacceptable or prior discontinuation due to unacceptable	<u>Inclusion</u> • Age ≥ 18 • HCV-2 or 3 • HCV RNA ≥ 104 IU/mL • BMI ≥ 18 kg/m2 • Discontinuation of previous interferon tx due to AE OR ineligible for interferon tx OR declined interferon tx • Up to 20% with	*Placebo; Intervention* <u>Age</u> <u>mean (range)</u> 52 (28 to 67) 52 (21 to 75) <u>BMI</u> <u>mean (range)</u> 28 (20 to 43) 28 (18 to 53)	<u>Intervention</u> SOF 400 mg/d and RBV 1000 to 12000 mg/d for 12w <u>Comparator</u> Placebo <u>Follow-up</u> 24w post tx	<u>Outcomes</u> • SVR 4 post tx • SVR 12 post tx • Relapse • Adverse events <u>Findings</u> n (%) **SVR 4 post tx** *Intervention* 172/207 (83%), 204 returned for	Gilead sponsored, analyzed data and prepared final version of report 63 sites in US, Canada, Australia, New

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	AEs N=278 *Intervention* n=207 *Comparator* n=71	compensated cirrhosis • ECG w/o abnormalities • AAT ≤ 10 x ULN • AST ≤ 10 x ULN • Hb ≥ 12 g/dL for men and ≥ 11 g/dL for women • Albumin ≥ 3 g/dL • Direct bilirubin ≤ 1.5 x ULN • HbA1c ≤ 10% • Creatine clearance ≥ 60mL/min • INR ≤ 1.5 x ULN • No investigational drug w/i 30d • Contraception <u>Exclusion</u> • Prior exposure to a direct-acting anti-viral targeting HCV NS5B polymerase • Pregnant/nursing/pregnant partner • Other clinically significant chronic liver disease • HIV or HBV positive	<u>Male n (%)</u> 34 (48%) 117 (57%) <u>Race n (%)</u> *White* 66 (93%) 188 (91%) *Black* 4 (6%) 9 (4%) *Hispanic* 11 (15%) 19 (9%) <u>HCV-2 n (%)</u> 34 (48%) 109 (53%) <u>HCV-3 n (%)</u> 37 (52%); 98 (47%) <u>IL28B genotype n (%)</u> *CC* 29 (41%)	6 pts (2.9%) did not complete tx, 2 pts lost to follow-up	visit *Placebo* 0/71 (0%), 71 returned for visit **SVR 12 post tx** n (%, 95% CI) *Intervention* 161/207 (78, 72 to 83) (only 171/207 pts returned for 12w post follow-up) **Factors significantly associated with SVR 12** *Sex (female vs male)* OR 2.668 (95% CI, 1.198 to 5.940) p=0.0163	Zealand Only reports SVR 12 Note that at the end of tx, all pts in intervention group showed HCV RNA < 25 IU/mL but by week 12 after tx had dropped to 78%. 22% had relapsed. What would happen by week 24?

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		• Contraindications to RBV therapy • Chronic use of immunosuppressive agents • Significant drug or alcohol abuse w/i 12m • Excessive alcohol consumption • Hx of malignancy, clinically significant hemoglobinopathy, solid organ transplantation, clinical hepatic decompensation, primary gastrointestinal disorder, significant pulmonary or cardiac disease or porphyria, or other serious clinical condition • Hx of difficulty with blood collection or venous access • Donation or loss of > 400mL of blood w/i 2m	97 (47%) *CT* 36 (51%) 84 (41%) *TT* 6 (8%) 26 (13%) Cirrhosis n (%) 13 (18%) 31 (15%) Baseline ALT > 1.5 x ULN 42 (59%) 117 (57%) INF tx classification *Unacceptable AE* 8 (11%) 17 (8%) *Contraindicated* 33 (46%) 88 (43%)		*HCV-2 vs HCV-3* OR 8.659 (95% CI, 3.616 to 20.732) p<0.0001 *Duration of prior HCV tx (>12w vs no tx)* OR 0.131 (95% CI 0.038 to 0.452) p<0.0013 **Relapse** 42 pts relapsed after stopping tx (42/207 = 20.3%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Pts decision 30 (42%) 102 (49%) <u>Response to previous tx</u> *No response* 2 (3%) 2 (1%) *Relapse* 4 (6%) 11 (5%)			
Jacobson , 2013a (Study 2) FUSION study	Active control RCT No prior response to prior INF containing regimen N=201 *Group 1* n=103	<u>Inclusion</u> • Age ≥ 18 • HCV-2 or 3 • Prior tx failure with INF for ≥ 12w (non-response or relapse/breakthrough) • Up to 30% with compensated cirrhosis • HCV RNA ≥ 104 IU/mL • BMI ≥ 18 kg/m2 • ECG w/o abnormalities • Discontinuation of previous INF tx due to AE *or* ineligible	*Group 1, Group 2* <u>Age</u> <u>mean (range)</u> 54 (30 to 69) 54 (24 to 70) <u>BMI</u> <u>mean (range)</u> 28 (19 to 43) 29 (20 to 44) <u>Male n (%)</u> 73 (71%)	<u>Group 1</u> SOF 400 mg/d and RBV 1000 to 1200 mg/d for 12w then 4w of placebo <u>Group 2</u> SOF 400 mg/d and RBV 1000 to 1200 mg/d for 16w 1 pt in group 1	<u>Outcomes</u> • SVR 4w post tx • SVR 12w post tx • Relapse • Adverse events <u>Findings</u> n (%) **SVR 4 post tx** *Group 1* 56/100 (56%), 99 returned for visit	Gilead sponsored, analyzed data and prepared final version of report

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	Group 2 n=98	for interferon tx OR declined interferon tx • Up to 20% with compensated cirrhosis • AAT ≤ 10 x ULN • AST ≤ 10 x ULN • Hb ≥ 12 g/dL for men and ≥ 11 g/dL for women • Albumin ≥ 3 g/dL • Direct bilirubin ≤1.5 x ULN • HbA1c ≤ 10% • Creatine clearance ≥ 60mL/min • INR ≤ 1.5 x ULN • Platelets ≥ 50,000 µL • No investigational drug w/i 30 days • Contraception <u>Exclusion</u> • Prior exposure to direct-acting anti-viral targeting HCV NS5B polymerase • Pregnant/nursing/pregnant partner	67 (68%) <u>Race n (%)</u> *White* 88 (85%) 86 (88%) *Black* 5 (5%) 1 (1%) *Hispanic* 10 (10%) 8 (8%) <u>HCV-1 n (%)</u> 3 (3%) 3 (3%) <u>HCV- 2 n (%)</u> 36 (35%) 32 (33%) <u>HCV-3 n (%)</u> 64 (62%) 63 (64%)	discontinued tx due to AE, 2 pts in group 1 lost to follow-up	*Group 2* 73/95 (77%), 95 returned for visit **SVR 12 post tx** *Group 1* 50/100 (50%), 54 returned for visit *Group 2* 69/95 (73%), 73 returned for visit **Factors associated with SVR 12 for Group 1** *HCV- 2 vs HCV- 3* OR 21.486 (95% CI, 6.144 to 75.142) p<0.0001 *Baseline weight-based RBV dose* OR 1.469 (95% CI, 1.089 to 1.983) p=0.0119	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		• Other clinically significant chronic liver disease • HIV or HBV positive • Contraindication to RBV tx • Chronic use of immunosuppressive agents • Significant drug or alcohol abuse w/i 12m • Hx of malignancy, clinically significant hemoglobinopathy, solid organ transplantation, clinical hepatic decompensation, primary gastrointestinal disorder, significant pulmonary or cardiac disease or porphyria, or other serious clinical condition • Excessive alcohol consumption • Hx of difficulty with blood collection or venous access • Donation or loss of > 400mL of blood w/i 2m	<u>IL28B genotype n (%)</u> *CC* 31 (30%) 30 (31%) *CT* 53 (51%) 56 (57%) *TT* 19 (18%) 12 (12%) <u>Cirrhosis n (%)</u> 36 (35%) 32 (33%) <u>Response to previous tx</u> <u>n (%)</u> *No response* 25 (24%) 25 (26%) *Relapse* 78 (76%) 73 (74%)		*Cirrhosis (no vs yes)* OR 3.117 (95% CI 1.019 to 9.537) p=0.0463 **Factors associated with SVR 12 for Group 2** *HCV- 2 vs HCV-3* OR 10.522 (95% CI 2.251 vs. 49.174) p=0.0028 *Female vs male* OR 3.978 (95% CI, 1.169 to 13.539) p=0.0271 **Relapse** 73 pts relapsed after stopping tx (73/201, 36.3%), *no details provided*	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
Kowdley, 2013	Open label Duration ranging 12w vs 24w PEG + RBV N=332 *Cohort A* n=52 (HCV-1) *Cohort B* n=125 (HCV-1 = 109; HCV-4 = 11; HCV-6 = 5) *Cohort C* n=155 (HCV-1)	<u>Inclusion</u> • Age ≥ 18 • HCV-1, 4, 5 or 6 • Tx naïve • HCV RNA ≥ 50,000 IU/mL <u>Exclusion</u> • Cirrhosis or other chronic liver disease • BMI ≤ 18 kg/m2 • HIV or HBV positive	*Cohort A; Cohort B; Cohort C except where noted* <u>Age</u> <u>(mean ± sd)</u> 51 ± 9.8 50 ± 11 50 ± 10.8 <u>Male n (%)</u> 35 (67%) 73 (58%) 106 (68%) <u>Race n (%)</u> *Black* 2 (4%) 17 (14%) 16 (10%) *Non-black* 50 (96%) 108 (86%) 139 (10%)	<u>Intervention</u> *Cohort A* SOF 400 mg/d + weight based RBV/d + PEG 180µg/w for 12w *Cohort B* SOF 400 mg/d + RBV/d + PEG/w for 24w *Cohort C* SOF 400 mg/d + RBV/d + PEG for 12w then 50% rec'd SOF mono tx for 12w; 50% rec'd SOF + RBV for 12w <u>Follow-up</u> 24w	<u>Outcome</u> • SVR 24 • Adverse events <u>Findings</u> **SVR 24 for HCV-1** n (%, 95% CI) *Cohort A* 46/52 (89, 77 to 96) *Cohort B* 97/109 (89, 82 to 94) *Cohort C* 135/155 (87, 81 to 92) **SVR 24 for HCV-4** n (%, 95% CI) *Cohort B* 9/11 (82, 48 to 98) **SVR 24 for HCV-6** n (%, 95% CI) *Cohort B*	Gilead sponsored, analyzed data and prepared final version of report Pooled efficacy data for Cohort C's 2 extended tx arms Per-protocol analysis also included in article

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Hispanic 10 (19%) 26 (21%) 31 (20%) <u>BMI</u> <u>(mean ± sd)</u> 27.2 ± 4.6 27.6 ± 5.0 28.4 ± 4.6 <u>HCV RNA log_{10} IU/mL</u> <u>(mean ± sd)</u> 6.5 ± 0.7 6.3 ± 0.7 6.4 ± 0.8 <u>HCV-1a, 1b, 4, 6</u> <u>n (%)</u> *Cohort A* 40 (77%) 12 (23%) 0 0 *Cohort B* 85 (68%)		5/5 (100, 48 to 100) **Difference in SVR 24 for HCV-1 by regime** A to B: p=0.94 A to C: p=0.78 **Relapse** *Cohort A* 2 (4%) *Cohort B* 1 (1%) *Cohort C* 4 (3%) **Adverse events** 13 serious AEs in 12 pts *9 adverse events reported t as "non-tx related"* arrythemia, ischaemic colitis,	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			24 (19%) 11 (19%) 5 (4%) *Cohort C* 116 (75%) 39 (25%) 0 0 <u>IL28B genotype n (%)</u> *CC* 13 (25%) 36 (29%) 39 (25%) *CT* 33 (64%) 63 (50%) 88 (57%) *TT* 6 (12%) 26 (21%) 28 (18%)		chest pain, acute cholecystitis, cholelithiasis, alcohol poisoning, road traffic accident, costochondritis, hip arthroplasty *4 adverse events reported as related to PEG and RBV but not SOF* anemia, auto-immune hepatitis, pyelonephritis, pancytopenia	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			No/minimal fibrosis n (%) 9 (17%) 14 (11%) 20 (13%) Portal fibrosis n (%) 36 (69%) 93 (74%) 99 (64%) Bridging fibrosis n (%) 7 (14%) 17 (14%) 23 (15%) Loss to f/u n (%) 26 (7.8%) *Cohort A* 4 (7.7%) *Cohort B* 13 (10.4%) *Cohort C* 9 (5.8%)			

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
Lawitz , 2013a (Lancet)	Dose finding placebo control RCT for HCV-1 and additional single group for HCV-2, 3; all tx naïve and non-cirrhotic N=147 *Cohort A* n=122 Group 1 n=48 Group n=48 Group 3 n=26 *Cohort B* n=25	Inclusion • Age ≥ 18 • HCV-1, 2 or 3 • Tx naïve • HCV RNA ≥ 50,000 IU/mL • Neutrophil count 1-5 x 109/L or ≥ 1-25 x 109/L for black patients • Hb ≥ 11 g/dL for women or ≥ 12 g/dL for men • Platelets ≥ 90x109/L • Total bilirubin ≤ 2xULN • Albumin ≤ 30 g/L Exclusion • Cirrhosis • HIV or HBV positive • Hx of psychiatric illness, pulmonary or cardiac disease, seizure disorder or other serious comorbid condition	*Cohort A (Group 1, Group 2, Group 3)* Age (mean ± sd) 48.4 ± 11.5 51.4 ± 9.4 48.6 ± 9.4 Male n (%) 33 (69%) 21 (45%) 19 (73%) Race n (%) *White* 39 (81%) 37 (78%) 21 (80%) *Black* 6 (13%) 7 (15%) 5 (19%) *Hispanic* 5 (10%)	Intervention *Cohort A* HCV-1 randomized 2:2:1 to 3 protocols in 2 steps. 1st step for 12w *Group 1* SOF 200 mg/d + weight based RBV/d + 180µg PEG weekly *Group 2* SOF 400 mg/d + RBV/d + PEG weekly *Group 3* Placebo + RBV + PEG If pts achieved eRVR (HCV RNA ≤ 15 IU/mL) in	Outcomes • Primary outcome – safety and tolerability • "study was not designed to statistically test efficacy" (p.403) • Secondary outcomes o RVR 4 o SVR 12 o SVR 24 Findings **Adverse Events** (Cohorts A & B) *Common side effects* Fatigue, headache, nausea, chills, pain, insomnia Fatigue, rash,	Gilead sponsored, analyzed data and prepared final version of report Placebo group (Cohort A, PEG-INF + RBV + placebo) very small (n=26)

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			6 (13%) 1 (4%) <u>BMI</u> <u>(mean ± sd)</u> 26.6 ± 3.4 26.8 ± 4.5 28.6 ± 4.1 <u>HCV RNA IU/mL</u> <u>(mean ± sd)</u> 6.5 ± 0.6 6.4 ± 0.8 6.5 ± 0.8 <u>HCV-1a n (%)</u> 37 (77%) 35 (74%) 20 (77%) <u>HCV-1b n (%)</u> 11 (23%) 12 (26%) 6 (23%) <u>IL28B genotype n (%)</u> *CC*	weeks 4 to 12, pts rec'd 12w of PEG + RBV If placebo or failure to achieve eRVR, pts rec'd 36w PEG + RBV *Cohort B* HCV-2 or -3 SOF 400 mg + RBV + PEG for 12w	fever, diarrhea "more common" in SOF groups than placebo (no p value) Headache more common in placebo group (no p-value) 3 pts in SOF regimens developed level 3 increase in AST levels 8 pts in Cohort A discontinued tx due to AE *Group 1* 2 pts – neutropenia, folliculitis *Group 2* 3 pts – aphthous	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			21 (44%) 18 (38%) 11 (42%) *CT* 24 (50%) 19 (40%) 11 (42%) *TT* 3 (6%) 10 (21%) 4 (15%) <u>No/minimal fibrosis n (%)</u> 12 (25%) 7 (15%) 3 (12%) <u>Portal fibrosis n (%)</u> 35 (73%) 38 (81%) 21 (81%)		ulcer; MI; depression & suicidal ideation Post SOF, 3 pts with severe AE: retinal vein occlusion; lynphangitis; chest pain & ECG ST segment elevation **RVR 4** n (%, 95% CI) *Cohort A* Group 1 47 (98, 89 to 100) Group 2 46 (98, 89 to 100) Group 3 5 (19, 7 to 39) *Cohort B* 24 (96, 80 to 100)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Bridging fibrosis n (%) 1 (2%) 2 (4%) 2 (8%) Loss to follow-up 2 *Cohort B* Age (mean ± sd) 47.2 ± 11.1 Male n (%) 16 (64%) Race n (%) *White* 20 (80%) *Black* 4 (16%) *Hispanic* 1 (4%) BMI (mean ± sd)		**SVR 12** n(%, 95% CI) *Cohort A* Group 1 43 (90, 77 to 97) Group 2 43 (91, 80 to 98) Group 3 15 (58, 40 to 77) *Cohort B* 23 (92, 74 to 99) **SVR 24** n (%, 95% CI) *Cohort A* Group 1 41 (85, 72 to 94) Group 2 42 (89, 77 to 96) Group 3 15 (58, 40 to 77)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			28.6 ± 4.8 <u>HCV RNA IU/mL (mean ± sd)</u> 6.1 ± 0.8 <u>HCV-2 n (%)</u> 15 (60%) <u>HCV-3 n (%)</u> 10 (40%) <u>IL28B genotype n (%)</u> *CC* 7 (28%) *CT* 17 (68%) *TT* 1 (4%) <u>No/minimal fibrosis n (%)</u> 7 (28%) <u>Portal fibrosis n (%)</u> 18 (72%)		*Cohort B* 23 (92, 74 to 99)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Loss to follow-up 1			
Lawitz, 2013b (NEJM) (Study 1) NEUTRINO study	Open label; single group; tx naïve; 89% HCV-1 (11% HCV-4, 5, 6); 17% cirrhotic N=327	Inclusion • Age ≥ 18 • HCV-1,4,5, or 6 • HCV RNA ≥ 10,000 IU/mL • HCV tx naïve • Up to 20% of pts could have evidence of cirrhosis • BMI ≥ 18 kgm2 • ALT ≤ 10x ULN • AST ≤ 10 x ULN • Hb ≥ 12 g/dL for males, ≥ 11 g/dL for females • White blood cell count ≥2500/µL • Absolute neutrophil count ≥1500/µL (or≥ 1000/µL if considered a physiologic variant in a subject of African descent) • Platelets ≥ 90,000/µL • INR ≤ 1.5 x ULN unless subject has known hemophilia or is stable on an	Age mean (range) 52 (19 to 70) Male n (%) 209 (64%) Race n (%) *White* 257 (79%) *Black* 54 (17%) *Hispanic* 46 (14%) HCV-1a n (%) 225 (69%) HCV-1b n (%) 66 (20%) HCV-4 n (%) 28 (9%)	Intervention SOF 400 mg/d, weight based RBV daily (1000mg < 75kg or 1200mg ≥ 75kg), and PEG alfa 2a 180 µg weekly for 12w Comparator *None* Follow up 12w post tx	Outcomes • SVR 12 post tx Findings n (%, 95% CI) **SVR 12** *Overall* 295/327 (90.2, 87 to 93) No significant difference in SVR by genotype or race *Cirrhosis* 43/54 (79.6, 67 to 89) *No cirrhosis* 252/273 (92.3, 88.5 to 5.2) (no p value)	Gilead sponsored, analyzed data and prepared final version of report

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		anticoagulant regimen affecting INR • Albumin ≥ 3 g/dL • Direct bilirubin ≤ 1.5 x ULN • Thyroid-stimulating hormone (TSH) ≤ ULN • HgbA1c ≤ 10% • Creatinine clearance ≥ 60 mL/min, as calculated by the Cockcroft-Gault equation • No investigational study participation w/i 30 days • Contraception <u>Exclusion</u> • Prior tx for HCV with an INF or RBV • Prior exposure to a direct-acting antiviral targeting the HCV NS5B polymerase • Pregnant/nursing/pregnant partner • Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, α1 antitrypsin	<u>HCV-5 n (%)</u> 1 (<1%) <u>HCV-6 n (%)</u> 6 (2%) <u>BMI</u> <u>Mean (range)</u> 29 (18 to 56) <u>Mean HCV RNA log_{10} UL/mL</u> <u>(mean ± sd)</u> 6.4 ± 0.7 <u>HCV RNA ≥ 800,000 IU/mL</u> <u>n (%)</u> 267 (82% <u>IL28B genotype</u> <u>n (%)</u> *CC* 95 (29%) *CT* 181 (55%)		*IL28B GT CC* 93/95 (97.9, 92.6 to 99.7) *IL28B GT non-CC* 202/232 (87.%,82.1 to 91.1) (no p value) **Adverse events** *Any AE* 310/327 (95%) 5 pts (2%) discontinued due to AE 4 pts (1%) serious AE (not specified)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		deficiency, cholangitis) • HIV or HBV positive • Contraindications for PEG or RBV therapy • Pre-existing significant psychiatric conditions including severe depression, severe bipolar disorder, and schizophrenia. Other psychiatric disorders are permitted if the condition is well controlled with a stable tx regimen for ≥ 1 yr from screening • Hx of autoimmune disorders, severe chronic obstructive pulmonary disease, significant cardiac disease, clinically significant retinal disease, clinically significant malignancy diagnosed or treated w/i 5 yrs, solid organ transplantation, hepatic decompensation, gastrointestinal disorder,	*TT* 51 (16%) Cirrhosis n (%) 54 (17%) AAT ≥ 1.5xUL n (%) 166 (51%) Loss to follow-up n (%) 2 (0.6%)			

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		porphyria, or other major illness. • Chronic use of systemically administered immunosuppressive agents • Clinically relevant drug or alcohol abuse w/i 12m of screening • Excessive alcohol ingestion • Hx of difficulty with blood collection and/or poor venous access for the purposes of phlebotomy • Donation or loss of >400 mL of blood w/i 2m prior to baseline/day 1 • Use of any prohibited concomitant medications w/i 28d of the baseline/day 1 visit • Known hypersensitivity to PEG, RBV, the study investigational medicinal product, the metabolites, or formulation excipients				

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
Lawitz , 2013b (NEJM) (Study 2) FISSION study	Open label RCT tx naïve; HCV-2, 3; 20% cirrhotic N=499 *Intervention* n=256 *Comparator* n=243	Inclusion • Age ≥ 18 • HCV-2 or 3 • HCV RNA ≥ 10,000 IU/mL • HCV tx naïve • Up to 20% of pts can have evidence of cirrhosis • BMI ≥ 18 kg m2 • Contraception Exclusion • HIV or HBV positive • Hx of clinically significant chronic liver disease, consistent decompensated liver disease, psychiatric illness, immunologic disorder, hemoglobinopathy, pulmonary disease (including pneumonia or pneumonitis), cardiac disease, seizure disorder or anticonvulsant use, poorly controlled diabetes, or cancer, malignancy, acute	*Intervention; comparator* Age mean (range) 48 (20 to 72) 48 (19 to 77) Male n (%) 171 (67%) 156 (64%) Race n (%) *White* 223 (87%) 212 (87%) *Black* 12 (5%) 5 (2%) *Hispanic* 41 (16%) 31 (13%) Genotype n (%) *HCV-2* 70 (27%)	Intervention SOF 400mg/d and weight based RBV for 12w Comparator PEG alfa2a 180 µg weekly and 800 mg/d RBV for 24w Follow-up 12w post tx	Outcomes • SVR 12 post tx Findings **SVR 12 post tx** 67% (170/253) vs 67% (162/243) **Relapse pts who completed tx** 29% (71/242) vs 20% (37/188) **Relapse pts who did not complete tx** 43% (3/7) vs 31% (9/29) **Total relapse** 74/249 (29.7%) vs 46/217 (21.2%) **SVR 12 by genotype** *Intervention* 97% of pts with	Gilead sponsored, analyzed data and prepared final version of report Comparator group rec'd a lower dose of RBV than SOC (800mg vs weight-based dose)

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		pancreatitis with elevated lipase, uncontrolled thyroid disease or abnormal TSH levels or solid organ transplantation • Clinically significant ECG • Active substance abuse, • Abnormal hematologic and biochemical parameters, including: a) neutrophil count < 1500 cells/mm3 (or < 1250 cells/mm^3 for African-American/black subjects or cirrhotic patients); b) Hb < 11 g/dL in females or <12 g/dL in males; c) Platelet count ≤ 90,000 cells/mm^3 (noncirrhotic) or ≤ 75,000 cells/mm^3 (cirrhotic); d) creatinine ≥ 1.5 x ULN; e) estimated glomerular filtration rate, calculated by the Chronic Kidney Disease-Epidemiology Collaboration equation, < 60 mL/min/1.73	67 (28%) *HCV-3* 183 (71%) 176 (72%) BMI mean (range) 28 (17 to 51) 28 (19 to 52) HCV RNA log_{10} UL/mL (mean ± sd) 6.0 ± 0.8 6.0 ± 0.8 HCV RNA ≥ 800,000 IU/mL n (%) 145 (57%) 157 (65%) IL28B genotype n (%) *CC* 108 (42%) 106 (44%)		HCV-2, 56% of pts with HCV-3 *Comparator* 78% of HCV-2, 63% of HCV-3 (*no p-values or CIs reported*) **SVR 12 by pts with cirrhosis at baseline n=50 both groups:** 47% vs 38% (*no p-values or CIs reported*) **Adverse Events** *Any AE* 220/256 (86%) vs 233/243 (96%) *Discontinuation due to AE* 3 (1%) vs 26 (11%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		m^2;f) ALT or AST ≥ 10 x ULN; g) total bilirubin ≥ 1.5 x ULN (except patients with Gilbert's syndrome); h) albumin ≤ 3.2 g/dL 11 • Donation or loss of >400 mL of blood w/i 2m prior to first dose administration • Hx of clinically significant drug allergy to nucleoside/nucleotide analogs • Systemic antineoplastic or radiation therapy w/i 6m prior to the first dose of study drug or the expectation that such tx will be needed at any time during the study • Subjects receiving oral or intravenous strong p-glycoprotein inhibitors (including cyclosporine, quinidine, dronedarone, itraconazole, verapamil, or ritonavir) w/i 28d of dosing	*CT* 121 (47%) 98 (40%) *TT* 25 (10%) 38 (16%) <u>Cirrhosis n (%)</u> 50 (20%) 50 (21%) <u>AAT ≥ 1.5xULN n (%)</u> 138 (54%) 146 (60%) <u>Loss to follow-up n (%)</u> 1 (0.3%) 1 (0.03%)		*Serious AEs (not specified)* 7 (3%) vs 3 (1%) *Specific AEs* Influenza/fever 3 % vs 16 to 18%% Depression 5% vs 14% Hemoglobin < 10g/dcl 9% vs 14% Neutrophil count 500 to 700 mm^3 0% vs 12% Neutrophil count < 500 0% vs 2% Decreased lymphocyte, platelet, white cell counts 0% vs 1 to 7%	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		• Participation in a clinical study with an investigational drug, biologic, or device w/i 3m prior to first dose administration • Pregnant/nursing/pregnant partner • Poor venous access making the pt unable to complete the required laboratory testing schedule				
Osinusi, 2013 (Study 1)	Proof of concept with HCV-1 and unfavorable tx characteristics N=10	<u>Inclusion</u> "pts with unfavorable tx characteristics" • HCV-1 • Tx naïve • Neutrophil count ≥ 750 cells µL • Platelet count ≥ 50,000 cells/µL • Hb ≥ 11 g/dL (women) or ≥ 12 g/dL (men) • HIV negative • HBV negative	<u>Age</u> <u>median (range)</u> 54 (50 to 57) <u>Men n (%)</u> 4 (40%) <u>BMI</u> <u>median (range)</u> 26 (26 to 34) <u>Race n (%)</u> *Black* 9 (90%)	<u>Intervention</u> SOF 400 mg/d and weight based RBV daily (<75 kg= 400 mg RBV am and 600 mg pm; >75 kg = 600 mg RBV both am and p.m.) for 24w <u>Follow-up</u> 24w post tx	<u>Findings</u> **SVR 24** 9/10 (90%)	None

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			White 1 (10%) *Hispanic* 0 <u>IL28B genotype</u> <u>n (%)</u> *CC* 3(33%) *CT/TT* 6(67%) <u>Knodell HAI fibrosis</u> <u>score n (%)</u> *0 to 1* 9 (90%) *3 to 4* 1 (10%) <u>HCV-1a n (%)</u> 6/10 (60%) <u>HCV-1b n (%)</u> 4/10 (40%)			

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
Osinusi, 2013 (Study 2)	Open label RCT with HCV-1 and unfavorable tx characteristics N=50 *Group 1* n=25 *Group 2* n=25	Inclusion "pts with unfavorable tx characteristics" • HCV-1 • Tx naïve • Neutrophil count ≥ 750 cells µL • Platelet count ≥ 50,000 cells/µL • Hemoglobin ≥ 11 g/dL (women) or ≥ 12 g/dL (men) • HIV negative • HBV negative	*Group1, Group2* Age median (range) 54 (51 to 56) 55 (48 to 59) Men n (%) 19 (76%) 14 (56%) BMI median (range) 28 (25 to 31) 30 (27 to 37) Race n (%) *Black* 18 (72%) 23 (92%) *White* 5 (20%) 2(8%) *Hispanic* 2(8%)	Intervention *Group 1* SOF 400mg/d and weight based RBV for 24w *Group 2* SOF 400 mg/d and RBV 600 mg/d for 24w Follow-up 24w post tx	Outcomes • SVR 24 post tx • HCV RNA < level of quantification • Safety and tolerability Findings n (%, 95% CI) **SVR 24 post tx** *Group 1* NR (68, 46 to 85) *Group 2* NR (48, 28 to 69) **HCV RNA level < level of quantification** *Group 1* Week 24 24 (96, 80 to 100) 24w post tx 17 (68, 46 to 85)	5/33 authors report relationship to Gilead, including three Gilead employees

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			0 <u>IL28B genotype</u> <u>n (%)</u> *CC* 4(16%) 4(16%) *CT/TT* 21(84%) 21(84%) <u>Knodell HAI fibrosis score</u> <u>n (%)</u> *0 to 1* 19 (76%) 18 (72%) *3 to 4* 6 (24%) 7 (28%) <u>HCV-1a n (%)</u> 20 (80%) 16 (64%)		*Group 2* Week 24 22 (88, 69 to 97) 24w post tx 12 (48, 28 to 69) **Characteristics associated with relapse** *Male* OR 6.09, 95% CI 1.17 to 31.6, p=0.03 *Advanced fibrosis* OR 4.27, 95% CI 1.10 to 16.54, p=0.04 *Baseline HCV RNA ≥ 800,000 IU/mL* OR 5.74, 95% CI 1.35 to 24.38, p=0.02	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			HCV-1b n (%) 5 (20%) 9 (36%)		**Adverse Events** *Common* Headache, anemia, fatigue, nausea *Grade 3 events* 6 total Group 1 Hyperbilirubinemia 1 (4%) Group 2 Anemia 1 (4%) Hypophosphatemia 2 (8%) Neutropenia 1 (4%) Nausea 1 (4%)	
Rodriguez, 2013	Randomized, placebo controlled, double-blind	Inclusion • Age 18 to 65 • HCV-1 • Tx naïve	*Group 1, Group 2, Group 3, Group 4*	*Stage 1* Four groups first stage for 28d	Outcomes • Change in circulating HCV RNA over first	Authors report significant relationships with

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	dose ranging study N= 64 *Group 1* n=16 *Group 2* n=18 *Group 3* n=15 *Group 4* n=14	• HCV RNA levels ≥10,000 IU/ml at screening • BMI 18 to 36 kg/m^2 <u>Exclusion</u> • Cirrhosis • Significant comorbidity • Positive for HBsAg, anti-HBc IgM Ab, or anti-HIV A	<u>Age</u> <u>mean (range)</u> 44.4 (23 to 57) 44.4 (30 to 57) 44.9 (29 to 62) 46.6 (27 to 62) <u>Male (%)</u> 11 (69%) 10 (56%) 11 (73%) 11 (19%) <u>Race n (%)</u> *White* 15 (94%) 16 (89%) 12 (80%) 14 (100%) *Other races not provided* <u>HCV -1a/1b (n/n)</u> 14/2 15/2 12/3	1. SOF 100 mg daily + PEG/RBV 2. SOF 200 mg daily + PEG/RBV 3. SOF 400 mg daily + PEG/RBV 4. Placebo + PEG/RBV **Stage 2** All pts continue with PEG/RBV alone for 44w Used response guided protocol & allowed early stopping Not all pts followed 48w <u>Follow-up</u> 24w post tx	28d • Rates of rapid virologic response (RVR = HCV RNA < limit of detection at week 4) • SVR 12 and 24 post tx • Viral breakthrough <u>Findings</u> **Change from baseline HCV RNA at Day 28** *Group 1* -5.3 log_{10}IU/ml *Group 2* -5.1 log_{10}IU/ml *Group 3* -5.3 log_{10}IU/ml	pharmaceutical companies Three authors are employed by and hold stock in Gilead Outcomes not reported for substantial minority of pts due to loss to follow-up and study withdrawal

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			10/4 Mean baseline HCV RNA (log_{10} IU/mL) (n) 6.64 6.28 6.49 6.48 IL28B genotype n (%) *CC* 4 (25%) 5 (28%) 4 (27%) 4 (29%) HOMA-IR ≤ 3 n (%) 10 (63%) 13 (72%) 7 (47%) 7 (50%) No/minimal fibrosis F0-1 n (%) 5 (31%)		*Group 4* -2.8 log_{10}IU/ml (*no p values provided*) **RVR at 28 days** *Group 1* 14 (88%) *Group 2* 17 (94%) *Group 3* 14 (93%) *Group 4* 3 (21%) (no p values provided) **SVR 12 post tx** n (%, 95% CI) *Group 1* 9 (56%, 30 to 80) *Group 2* 13 (72%, 47 to 90)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			6 (33%) 5 (33%) 4 (29%) <u>Portal fibrosis – F1-2 n (%)</u> 11(69%) 10(56%) 9(60%) 9(64%) <u>Bridging fibrosis – F3 n (%)</u> 0 2(11%) 1(7%) 1(7%) <u>Loss to follow-up</u> Stage 1 1 pt Stage 2 16 pts		*Group 3* 13 (87%), 60 to 98) *Group 4* 7 (50%, 23 to 77) **SVR 24 post tx** n (%, 95% CI) *Group 1* 9 (56%, 30 to 80) *Group 2* 15 (83%, 59 to 96) *Group 3* 12 (80%, 52 to 96) *Group 4* 6 (43%, 18 to 71) **Viral breakthrough** *Phase I* No viral breakthrough *Phase II* 4 pts in Group 1; 2 pts in Group 3; 2	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
					pts in Group 4 **Relapse** *Not reported* **Adverse Events** 54/63 pts reported "mild" or "moderate" AEs during 28d initial tx phase No pts discontinued therapy during 1st phase Most common AEs = fatigue, nausea, chills, headache, and arthralgia No difference between SOF groups and placebo group in 1st phase AEs	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
					In 2nd phase, 5 serious AEs occurred > 50 days after ending SOF tx: peripheral ischemia, acute pancreatitis, anemia, depression, abdominal pain	
Non-published Studies Used in FDA Approval						
GS-US-334-0133 VALENCE study	Open-label N= 323 *Group 1 (genotype 2)* n=73 *Group 2 (genotype 3)* n=250 Trial originally planned as a randomized placebo-	Inclusion • Age > 18 • HCV genotype 2 or 3 • Tx naïve or tx experienced • HCV RNA levels ≥10,000 IU/ml at screening • Cirrhosis screening • Otherwise healthy • Contraception Exclusion • Hx of other significant chronic liver disease • Decompensated liver disease	*Group 1, Group 2;* Age mean (SD) 58 (10) 48 (10) Male (%) 40 (55%) 155 (62%) Race n (%) *White* 65 (89%) 236 (94%)	Intervention *Group 1* SOF 400mg/d and weight based RBV for 12w *Group 2* SOF 400 mg/d and weight based RBV for 24w Follow-up 24w post tx	Outcomes • SVR 12 post tx • Safety and tolerability Findings n (%) **Overall SVR 12 post tx** *Group 1* 68/73 (93%) *Group 2* 210/250 (84%)	Trial was on-going at time of FDA approval and results were preliminary. No final results have been published on clinicaltrials.gov or in the literature. Trial sponsored by Gilead. No

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	controlled trial with intervention group to receive SOF + RBV for 12 weeks. Altered in course to direct all genotype 3 pts to receive SOF + RBV for 24 w, and genotype 2 pts to SOF + RBV for 12 w; placebo group discontinued. Safety analysis includes discontinued pts – n = 419	• HIV, HBV, HCC, or other malignancy • Any condition, therapy or laboratory abnormality that might interfere with study • Chronic use of immunosuppressive agents or immunomoedulatory agents	*Black* 5 (7%) 0 (0%) *Asian* 1 (1%) 9 (4%) *Hispanic* 6 (8%) 36 (14%) Tx naïve 32 (44%) 105 (42%) Tx experienced 41 (56%) 145 (58%) *IFN Intolerant* 3 (4%) 10 (4%) *Non-Response* 10 (14%) 41 (16%)		**SVR 12 (Tx Naïve)** *Group 1* 31/32 (97%) *Group 2* 98/105 (93%) **SVR 12 (tx experienced)** *Group 1* 37/41 (90%) *Group 2* 112/145 (77%) **Overall relapse rate** *Group 1* 5/73 (7%) *Group 2* 32/249 (14%) **Relapse(tx naïve)** *Group 1* 1/32 (3%) *Group 2*	COI information available Study conducted in 10 countries in Europe

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Relapse/Breakthrough 28 (38%) 94 (38% <u>Baseline BMI (Kg/m^2)</u> <u>Mean (SD)</u> 26 (4) 25 (4) <u>Mean baseline HCV RNA (log_{10} IU/mL) (n)</u> 6.5 (0.7) 6.3 (0.7) <u>IL28B genotype n (%)</u> *CC* 24 (33%) 86 (34%) <u>Baseline cirrhosis</u> *No* 63 (86%) 192 (77%) *Yes* 10 (14%) 58 (23%0		5/105 (5%) **Relapse (tx experienced)** *Group 1* 4/41 (10%) *Group 2* 29/144 (20%) **Adverse events** N= 419 Group 1 (placebo) n=85 Group 2 (12wks) n=84 Group 3 (24 w) n=250 *Group 1, group 2, group 3* <u>Any AE n (%)</u> 61 (72%) 72 (86%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Baseline ALT *≤ 1.5 x ULN* 39 (53%) 64 (26%) *1.5 x ULN* 34 (47%) 186 (74% Lost to follow-up 0 1 (< 1%)		228 (91%) Common AEs Fatigue, headache, pruritus, asthenia, insomnia, nasopharyngitis, nausea, dry skin, diarrhea, dyspnea, cough, irritability Serious AE n (%) *Group 1* 2 (2.4%) one each of adenocarcinoma of colon, gastroenteritis *Group 2* 0 *Group 3* 10 (4%), one each of: arrhythmia, haemorrhoidal haemorrhage, biliary colic, road	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
					traffic accident, amylase increased, lipase increased, hyperglyacemia, HCC, invasive ductal breast carcinoma, complex regional pain syndrome, suicide attempt <u>Grade 3 or 4 AE</u> 4 (5%) 3 (4%) 17 (7%)	
GS-US-334-0123 PHOTON-1 study	Open label study N= 223 N for efficacy analysis = 210 (13 group 2 pts had not completed trial at FDA review)	<u>Inclusion</u> • Age ≥ 18 • HCV genotype 1, 2 or 3 • HIV-1 infection • HCV RNA levels ≥10,000 IU/ml at screening • Cirrhosis screening • HIV antiretroviral therapy (ARV) criteria: o ARV untreated, CD4 T-cell count > 500	*Group 1, Group 2, Group 3* <u>Age</u> <u>mean (SD)</u> 49 (10) 54 (6) 48 (8) <u>Male (%)</u> 55 (81%) 37 (90%)	<u>Intervention</u> *Group 1* SOF 400mg/d and weight based RBV for 12w *Group 2* SOF 400 mg/d and weight based RBV for	<u>Outcomes</u> • SVR 12 post tx • Safety and tolerability <u>Findings</u> *Group 1, Group 2, Group 3* **Overall SVR 12 Post Tx** **n (%, 95% CI)**	Trial not completed at FDA review. 13 pts in group 2 not included in efficacy data set.

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	Group 1 (genotype 2/3 tx naive) n=68 *Group 2 (genotype 2/3 tx experienced)* n=28 (completed trial, 41 enrolled in group) *Group 3 (genotype 1 tx naïve)* n=114	cells/mm3 o Stable, protocol approved ARV regimen > 8 w, CD4 T-cell count > 200 cells/mm2, undetectable plasma HIV-1 RNA level for ≥ 8 w • Approved ARV regimen • No investigational drug use within 30 days • Otherwise healthy • Contraception <u>Exclusion</u> • Prior tx for genotype 1 pts • Other chronic liver disease • Decompensated liver disease • HBV • Hx solid organ transplant • Contradiction to RBV tx • Serious infection requiring parenteral antibiotics, antivirals or antifungals within 30 days • Chronic use of	93 (82%) <u>Race n (%)</u> *White* 52 (76%) 32 (78%) 69 (61%) *Black* 8 (12%) 7 (17%) 37 (32%) *Asian* 1 (1%) 1 (2%) 6 (5%) *Hispanic* 19 (28%) 10 (24%) 25 (22%) <u>HCV genotype</u> *HCV-1a* 0 0	24w *Group 3* SOF 400 mg/d and weight based RBV for 24w <u>Comparator</u> *None* <u>Follow-up</u> 24w post tx	51/68 (75, 63-85) 26/28 (93, 77-99) 87/114 (76, 67-84) **SVR 12 Genotype HCV-1a** *(Group 3)* 74/90 (82, 73-89) **SVR 12 Genotype HCV-1b** *(Group 3)* 13/24 (54, 33-74) **SVR 12 Genotype HCV-2** *(Group1, Group 2)* 23/26 (88, 70-98) 14/15 (93, 68-99.8) **SVR 12 Genotype HCV-3** *(Group 1, Group2)* 28/42 (67, 50-80) 12/13 (92, 64-99.8) **Overall Relapse Rate n (%)** 12/67 (18%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		immunosuppressive agents or immunomoedulatory agents	90 (79%) *HCV-1b* 0 0 24 (21%) *HCV-2* 26 (38%) 24 (59%) 0 *HCV-3* 42 (62%) 17 (41%) 0 <u>Group 2 Tx experienced</u> *IFN intolerant* 9 (22%) *Partial/null-response* 7 (17%) *Relapse/Breakthrough* 25 (61%)		2/28 (7%) 25/113 (22%) **Adverse Events (Safety Analysis n=223)** *Group 1, Group 2, Group 3* <u>Any AE n (%)</u> 57 (84%) 37 (90%) 106 (93%) <u>Common AEs</u> Fatigue, insomnia, nausea, headache, upper respiratory tract infection, diarrhea, irritability anemia, cough, dizziness <u>Serious AE n (%)</u> *Group 1* 5 pts (7.4%), 14 events - one each	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Cirrhosis *No* 61 (90%) 31 (76%) 109 (96%) *Yes* 7 (10%) 10 (24%) 5 (4%) Baseline BMI (Kg/m^2) mean (SD) 27 (4) 27 (5) 27 (5) Mean baseline HCV RNA *< 6 log_{10} IU/mL* 21 (31%) 7 (17%) 22 (19%) *≥ 6 log_{10} IU/mL* 47 (69%) 34 (83%)		of acute MI, pneumonia, incision site infection, septic shock, staphylococcal bacteremia, intentional overdose, fracture, encephalopathy, completed suicide, drug abuse, suicide attempt, acute renal failure, pulmonary embolism, respiratory failure *Group 2* 1 pt (2.4%), 3 events: pneumonia, COPD, leukocytoclastic vasculitis	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			92 (81%) <u>IL28B genotype n (%)</u> *CC* 25 (37%) 20 (49%) 30 (26%) *CT* 37 (54%) 17 (41%) 57 (50%) *TT* 6 (9%) 4 (10%) 26 (23%) <u>ARV Tx at Enrollment</u> *No* 7 (10%) 2 (5%) 2 (2%) <u>Baseline HIV-1 RNA</u> *< 50 copies/mL* 60 (88%)		*Group 3* 8 pts (7%), 18 events: one each (unless noted) of anemia, leukocytosis, atrial fibrillation, atrial flutter, abdominal pain, colitis, enteritis, chest pain, cellulitis (2), gastroenteritis salmonella, respiratory tract infection, intentional overdose, diabetic ketoacidosis, altered state of consciousness, bi-polar disorder, acute renal failure (2) <u>Grade 3 or 4 AE</u> 7 (10.3%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			40 (98%) 108 (95%) *≥ 50 copies/mL* 8 (12%) 1 (2%) 6 (5%) Baseline CD4 (cells/mm^3)[3] mean (SD) 585 (246) 658 (333) 636 (251) Lost to follow-up 5 (7%) 1 (2%) 1 (2%)		3 (7.3%) 15 (3.2%)	
P7977-2025 Pre-transplant study	Open-label trial On-going N=61 (protocol on clinical trials.gov states 50, FDA analysis	Inclusion • Age ≥ 18 years • Patients meeting the MILAN criteria for liver transplantation for HCC secondary to HCV with a MELD < 22 and a HCC weighted MELD of ≥ 22	Status of pts at time of FDA analysis (n=61) n (%) In tx/pre transplant 9 (14.8%) Had liver transplant while on tx	Intervention SOF 400mg/d and weight based RBV for up to 48 weeks prior to transplantation or until	Outcomes • Post transplant reinfection as defined by SVR at 12 w post transplant (pTVR12) and 24 w post	Trial is not completed. FDA presentation of data is incomplete, does not include n's for

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	reports 61 patients received at least one dose of drug) Study was originally designed to test SOF + RBV for 24 w prior to transplant. FDA reports that 11/15 pts (73%) who completed 24 w tx relapsed in the pre-transplant phase, so tx time was extended to 48w for pts who had not been transplanted	• Child-Pugh Score ≤ 7 • HCV RNA levels ≥10,000 IU/ml at screening • No investigational drug use within 30 days • Contraception <u>Exclusion</u> • Pregnant, nursing, pregnant partner • Other chronic liver disease • Post transplant immunosuppressive regimen not consistent with protocol • Decompensated cirrhosis • HBV • Hx or previous solid organ transplant • Evidence of renal impairment • Hx or current psychiatric illness, immunologic disorder, hemoglobinopathy, pulmonary or cardiac	29 (47.5%) Completed 24 w tx and then had transplant 8 (13.1%) Completed 24 w tx and terminated from trial due to disease progression 2 (3.3%) Completed 24 w tx, relapsed in post tx and currently being tx again in re-tx sub-study 7 (11.5%) Prematurely discontinued tx 6 (9.8%) for • Adverse event 2 (3.3%) • Efficacy failure	transplantation <u>Mean exposure to SOF+RBV prior to transplantation</u> 17.7 w (no n) <u>Follow-up</u> 48 w post transplant	transplant (pTVR24) • SVR 12 w post treatment • Safety and tolerability <u>Findings n (%)</u> **Virological response** 41 pts who had tx underwent transplant. Only 38 of those had HCV RNA < LLOQ at time of transplantation and were considered for further analysis. One of those 38 pts was transplanted with an HCV infected liver and excluded from analysis. Of the 37	many measures and does not provide clear information on tx failure/relapse. FDA reviewer notes that study population limited to patients with HCV related HCC and may not be applicable to all transplant candidates.

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		disease, porphyria, poorly controlled diabetes, cancer other than HCC, acute pancreatitis • Hx of receiving systemic antineoplastic or immunomodulatory treatment (including radiation) w/I 6 months • Tx with transcatheter arterial chemoembolization (TACE) or radio frequency ablation (RFA) w/I 30 days • Participation in a clinical trial w/i 3 months • Contradiction to RBV tx • Chronic use of immunosuppressive agents prior to tx	4 (6.6%) Age mean (range) 59 (46 to 73) Male (%) 80.3% (*no n reported*) Race n (%) *White* 90.2% (*no n reported*) HCV genotype *HCV-1a* 39.3% (*no n reported*) *HCV-1b* 34.4% (*no n reported*) *HCV-2* 13.1% (*no n reported*) *HCV-3* 11.5% (*no n reported*) *HCV-4* 1.6% (*no n reported*)		included patients, 35 had been followed to 12 w post transplant and 24 patients to 24 w post transplant. Post-transplant virological response n (%, 95% CI) **pTVR 12** 23/35 (65.7, 50.4-78.9) **pTVR 24** 17/24 (70.8, 52.1-85.4) ***Inadequate information to identify relapse rates*** **Adverse Events** (n=61 for safety	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Tx experienced *75.4%* (*no n reported*) Mean baseline HCV RNA *≥ 6 log_{10} IU/mL* 67.2% (*no n reported*) IL28B genotype n (%) *Non-CC* 78.3% (*no n reported*) ARV tx at enrollment *No* 7 (10%) 2 (5%) 2 (2%) Baseline Child-Pugh Turcotte Score *5* 42.6% (no n) *6* 29.5% (no n) *7*		analysis) Any adverse event 52/61 (85.2%) Common AEs Fatigue (36.1%), anemia (23.0%), headache (21.3%) Significant AEs 11/61 (18%), not considered related to study drug Grade 4 laboratory abnormality 6 (9.8%) • Decreased lymphocyte count 4 (6.6%) • Increased aspartate aminotransferase 1 (1.6%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			23.0% (no n) *8* 4.9% (no n) <u>Baseline MELD Score = 7 or 8</u> 49.2%		• Total bilirubin 1 (1.6%) <u>Grade 3 laboratory abnormality</u> 21 (31.4%) • Decreased hemoglobin 9 (14.8%) • Increased non-fasting glucose 7 (11.5%) • Increased total bilirubin 5 (8.2%)	
Non-published Study on Sofosbuvir and Simeprevir Combination Treatment						
COSMOS trial NCT01466790 Completed January 2014 ***Preliminary results***	Randomized open-label trial N=167 (in published abstract; n=168 in clinical trials.gov)	<u>Inclusion</u> • Age 18 to 70 • HCV genotype 1 • HCV RNA levels ≥10,000 IU/ml at screening • Cohort inclusion: o Cohort 1: previous tx with PEG+RBV for at least 12 w with a null response and	*No patient characteristic information available*	<u>Intervention</u> Divided into two cohorts, enrolled sequentially, and each cohort divided into four groups.	<u>Outcomes</u> • SVR 12 post tx • Safety and tolerability ***<u>NOTE:</u> The published abstract only reports SVR12 data on***	VERY small N Allocation to treatment weighted such that nearly twice as many subjects received SOF + SME + RBV as

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
presented at the American Association for the Study of Liver Diseased Conference and abstract published in *Hepatology* December, 2013. (Jacobson 2013b) full article not available.	<u>Cohort 1</u> *Group 1* n=14 *Group 2* n=27 *Group 3* n=15 *Group 4* n=24 <u>Cohort 2</u> *Group 1* n=14 *Group 2* n=27 *Group 3* n=16 *Group 4* n=30	Metavir score F0-F2 o Cohort 2: Tx naïve or previous tx with PEG+RBV for at least 12 w with a null response and Meativr score F3-F4 o Null response defined as < 2log10 IU/mL reduction in HCV RNA from baseline at week 12 of tx • Liver biopsy • Contraception <u>Exclusion</u> • Hepatic decompensation • Other significant liver disease • HIV, HBV, or non-genotype 1 HCV • Hx of malignancy w/I 5 yrs		*Group 1* SOF 400 mg/d + simeprevir (SME) 150 mg/d for 12 w *Group 2* SOF 400 mg/d + simeprevir (SME) 150 mg/d + weight based RBV for 12 w *Group 3* SOF 400 mg/d + simeprevir (SME) 150 mg/d for 24 w *Group 4* SOF 400 mg/d + simeprevir (SME) 150 mg/d + weight based RBV for	***Cohort 1*** ***The total number of patients reported on who received SOF + SME alone = 28*** <u>Findings n (%)</u> **SVR 12 – Cohort 1** *Group 1* 13/14 (92.9%) *Group 2* 26/27 (96.3%) *Group 3* 14/14 (100%) *Group 4* 19/24 (79.2%)	SOR + SME alone.

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
				24 w <u>Follow-up</u> 24 w post tx		

Abbreviations

AAT – alpha1-antitrypsin; AEs – adverse events; ALT =Alanine aminotransferase; AST – aspartate aminotransferase; BMI – body mass index; d – day; ECG – electrocardiogram; eRVR – extended rapid virologic response; f/u – follow-up; HAI = histology activity index; Hb – hemoglobin; HbA1c – glycated hemoglobin; HBV – hepatitis B virus; HCV – hepatitis C virus; HCV-1 – HCV genotype 1 (and equivalents for genotypes 2, 3, 4, 5, 6);HIV – human immunodeficiency virus; HOMA-IR – homeostasis model assessment of insulin resistance; Hx – history; INF – interferon; INR – international normalized ratio; m – months; mg – milligrams; pt – patient; PEG – pegalated interferon alpha; pTVR – post-transplant virological response; rec'd – received; RNA – ribonucleic acid; RBV – ribavirin; RCT – randomized controlled trial; RVR = rapid virologic response or HCV RNA below levels of detection; SOF – sofosbuvir; tx – treatment; SVR – sustained virologic response; ULN – upper limit of normal; w – weeks; w/I – within; w/o – without

Appendix D. Critical Appraisal Summary

Table 1. Internal Validity (Risk of Bias) Criteria

Author, Year (Trial)	Internal Validity (Risk of Bias) Criteria											
	Randomization adequate?	Allocation concealment adequate?	Groups comparable at baseline?	Masking of investigator to treatment assignment?	Masking of treatment team to treatment assignment?	Masking of patient to treatment assignment?	All treatment groups received same care aside from intervention(s)?	Appropriate length of follow-up? (follow-up length)	Groups followed for equal amount of time or analysis adjusted for time?	Intention to treat analysis performed or possible with data provided?	Outcomes measured in valid and reliable way?	Outcome assessors masked to treatment assignment?
Gane, 2013 (ELECTRON)	U	U-NR	N	N	N	N	U-NR	Y (≥ 24w)	Y	Y	Y	N
Jacobson, 2013a (Study 1) (POSITRON)	U	U-NR	Y	U	U	U	U	N (12w)	Y	Y (modified)	Y	U
Jacobson, 2013a (Study 2) (FUSION)	U	U-NR	Y	U	U	U	U-NR	N (12w)	Y	Y (modified)	Y	U
Kowdley, 2013 (ATOMIC)	N	Y	N	N	N	N	U-NR	Y (≥ 24w)	Y	Y (modified)	Y	N
Lawitz, 2013 (Lancet) (Study 1)	Y (Cohort A)	Y (Cohort A)	U (Cohort A)	Y (Cohort A to 12 w)	U-NR	Y (Cohort A to 12 w)	U	Y (≥ 24w)	Y	Y	Y	U-NR

Author, Year (Trial)	Internal Validity (Risk of Bias) Criteria											
	Randomization adequate?	Allocation concealment adequate?	Groups comparable at baseline?	Masking of investigator to treatment assignment?	Masking of treatment team to treatment assignment?	Masking of patient to treatment assignment?	All treatment groups received same care aside from intervention(s)?	Appropriate length of follow-up? (follow-up length)	Groups followed for equal amount of time or analysis adjusted for time?	Intention to treat analysis performed or possible with data provided?	Outcomes measured in valid and reliable way?	Outcome assessors masked to treatment assignment?
Lawitz, 2013 (NEJM) (Study 1) (NEUTRINO)	N	NA	NA	N	N	N	NA	N (12w)	NA	NA	Y	N
Lawitz, 2013 (NEJM) (Study 2) (FISSION)	U	U-NR	Y	N	N	N	U-NR	Y (≥ 24w)	Y	U	Y	N
Osinusi, 2013 (Study 1)	NA	NA	NA	N	N	N	NA	Y (≥ 24w)	NA	NA	Y	N
Osinusi, 2013 (Study 2)	U	U-NR	U	N	N	N	U-NR	Y (≥ 24w)	Y	Y	Y	N
Rodriguez-Torres, 2013	Y	U-NR	U	Y	U	Y	Y	Y (≥ 24w)	N	N	Y	U

Key: Y – Yes; N – No; U – Unclear; NA – Not applicable; NR – Not reported

Table 2. External Validity (Risk of Bias) Criteria

Author, Year (Trial)	External Validity (Applicability) Criteria					
	Study reports on important end outcomes? (or adequate rationale if surrogate used)	Single primary outcome used? (or adequate rationale if composite outcome used)	Author(s) have financial or other substantive conflicts of interest?	Sponsor(s) have financial or other substantive conflicts of interest?	Study population similar to population to whom intervention will be applied?	Control group received standard of care (adequate comparator)?
Gane, 2013 (ELECTRON)	Y (SVR 24)	Y	Y	Y	U (no HCV-1 enrolled)	N (HCV-1; various regimens with SOF + RBV, but no PEG, bocep or telap) N (HCV-2,3; various regimens & duration of SOF +/- RBV +/- PEG, but all grps rec'd SOF)
Jacobson, 2013a (Study 1) (POSITRON)	N (SVR 12)	Y	Y	Y	U (no HCV-1 enrolled)	N (placebo)
Jacobson, 2013a (study 2) (FUSION)	N (SVR 12)	Y	Y	Y	U (no HCV-1 enrolled)	N (HCV 2,3 w/o PEG)
Kowdley, 2013 (ATOMIC)	Y (SVR 24)	Y	Y	Y	U (no HCV-2,3 enrolled)	N (HCV-1 w/o bocep or telap)
Lawitz, 2013 (Lancet)	Y (SVR 24)	Y	Y	Y	U (no HCV-2,3 enrolled in RCT portion)	N (HCV-1 w/o bocep or telap)

Author, Year (Trial)	External Validity (Applicability) Criteria					
	Study reports on important end outcomes? (or adequate rationale if surrogate used)	Single primary outcome used? (or adequate rationale if composite outcome used)	Author(s) have financial or other substantive conflicts of interest?	Sponsor(s) have financial or other substantive conflicts of interest?	Study population similar to population to whom intervention will be applied?	Control group received standard of care (adequate comparator)?
Lawitz, 2013 (NEJM) (Study 1) (NEUTRINO)	N (SVR 12)	Y	Y	Y	U (largely HCV-1)	NA
Lawitz, 2013 (NEJM) (Study 2) (FISSION)	N (SVR 12)	Y	Y	Y	U (HCV-2,3)	Y (HCV-2,3 24w RBV + PEG)
Osinusi, 2013 (Study 1)	Y (SVR 24)	Y	Y	N	U (HCV-1 w/unfavorable characteristics)	NA
Osinusi, 2013 (Study 2)	Y (SVR 24)	Y	Y	N	U (HCV-1 w/unfavorable characteristics)	N (RBV 600mg rather than 1000 or 1200mg)
Rodriguez-Torres, 2013	Y (SVR 24)	Y	Y	Y	U (no HCV-2,3 enrolled)	N (HCV-1 w/o bocep or telap)

Key: Y – Yes; N – No; U – Unclear; NA – Not applicable

Abbreviations: bocep – boceprivir; grps – groups; HCV – hepatitis C virus; PEG – pegalated interferon alpha; RBV – ribavirin; SVR – sustained virologic response; telap – telaprevir

Table 3. Overall Quality Summary

Overall Quality Summary				
Author, Year (Trial)	**How well was the study done to minimize bias in study design? (Good, Fair, Poor)**	**How well did the study respond to the PICO of this report? (Good, Fair, Poor)**	**Overall Study Quality (Good, Fair, Poor)**	**Comments**
Gane, 2013 (ELECTRON)	Poor	Poor	**Poor**	Open label study; largely a PEG regimen ranging study for HCV-2,3 and PEG-sparing for HCV-1
Jacobson, 2013a (Study 1) (POSITRON)	Poor	Poor	**Poor**	Placebo control RCT; interferon treatment contraindicated, unacceptable or prior discontinuation due to unacceptable AEs
Jacobson, 2013a (Study 2) (FUSION)	Poor	Poor	**Poor**	Active control RCT; no response to prior interferon containing regimen; duration ranging length of RBV tx (12w vs 16w)
Kowdley, 2013 (ATOMIC)	Poor	Poor	**Poor**	Open label study; duration ranging 12w vs 24w PEG + RBV
Lawitz, 2013 (Lancet)	Poor	Poor	**Poor**	Dose finding placebo control RCT for HCV-1 and additional single group for HCV-2, 3; all tx naïve and non-cirrhotic
Lawitz, 2013 (NEJM) (Study 1) (NEUTRINO)	Poor	Poor	**Poor**	Open label, single group study; tx naïve; 89% HCV-1 (11% HCV-4, 5, 6); 17% cirrhotic
Lawitz, 2013 (NEJM) (Study 2) (FISSION)	Poor	Poor	**Poor**	Open label non-inferiority RCT; tx naïve; HCV-2, 3; 20% cirrhotic

Overall Quality Summary				
Author, Year (Trial)	How well was the study done to minimize bias in study design? (Good, Fair, Poor)	How well did the study respond to the PICO of this report? (Good, Fair, Poor)	Overall Study Quality (Good, Fair, Poor)	Comments
Osinusi, 2013 (Study 1)	Poor	Poor	**Poor**	Proof of concept study (n=10) with HCV-1 and unfavorable tx characteristics
Osinusi, 2013 (Study 2)	Poor	Fair	**Poor**	Open label RCT with HCV-1 and unfavorable tx characteristics
Rodriguez-Torres, 2013	Poor	Poor	**Poor**	Open label RCT; tx naïve; with HCV-1; dose ranging

Abbreviations: AEs – adverse events; HCV – hepatitis C virus; HCV-1 – HCV genotype 1 (and equivalents for genotypes 2, 3, 4, 5, 6); mg – milligrams; PEG – pegalated interferon alpha; RBV – ribavirin; RCT – randomized controlled trial; rec'd – received; tx – treatment; w – weeks

Definitions Used for Domains with Unique Features for Condition

Masking: If study was open label did not consider masking/blinding adequate for investigators, clinicians, patients or outcome assessors

Length of follow-up: Considered inadequate if greater than 24 weeks post-treatment

Important outcomes/surrogates: Accepted any important clinical outcomes such as development of end-state liver disease and considered SVR 24 to represent an adequate surrogate measure because strongly linked to clinical outcomes; considered inadequate if measure reported was SVR 12.

Comparability of study population to likely use population: Rated as uncertain if study restricted population to those likely to need treatment in real world situations, including representative populations of those with poor prognostic factors such as male sex, black race, and cirrhosis or advanced hepatic fibrosis, as well as those who are HBV or HIV positive, actively misusing alcohol and other drugs, and those who are unable to use interferon.

Standard of care: Current standard of care regimen for HCV-1 includes triple therapy with PEG, RBV, and a polymerase inhibitor (boceprevir or telaprevir) using response guided therapy; for HCV-2 or -3 standard of care is 24 weeks of treatment with PEG and RBV.

Appendix E: Private Payer Policies

aetna℠

Pharmacy Clinical Policy Bulletins
Aetna Non-Medicare Prescription Drug Plan

Subject: Hepatitis C

Status	Drug	PR	PR-QL	PR-AL	ST	M EX‡
P	*ribavirin*					
P	**Incivek™** *(telaprevir)*	X	X			
P	**Intron-A ®** *(interferon alfa-2b)*	X				
P	**Peg-Intron ®** *(peginterferon alfa-2b)*	X				
P	**Peg-Intron Redipen/pak ®** *(peginterferon alfa-2b)*	X				
P	**Pegasys ®** *(peginterferon alfa-2a)*	X				
NP	**Infergen ®** *(interferon alfacon-1)*	X				
NP	**Victrelis™** *(boceprevir)*	X	X			
FE	**Olysio™** *(simeprevir)*	X	X			X
FE	**Sovaldi™** *(sofosbuvir)*	X	X			X

Note: Note: Precertification review for Incivek, Infergen, Intron-A, Olysio, Peg-Intron, Pegasys, Sovaldi,and Victrelis are handled through Aetna Specialty Precert Unit

Refer to Medical CPB 400 http://aetnet.aetna.com/mpa/cpb/400_499/0404.html for precertification criteria for these drugs.

Additional Information

› Clinical Policy Bulletin Notes

*P = Preferred
FE = Formulary Excluded
NP = Nonpreferred
PR = Precertification
QL = Quantity Limits
AL = Age Limits
ST = Step-Therapy
‡M EX = Medical Exception
+RxStep=Rx Step
^ETM=Essential Therapy Management

*The lists above are subject to change. Not all programs - for example step-therapy, precertification, and quantity limits - are available in all service areas.

Policy:

I. Precertification Criteria

Under some plans, including plans that use an open or closed formulary, **Incivek, Infergen, Intron-A, Olysio, Pegasys, Peg-Intron/ Redipen/pak, Sovaldi,** and **Victrelis** are subject to precertification. If precertification requirements apply Aetna considers these medications to be medically necessary for those members who meet all of the following precertification criteria:

For **Sovaldi**

(In order to be eligible for the max time of approval, members must meet both intial and reauthorization criteria.)

<u>For initial authorizaion:</u>

- A documented diagnosis of one of the following:
  - Chronic Hepatits C Virus (HCV) infection, genotype 1, **AND**
    - Concurrent therapy with *peginterferon alfa* (PEG) and *ribavirin* (RBV) (Max Time of Approval 12 weeks)
  - HCV infection, genotype 1, PEG-ineligible patient*, **AND**
    - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 weeks); **OR**
    - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
  - HCV infection, genotype 1, PEG/ RBV (without HCV protease inhibitor (PI)) nonresponder patients, **AND**
    - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 weeks)
  - HCV or HCV/ HIV infection, genotype 1, PEG/ RBV (with or without HCV (protease inhibitor) PI) nonresponder patients, **AND**
    - Concurrent therapy with PEG and RBV (Max Time of Approval 12 to 24 weeks, 12 weeks for Sovaldi only.)
  - HCV/ HIV coinfected patients, genotype 1, treatment naive or prior nonresponder, **AND**
    - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)

- HCV/ HIV coinfected patients, genotype 1, treatment naive or prior nonresponder, PEG-ineligible patient*, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks); **OR**
  - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 weeks)
- HCV infection, genotype 1, post-liver transplant, **AND**
  - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 to 24 weeks); **OR**
  - Concurrent therapy with RBV with or without PEG (Max Time of Approval 24 weeks)
- HCV or HCV/ HIV infection, genotype 2, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 12 weeks)
- HCV infection, genotype 2, PEG/ RBV nonresponder, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 12 weeks (16 weeks in cirrhosis)); **OR**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV infection, genotype 2 or 3, post-liver transplant, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
- HCV or HCV/ HIV infection, genotype 3, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks); **OR**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV or HCV/ HIV infection, genotype 3, PEG/ RBV nonresponder, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks); **OR**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV or HCV/ HIV infection, genotype 4, **AND**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV or HCV/ HIV infection, genotype 4, PEG-ineligible patients*, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
- HCV infection, genotype 4, PEG/ RBV nonresponder, **AND**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks); **OR**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
- HCV or HCV/ HIV infection, genotype 5 or 6, **AND**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV infection, genotype 5 or 6, PEG/ RBV nonresponder, **AND**

        - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
    - HCV infection, in decompensated cirrhosis or in patient with documented hepatocellular carcinoma (HCC) awaiting liver transplantation, **AND**
        - Concurrent therapy with RBV (Max Time of Approval 48 weeks or until liver transplantation)

<u>For reauthorization at 8 weeks:</u>

- Initial authorization criteria above has been met **AND**
    - HCV RNA levels have declined > 2 $\log_{10}$ IU/ mL at 4 weeks of therapy

*Interferon ineligible is defined as meeting one or more of the following criteria:

- Uncontrolled seizures
- Suicidal attempt within past year
- Moderate to severe retinopathy
- Neutrophils <750 cells/ mm^3, results within the past month
- Hemoglobin <10 g/ dL, results within the past month
- Platelets <50 000 cells/ mm^3, results within the past month
- Major uncontrolled depressive illness
- Solid organ transplant (renal, heart, or lung)
- Autoimmune hepatitis or other autoimmune condition known to be exacerbated by peginterferon and ribavirin
- Untreated thyroid disease
- Pregnant or unwilling to comply with adequate contraception
- Severe concurrent medical disease such as severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, COPD
- Age less than 2 years
- Known hypersensitivity to drugs used to treat HCV
- Known hypersensitivity reactions such as urticaria, angioedema, bronchoconstriction, anaphylaxis, or Stevens-Johnson syndrome to alpha interferons, or any of its components
- Hepatic decompensation (Child-Pugh score greater than 6 [class B and C]) in cirrhotic patients before treatment
- Hepatic decompensation with Child-Pugh score greater than or equal to 6 in cirrhotic CHC patients coinfected with HIV before treatment

According to the manufacturer, **Incivek, Olysio, Sovaldi,** and **Victrelis** can be dosed up to a maximum daily dose indicated in the table below. A quantity of these drugs will be considered medically necessary as indicated below:

Drug	Maximum Daily Dose	Dosage Strength	Quantity Limits
Incivek	2250 mg	375 mg	Up to 180 tablets in days
Olysio	150 mg	150 mg	Up to 30 capsules i days
Sovaldi	400 mg	400 mg	Up to 30 tablets in 3 days
Victrelis	2400 mg	200 mg	Up to 360 tablets in days

II. Medical Exception Criteria

Olysio and **Sovaldi** are currently listed on the Aetna Formulary Exclusions list. Therefore, they are excluded from coverage for members enrolled in a prescription drug benefit plan that uses a closed formulary unless a medical exception is granted. Aetna considers these medications to be medically necessary for those members who meet the following criteria:

For **Olysio**

(In order to be eligible for the max time of approval, members must meet both intial and reauthorization criteria.)

<u>For initial authorizaion:</u>

- A documented diagnosis of one of the following:
  - Chronic Hepatits C Virus (HCV) infection or HCV/ HIV coinfection, genotype 1, **AND** all of

the following:

- Concurrent therapy with *peginterferon alfa* (PEG) and *ribavirin* (RBV) (Max Time of Approval 24 weeks. Olysio approval for 12 weeks.)
- If HCV genotype 1a, NS3 Q80K polymorphism is not detected prior to treatment
- Patient has not failed previous therapy with a treatment regimen that includes HCV protease inhibitors (i.e., Incivek, Olysio, Victrelis)

- HCV infection or HCV/ HIV coinfection, genotype 1, PEG/ RBV (without HCV protease inhibitor (PI)) nonresponder patients, **AND** all of the following:
  - Concurrent therapy with PEG and RBV (Max Time of Approval 48 weeks. Olysio approval for 12 weeks.)
  - If HCV genotype 1a, NS3 Q80K polymorphism is not detected prior to treatment
  - Patient has not failed previous therapy with a treatment regimen that includes HCV protease inhibitors (i.e., Incivek, Olysio, Victrelis)
- HCV infection, genotype 1, PEG-ineligible patient* **AND** all of the following:
  - Concurrent therapy with Sovaldi with or without RBV (Max Time of Approval 12 weeks.)
- HCV infection, genotype 1, post-liver transplant **AND** all of the following:
  - Concurrent therapy with Sovaldi with or without RBV (Max Time of Approval 12 to 24 weeks.)
- HCV infection, genotype 4, **AND** all of the following:
  - Concurrent therapy with PEG and RBV (Max Time of Approval 24 to 48 weeks. Olysio approval for 12 weeks.)
  - Patient has not failed previous therapy with a treatment regimen that includes HCV protease inhibitors (i.e., Incivek, Olysio, Victrelis)

<u>For reauthorization at 8 weeks:</u>

- Initial authorization criteria above has been met **AND**
  - HCV RNA levels are < 25 IU/ mL at 4 weeks of therapy

For **Sovaldi**

(In order to be eligible for the max time of approval, members must meet both intial and reauthorization criteria.)

<u>For initial authorizaion:</u>

- A documented diagnosis of one of the following:
  - Chronic Hepatits C Virus (HCV) infection, genotype 1, **AND**
    - Concurrent therapy with *peginterferon alfa* (PEG) and *ribavirin* (RBV) (Max Time of Approval 12 weeks)
  - HCV infection, genotype 1, PEG-ineligible patient*, **AND**
    - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 weeks); **OR**
    - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
  - HCV infection, genotype 1, PEG/ RBV (without HCV protease inhibitor (PI)) nonresponder patients, **AND**
    - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 weeks)
  - HCV or HCV/ HIV infection, genotype 1, PEG/ RBV (with or without HCV (protease inhibitor) PI) nonresponder patients, **AND**
    - Concurrent therapy with PEG and RBV (Max Time of Approval 12 to 24 weeks, 12 weeks for Sovaldi only.)
  - HCV/ HIV coinfected patients, genotype 1, treatment naive or prior nonresponder, **AND**
    - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
  - HCV/ HIV coinfected patients, genotype 1, treatment naive or prior nonresponder, PEG-ineligible patient*, **AND**
    - Concurrent therapy with RBV (Max Time of Approval 24 weeks); **OR**
    - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 weeks)
  - HCV infection, genotype 1, post-liver transplant, **AND**
    - Concurrent therapy with Olysio with or without RBV (Max Time of Approval 12 to 24 weeks); **OR**
    - Concurrent therapy with RBV with or without PEG (Max Time of Approval 24

weeks)

- HCV or HCV/ HIV infection, genotype 2, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 12 weeks)
- HCV infection, genotype 2, PEG/ RBV nonresponder, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 12 weeks (16 weeks in cirrhosis)); **OR**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV infection, genotype 2 or 3, post-liver transplant, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
- HCV or HCV/ HIV infection, genotype 3, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks); **OR**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV or HCV/ HIV infection, genotype 3, PEG/ RBV nonresponder, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks); **OR**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV or HCV/ HIV infection, genotype 4, **AND**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV or HCV/ HIV infection, genotype 4, PEG-ineligible patients*, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
- HCV infection, genotype 4, PEG/ RBV nonresponder, **AND**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks); **OR**
  - Concurrent therapy with RBV (Max Time of Approval 24 weeks)
- HCV or HCV/ HIV infection, genotype 5 or 6, **AND**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV infection, genotype 5 or 6, PEG/ RBV nonresponder, **AND**
  - Concurrent therapy with PEG and RBV (Max Time of Approval 12 weeks)
- HCV infection, in decompensated cirrhosis or in patient with documented hepatocellular carcinoma (HCC) awaiting liver transplantation, **AND**
  - Concurrent therapy with RBV (Max Time of Approval 48 weeks or until liver transplantation)

For reauthorization at 8 weeks:

- Initial authorization criteria above has been met **AND**
  - HCV RNA levels have declined > 2 $\log_{10}$ IU/ mL at 4 weeks of therapy

*Interferon ineligible is defined as meeting one or more of the following criteria:

- Uncontrolled seizures
- Suicidal attempt within past year
- Moderate to severe retinopathy
- Neutrophils <750 cells/ mm^3, results within the past month
- Hemoglobin <10 g/ dL, results within the past month
- Platelets <50 000 cells/ mm^3, results within the past month
- Major uncontrolled depressive illness
- Solid organ transplant (renal, heart, or lung)
- Autoimmune hepatitis or other autoimmune condition known to be exacerbated by peginterferon and ribavirin
- Untreated thyroid disease
- Pregnant or unwilling to comply with adequate contraception
- Severe concurrent medical disease such as severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, COPD
- Age less than 2 years
- Known hypersensitivity to drugs used to treat HCV
- Known hypersensitivity reactions such as urticaria, angioedema, bronchoconstriction, anaphylaxis, or Stevens-Johnson syndrome to alpha interferons, or any of its components
- Hepatic decompensation (Child-Pugh score greater than 6 [class B and C]) in cirrhotic patients before treatment
- Hepatic decompensation with Child-Pugh score greater than or equal to 6 in cirrhotic CHC patients coinfected with HIV before treatment

Special Notes:

Place of Service:
Outpatient

The above policy is based on the following references:

1. AHFS Drug Information® with AHFSfirstReleases®. (www.statref.com), American Society Of Health-System Pharmacists®, Bethesda, MD. Updated periodically.
2. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically.
3. Drug Facts and Comparisons on-line. (www.drugfacts.com), Wolters Kluwer Health, St. Louis, MO. Updated periodically.
4. PDR® Electronic Library™ [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically.
5. Clinical Pharmacology [Internet database]. Gold Standard Inc. Tampa, FL. Updated periodically.
6. Olysio™ [package insert]. Titusville, NJ: Janssen Products, LP; November 2013.
7. Sovaldi™ [package insert]. Foster City, CA: Gilead Sciences, Inc.; December 2013
8. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America: Recommendations for Testing, Managing, and Treating Hepatitis C. http://www.hcvguidelines.org/full-report-view [retrieved on 01/29/2014]

March 5, 2014

Medication	Quantity Limit
Sovaldi (sofosbuvir)	1 tablet per day

OVERRIDE(S)
Prior Authorization of Benefits

APPROVAL DURATION
Based on Genotype or hepatocellular carcinoma status:

Status type (HCV Mono-infected or HCV/HIV-1 Co-infected)	Total Approval Duration
Genotype 1 or 4 CHC	12 weeks
Genotype 1 CHC ineligible for an interferon-based regimen	24 weeks
Genotype 2 CHC	12 weeks
Genotype 3 CHC	24 weeks
Hepatocellular Carcinoma awaiting liver transplant	Up to 48 weeks*

* Therapy duration is recommended for up to 48 weeks or until the time of liver transplantation, whichever occurs first.

APPROVAL CRITERIA

Requests for Sovaldi (sofosbuvir) may be approved if the following criteria are met:

I. Individual is 18 years of age or older; **AND**
II. Documentation is provided for a diagnosis of chronic hepatitis C (CHC) infection; **AND**
III. Individual has compensated liver disease (including cirrhosis); **AND**
IV. Individual is using with one of the following antiviral treatment regimens:
    a. In combination with peg interferon and ribavirin for the following:
        1. Individuals with hepatitis C virus (HCV) Genotype 1; **OR**
        2. Individuals with HCV Genotype 4;

    OR
    b. In combination with ribavirin alone for the following:
        1. Individuals with HCV Genotype 1 that are ineligible for an interferon-based regimen, as defined by the presence of **one** of the following:
            A. Autoimmune hepatitis; **OR**
            B. Child-Pugh score greater than 6 (Class B or C) before or during interferon treatment; **OR**
            C. Known hypersensitivity to interferon products; **OR**
        2. Individuals with HCV Genotype 2; **OR**
        3. Individuals with HCV Genotype 3; **OR**
        4. Individuals with CHC and concurrent hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation).

Requests for concomitant use of two or more of the following; Incivek (telaprevir), Victrelis (boceprevir), Olysio (simeprevir), or Sovaldi (sofosbuvir) will not be approved.

Child Pugh Classification

Parameters			
Points Assigned	1 point	2 points	3 points
Encephalopathy	None	Minimal	Advanced coma
Ascites	None	Easily controlled	Poorly controlled
Serum Bilirubin	<2mg/dL	2-3 mg/dL	>3 mg/dL
Serum Albumin	>3.5 g/dL	2.8-3.5 g/dL	<2.8 g/dL
INR	INR <1.7	INR 1.7-2.3	INR >2.3

Child Pugh Score Interpretation

Class A	5-6 points	Well compensated liver disease
Class B	7-9 points	Significant functional compromise
Class C	10-15 points	Uncompensated liver disease

Sovaldi
(sofosbuvir)

SOVALDI with RIBAVIRIN

Sovaldi (sofosbuvir) RIBAVIRIN
(Copegus, Rebetol, Ribapak, Ribasphere, Ribatabs, ribavirin - all strengths)

Pre - PA Allowance
None

Prior-Approval Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

Chronic Hepatitis C

AND ONE of the following:

1. Genotype 1

   AND ONE of the following:
   a. Interferon ineligible, intolerant, or unwilling

2. Genotype 2 or 3

3. Genotype 1, 2, 3, or 4

   AND MUST have the following:
   a. Hepatic carcinoma(s) awaiting liver transplantation
      AND
      i. Meets Milan criteria which meets **ONE** of the following:
         1. Single hepatocellular carcinoma, presence of tumor 5cm or less in diameter, **OR**
         2. Multiple tumors, each less than 3cm in diameter and no extrahepatic manifestations of the cancer or evidence of vascular invasion of the tumor.

AND ALL of the following:

1. Sovaldi and Ribavirin are **NOT** to be used as monotherapy
2. Patient is **NOT** taking concurrent therapy with Pegasys or Pegintron
3. Absence of renal impairment

   a. eGFR must be > 30mL/min/1.73m^2
4. Absence of end stage renal disease (ESRD)
5. Patient does **NOT** have decompensated cirrhosis
6. Patient has **NOT** had a liver transplant
7. Therapy will be discontinued if liver transplantation occurs
8. Absence of significant or unstable cardiac disease
9. Neither the patient nor the partner of the patient is pregnant
10. If patient or their partner are of child bearing age, the patient has been or will be instructed to practice effective contraception during therapy and for 6 months after stopping ribavirin therapy

Prior - Approval Limits

Duration

Genotype 1 without hepatocellular carcinoma(s):
24 weeks Sovaldi (168 tablets per 168 days) / 24 weeks Ribavirin

Genotype 2 without hepatocellular carcinoma(s):
12 weeks Sovaldi (84 tablets per 84 days) / 12 weeks Ribavirin

Genotype 3 without hepatocellular carcinoma(s):
24 weeks Sovaldi (168 tablets per 168 days) / 24 weeks Ribavirin

Genotype 1,2,3,or 4 with hepatocellular carcinoma(s):
24 weeks Sovaldi (168 tablets per 168 days) / 24 weeks Ribavirin

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Prior – Approval *Renewal* Requirements

Same as above

Prior - Approval *Renewal* Limits

Duration

Genotype 1, 2, 3 without hepatocellular carcinoma(s):
None

Genotype 1, 2, 3, 4 with hepatocellular carcinoma(s):
24 weeks Sovaldi (168 tablets per 168 days) / 24 weeks Ribavirin

Sovaldi
(sofosbuvir)

Sovaldi (sofosbuvir) with (PEGASYS or PEGINTRON) AND RIBAVIRIN

Sovaldi (sofosbuvir) with PEGASYS or PEGINTRON (peginterferon alfa-2b**,**
AND RIBAVIRIN
(Copegus, Rebetol, Ribapak, Ribasphere, Ribatabs, ribavirin - all strengths)

Pre - PA Allowance
None

Prior-Approval Requirements
Age 18 years of age or older

Diagnosis

Patient must have the following:

Chronic Hepatitis C

AND ALL of the following:

1. Viral genotype 1 or 4
2. Sovaldi and Ribavirin will **NOT** be used as monotherapy
3. Patient does **NOT** have hepatocellular carcinoma awaiting transplant (these patients should be treated with Sovaldi and ribavirin without interferon)
4. Absence of renal impairment
    a. eGFR must be > 30mL/min/1.73m^2
5. Absence of end stage renal disease (ESRD)
6. Patient does **NOT** have decompensated cirrhosis
7. Patient has **NOT** had a liver transplant
8. Absence of significant or unstable cardiac disease
9. Neither the patient nor the partner of the patient is pregnant
10. If patient or their partner are of child bearing age, the patient has been or will be instructed to practice effective contraception during therapy and for 6 months after stopping ribavirin therapy

Prior - Approval Limits
Duration

Sovaldi 12 weeks (84 tablets for 84 days)
Pegasys 12 weeks / Ribavirin 12 weeks

Sovaldi
(sofosbuvir)

Prior – Approval *Renewal* Requirements
None

Hepatitis Prior Authorization & Fax Order Form

Please indicate the intention of this request:

☐ Prior authorization and Cigna Home Delivery Pharmacy to fill ***Please deliver by:*** _____

☐ Prior authorization only (or call (800) 244-6224)

Order #:_____ **Referral Source Code:**_____ **Fax:** 1.800.351.3616 **Phone:** 1.800.351.3606

PATIENT INFORMATION (Please Print)		PHYSICIAN INFORMATION		
PATIENT NAME:	DATE OF BIRTH :	NAME:		
HEALTH CARE ID #:	GENDER: ☐ M ☐ F	DEA #:	NPI:	TIN:
HOME PHONE:	ALT PHONE:	ADDRESS: (Street/Suite #) (City) (State) (Zip Code)		
ADDRESS: (Street) (City) (State) (Zip Code)				
ALLERGIES: If no allergies are specified, for new customers this indicates no known allergies and for existing customers this indicates no change from information previously provided to Cigna.		TELEPHONE:	FAX:	

SHIP MEDICATIONS TO: ☐ Patient's Home (Please provide all available patient phone numbers as they are REQUIRED for scheduling delivery.) ☐ Physician's Office

PRESCRIPTION INFORMATION

PEGASYS® (Peginterferon Alfa-2a - S0145): ☐ **180 mcg/0.5 ml Prefilled Syringe** ☐ **180 mcg/0.5ml Proclick** ☐ Pharmacy asks patient for preference	**Directions:** DIRECTIONS: ☐ Inject 180 mcg SQ weekly ☐ Other (please specify):	**Refills:** QTY/REFILLS ☐ 1 month supply _____ refills ☐ 3 month supply _____ refills ☐ Other: _____QTY _____ refills
PEGASYS® (Peginterferon Alfa-2a - S0145): ☐ **180 mcg/1 ml Vial** **Note: Concentration of Syringe vs. Vial**		
PEG-INTRON® (Peginterferon Alfa-2b – S0146): ☐ 50 mcg/0.5 ml **Vial** ☐ 50 mcg/0.5 ml **Redipen** ☐ 80 mcg/0.5 ml **Vial** ☐ 80 mcg/0.5 ml **Redipen** ☐ 120 mcg/0.5 ml **Vial** ☐ 120 mcg/0.5 ml **Redipen** ☐ 150 mcg/0.5 ml **Vial** ☐ 150 mcg/0.5 ml **Redipen**	DIRECTIONS: ☐ Inject 0.4 ml SQ weekly ☐ Inject 0.5 ml SQ weekly ☐ Other (please specify):	
INFERGEN® (Interferon Alfacon-1 – J9212): ☐ **9 mcg/0.3 ml Vial** ☐ **15 mcg/0.5 ml Vial**	DIRECTIONS: ☐ Inject 9 mcg SQ 3 times per week ☐ Inject 15 mcg SQ 3 times per week ☐ Other (please specify):	
Intron® A (Interferon alfa-2b, recombinant – J9215): **18 million units multidose vial** **3 million units/dose multidose pen** **Other:**	DIRECTIONS: Inject 3 million units 3 times a week IM or SQ Other (please specify):	QTY/REFILLS ☐ 1 month supply _____ refills ☐ 3 month supply _____ refills ☐ Other: _____QTY _____ refills
☐ **Rebetol®** 200 mg capsules ☐ **Copegus®** 200 mg tablets	DIRECTIONS: _____ QAM AND _____ QPM	QTY/REFILLS ☐ 1 month supply _____ refills ☐ 3 month supply _____ refills ☐ Other: _____QTY _____ refills
INCIVEK (Telaprevir) ☐ 375 mg tablets	DIRECTIONS: ☐ Take 750mg (2 tablets) by mouth 3 times a day with food containing 20gm of fat	QTY/REFILLS ☐ 1 month supply _____ refills ☐ 3 month supply _____ refills ☐ Other: _____ QTY _____ refills
OLYSIO (Simeprevir) ☐ 150 mg tablets	DIRECTIONS: ☐ Take 1 capsule once daily with food	
SOVALDI (Sofosbuvir) ☐ 400 mg tablets	DIRECTIONS: ☐ Take 1 tablet once daily	
VICTRELIS (Boceprevir) ☐ 200 mg capsules	DIRECTIONS: ☐ Take 800mg (4 capsules) by mouth 3 times a day with food, start at day 29 (week 5).	

Hepatitis Prior Authorization & Fax Order Form

☐ **Lab reminder coordination and injection training**

SUPPLIES NEEDED *(if medication is to be administered in patient's home)*: If checked, please specify the size and type (if applicable):

☐ Syringes/Needles ☐ Swabs ☐ Sharps Container ☐ Other:

PHYSICIAN'S SIGNATURE: (Physician's signature indicates accuracy and completeness of prescription information)

In order for a brand name product to be dispensed, the prescriber must handwrite ***"Brand Necessary"*** or ***"Brand Medically Necessary"*** on the prescription

PATIENT NAME:	HEALTH CARE ID #:	DATE OF BIRTH:

The following levels are needed for approval of the below corresponding treatments.

HCV RNA Levels

Week of Therapy	Incivek	Olysio	Victrelis	Dual or Mono Therapy	Date Taken
Pretreatment			iu/ml*	iu/ml	
4	iu/ml	iu/ml	iu/ml*		
8			iu/ml*		
12	iu/ml	iu/ml	iu/ml	iu/ml	
24	iu/ml	iu/ml	iu/ml	iu/ml	
other	iu/ml	iu/ml	iu/ml	iu/ml	

*Pretreatment, 4 and 8 week levels are needed to determine length of Victrelis therapy

Clinical Information:

What is the patient's current weight? _____ ☐ lbs ☐ kg

Diagnosis related to use: ☐ (070.7) Hepatitis C ☐ Hepatitis B ☐ Other (please specify):

Does the patient have decompensated liver disease ☐ Yes ☐ No

(e.g. *of decompensated liver disease include: Ascites, Hepatic Encephalopathy, bleeding esophagogastric varicie*)?

What is the patient's genotype? ☐ 1 or 1a ☐ 1b ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ Other:

(if requesting **Olysio** and patient has genotype 1 or 1a) Has your patient been screened for one of the following: boceprevir resistance, telaprevir resistance, HCV drug resistance, NC3/4 resistance, or Q80K polymorphism?

☐ yes and resistance was detected

☐ yes and resistance was NOT detected

☐ no, this testing was not done

Does the patient have HIV/AIDS? ☐ Yes ☐ No

Does the patient have bridging fibrosis? ☐ Yes ☐ No

Does the patient have cirrhosis? ☐ Yes ☐ No

Has your patient had failure, contraindication, or intolerance to any of the following? (check all that apply)

☐ Infergen ☐ Intron ☐ Pegasys ☐ PegIntron ☐ Other_____

Has the patient previously taken Pegasys or Peg-Intron plus ribavirin? ☐ Yes ☐ No

If *yes*: Which one of the following describes previous therapy:

- ☐ completed therapy but relapsed
- ☐ partial response
- ☐ stopped treatment early (weeks completed _____)
- ☐ no response (did not have at least a 2 log drop in HCV after 12 weeks of prior treatment)

If *no*: Is the patient currently on therapy? ☐ Yes ☐ No

How many weeks has the patient completed? _____ weeks

Date started therapy? __/__/__

Does your patient have a contraindication to any of the following:

☐ Pegasys ☐ PegIntron ☐ Incivek ☐ Olysio ☐ Sovaldi ☐ Victrelis ☐ Other

Please explain:

Infergen requests:

Did the patient have intolerance to treatment with Pegasys or Peg-Intron? ☐ Yes ☐ No

Hepatitis Prior Authorization & Fax Order Form

For Incivek, Olysio, Sovaldi, or Victrelis requests:

Will this be used in combination with ribavirin? ☐ Yes ☐ No

Will this be used in combination with Pegasys or Peg-Intron? ☐ Yes ☐ No

For **Sovaldi** requests:

Does your patient also have a diagnosis of hepatocellular carcinoma (HCC, hepatocellular cancer, malignant hepatoma? ☐ Yes ☐ No

(if HCC) Has your patient previously had a liver transplant? ☐ Yes ☐ No

(if HCC) Is your patient waiting to undergo a liver transplant? ☐ Yes ☐ No

(if yes) Does your patient meet MILAN criteria for liver transplantation? ☐ Yes ☐ No

(Please note: there are different preferred products depending on your patient's plan. Please refer to the applicable Cigna health care professional resource [e.g. cignaforhcp.com] to determine benefit availability and the terms and conditions of coverage

Additional pertinent information:

PHYSICIAN'S SIGNATURE: (Physician's signature indicates accuracy and completeness of prescription information)

Our drug list can be viewed online at http://www.cigna.com. Prior authorization requests may also be submitted by calling (800) 244-6224. V010414

v1/1/14

Cigna Preferred Status:

- It is the decision of the prescribing physician in the exercise of his/her independent clinical judgment to determine which medication to prescribe. Coverage is not limited to the preferred drug.
- Cigna may receive payments from manufacturers whose medications are included on the Preferred Specialty (Injectable) Drug List. These payments may or may not be shared with the member's benefit plan dependent on the contractual arrangement between the plan and Cigna.
- Depending upon plan design, market conditions, the extent to which manufacturers' payments are shared with the member's benefit plan, and other factors as of the date of service, the preferred medication may or may not represent the lowest cost medication within the therapeutic class for the member and/or the benefit plan.
- Cigna reserves the right to make changes to its Preferred Specialty (Injectable) Drug List without notice.

HealthNet Coverage Policy

SOVALDI® (sofosbuvir)

NATL

Coverage of drugs is first determined by the member's pharmacy or medical benefit. Please consult with or refer to the Evidence of Coverage document.

1. FDA Approved Indications:
    - Indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. Sovaldi efficacy has been established in subjects with hepatitis C virus (HCV) genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplant) and those with HCV/HIV-1 co-infection.
2. Health Net Approved Indications and Usage Guidelines:
    - Diagnosis of CHC confirmed by detectable serum HCV RNA by quantitative assay. Genotype is required to determine length of approval.

      AND

    - Liver biopsy showing fibrosis corresponding to a Metavir score of greater than or equal to 2 or Ishak score of greater than or equal to 3 or other accepted test demonstrating liver fibrosis

      AND

    - Prescribed by or in consultation with a gastroenterologist, hepatologist or infectious disease physician.

      AND

    - For genotype 1 and 4 CHC: should be used as triple therapy in combination with peginterferon alfa and ribavirin or as double therapy in combination with ribavirin for patients who are 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) or interferon-intolerant (patients who discontinued interferon therapy prematurely due to side effects)

OR

- For genotype 2 or 3 CHC: must be used in combination with ribavirin

OR

- For treatment of CHC in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation): must be used in combination with ribavirin. Milan criteria is defined as 1 lesion ≤5 cm, up to 3 lesions each of which are ≤3 cm, and no extrahepatic manifestations/no vascular invasion.

3. Coverage is Not Authorized For:
   - Treatment of HCV as monotherapy.
   - Quadruple therapy (Sovaldi+(Olysio, Incivek,or VIctrelis)+peginterferon+ribavirin) combination
   - Treatment regimen that patient who has failed therapy with an NS3/4A protease inhibitor (e.g., boceprevir,simeprevir, telaprevir)
   - Non-FDA approved indications, which are not listed in the Health Net Approved Indications and Usage Guidelines section, unless there is sufficient documentation of efficacy and safety in the published literature
   - Post liver transplant
   - **Additional contraindications for use with peginterferon**
   - Autoimmune hepatitis
   - Hepatic decompensation (Child-Pugh score greater than 6 [class B and C]) in cirrhotic patients before treatment
   - Hepatic decompensation with Child-Pugh score greater than or equal to 6 in cirrhotic CHC patients coinfected with HIV before treatment
   - **Additional contraindications for use with ribavirin**
   - Women who are pregnant
   - Men whose female partners are pregnant
   - Patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
   - Combination with didanosine. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials
4. General Information:
   - Interim results from the COSMOS study evaluated Olysio and Sovaldi in HCV patients including treatment naive or previous null responder HCV patients. In HCV patients with advanced liver fibrosis or cirrhosis (METAVIR F3 or F4) 12 weeks all oral treatment with Olysio and Sovaldi with or without ribavirin led to SVR4 rates of 96% and

100%,respectively. These are interim results, further data are needed to prove efficacy.

- Gane et al. studied 10 patients treated with Sovaldi monotherapy for 12 weeks who had genotype 2 or 3 disease. The primary efficacy (SVR at 12 weeks after therapy stopped) was much lower (60%) on monotherapy versus 100% on combination therapy.
- The triple therapy (Sovaldi+peginterferon+ribavirin) combination study included patients with genotype 1, 4, 5 or 6 disease (NEUTRINO study).
- The POSITRON trial defines contraindications to interferon as those patients with psychiatric disorders (57% of patients in the trial) and autoimmune disorders (19% of patients in the trial). Unacceptable side effects with interferon were influenza-like symptoms (32% of patients), psychiatric disorders (20% of patients), thrombocytopenia (16% of patients) or local or systemic adverse reactions (12% of patients). Per AASLD Practice guideline (2009), additional characteristics of persons for whom therapy with interferon/ribavirin may be contraindicated include untreated thyroid disease, pregnancy, severe concurrent medical conditions (uncontrolled diabetes, uncontrolled hypertension, significant coronary heart disease) or solid organ transplant (renal, heart, lung).
- Preliminary results of a phase IIa trial evaluating combination therapy of Olysio and Sovaldi with or without ribavirin in genotype 1 patients was recently presented at the November 2013 AASLD meeting (COSMOS study [Combination of Simeprevir and sofosbuvir in HCV genotype 1 infected patients]). Preliminary results indicate SVR over 90% (approximately 187 patients).
- There are no data to support combination quadruple therapy with peginterferon, ribavirin, Sovaldi and a protease inhibitor (Olysio, Incivek or Victrelis).

5. Therapeutic Alternatives:

Drug	Dosing Regimen	Dose Limit/ Maximum Dose
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6. *** Requires Prior Authorization**
7. Recommended Dosing Regimen and Authorization Limit:

Drug	Dosing Regimen	Authorization Limit
Sovaldi	Genotype 1 or 4: 400 mg PO QD	12 weeks in combination with peginterferon alfa + ribavirin

		OR 24 weeks in combination with ribavirin for interferon ineligible patients
Sovaldi	<u>Genotype 2:</u> 400 mg PO QD (in combination with ribavirin)	12 weeks
Sovaldi	<u>Genotype 3:</u> 400 mg PO QD (in combination with ribavirin)	24 weeks
Sovaldi	<u>Hepatocellular carcinoma patients awaiting liver transplantation:</u> 400 mg PO QD (in combination with ribavirin)	48 weeks or until liver transplantation, whichever occurs first

8. Product Availability:

   Sovaldi tablets: 400 mg

9. References:

   1. Sovaldi [Prescribing Information]. Foster City, CA: Gilead Sciences, Inc.; December 2013.

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Sovaldi™ (sofosbuvir)

Humana

Pharmacy Coverage Policy

Effective Date: December 19, 2013
Revision Date: January 9, 2014
Review Date: January 9, 2014
Line of Business: Commercial, Florida Medicaid, Medicare
Policy Type: Prior Authorization

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Disclaimer

Description

Sovaldi (sofosbuvir) is a nucleotide analog NS5B polymerase inhibitor.

Sovaldi (sofosbuvir) is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate which acts as a chain terminator when incorporated into HCV RNA by NS5B polymerase.

Sovaldi is indicated for the treatment of chronic hepatitis C infection as a component of a combination antiviral treatment regimen.

Sofosbuvir is available as Sovaldi in 400 mg tablets.

Coverage Determination

Please note the following regarding medically accepted indications:

All reasonable efforts have been made to ensure consideration of medically accepted indications in this policy. Medically accepted indications are defined by CMS as those uses of a covered Part D drug that are approved under the federal Food, Drug and Cosmetic Act, or the use of which is supported by one or more citations included or approved for inclusion in any of the compendia described in section 1927(g)(1)(B)(i) of the Act. These compendia guide review of off-label and off-evidence prescribing and are subject to minimum evidence standards for each compendium. Currently, this review includes the following references when applicable and may be subject to change per CMS:

- American Hospital Formulary Service (AHFS) Compendium
- Thomson Micromedex/DrugDex (not Drug Points) Compendium
- National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium™
- Elsevier Gold Standard's Clinical Pharmacology Compendium

Sovaldi (sofosbuvir) will require prior authorization. This agent may be considered medically necessary when the following criteria are met:

Chronic Hepatitis C

- The member must have a diagnosis of chronic hepatitis C with compensated liver disease.
- The member must be at least 18 years of age.
- Baseline HCV RNA must be documented.
- Member has documented genotype 1, 2, 3, or 4 infection
  - Genotype 1
    - Member must have failed to achieve SVR on a prior regimen containing a HCV NS3/4A protease inhibitor
      - Sovaldi will be used in combination with peginterferon and ribavirin **OR**
      - Sovaldi will be used in combination with ribavirin for an interferon ineligible member defined as one of the following:
        - Contraindication to interferon therapy defined as: known hypersensitivity to interferon alfa, autoimmune hepatitis,

hepatic decompensation, pregnant females or male partners of pregnant females, hemoglobinopathies, creatinine clearance less than 50 mL/min, coadministration with didanosine

- Previous intolerance to an interferon alfa containing regimen resulting in discontinuation of therapy

- Genotype 2, 3
  - Sovaldi will be used in combination with ribavirin
- Genotype 4
  - Sovaldi will be used in combination with peginterferon and ribavirin

Chronic Hepatitis C with HIV co-infection

- The member must have a diagnosis of chronic hepatitis C with compensated liver disease.
- Member has HIV co-infection
- The member must be at least 18 years of age.
- Baseline HCV RNA must be documented.
- Member has documented genotype 1, 2, 3, or 4 infection
  - Genotype 1
    - Sovaldi will be used in combination with peginterferon and ribavirin OR
    - Sovaldi will be used in combination with ribavirin for an interferon ineligible member defined as one of the following:
      - Contraindication to interferon therapy defined as: known hypersensitivity to interferon alfa, autoimmune hepatitis, hepatic decompensation, pregnant females or male partners of pregnant females, hemoglobinopathies, creatinine clearance less than 50 mL/min, coadministration with didanosine
      - Previous intolerance to an interferon alfa containing regimen resulting in discontinuation of therapy
  - Genotype 2, 3
    - Sovaldi will be used in combination with ribavirin
  - Genotype 4
    - Sovaldi will be used in combination with peginterferon and ribavirin

Hepatocellular Carcinoma

- The member must have a diagnosis of chronic hepatitis C with compensated liver disease.
- The member must be at least 18 years of age.
- Member has documented genotype 1, 2, 3, or 4 infection
- Member has a diagnosis of hepatocellular carcinoma and is awaiting liver transplantation (meets Milan criteria)
- Sovaldi will be used in combination with ribavirin

Dosing

Chronic Hepatitis C and Chronic Hepatitis C with HIV co-infection:

- Genotype 1
  - Interferon-based dosing
    - Sovaldi 400 mg daily in combination with peginterferon alfa and ribavirin for 12 weeks
  - Interferon-ineligible
    - Sovaldi 400 mg daily in combination with ribavirin for 24 weeks
- Genotype 2
  - Sovaldi 400 mg daily in combination with ribavirin for 12 weeks
- Genotype 3
  - Sovaldi 400 mg daily in combination with ribavirin for 24 weeks
- Genotype 4
  - Sovaldi 400 mg daily in combination with peginterferon alfa and ribavirin for 12 weeks

Hepatocellular Carcinoma:

- Sovaldi 400 mg daily in combination with ribavirin for up to 48 weeks or until liver transplantation, whichever occurs first

Sovaldi (sofosbuvir) will be approved based on indication and treatment regimen or as determined through clinical review.

The quantity limit for all strengths of Sovaldi (sofosbuvir) is 28 tablets per 28 days.

Coverage Limitations

Sovaldi (sofosbuvir) therapy is not considered medically necessary for members with the following concomitant conditions:

- Monotherapy with Sovaldi
- Concurrent use with a HCV NS3/4A protease inhibitor.
- Coadministration with a potent P-glycoprotein (P-gp) inducer (e.g. rifampin, St. John's wort)
- Experimental/investigational use – Indications not supported by CMS recognized compendia or acceptable peer reviewed literature

Background

This is a prior authorization policy about Sovaldi (sofosbuvir).

- Ribavirin may cause birth defects and/or death of the exposed fetus and animal studies have shown that interferons have abortifacient effects. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.
- Persistent viremia with HCV is virtually universal after liver transplantation, and the majority of patients develop recurrent liver injury.
- The Milan Criteria for liver transplantation:
  - No lesion larger than 5 cm
  - ≤ 3 lesions with diameter ≤ 3 cm
  - No extrahepatic involvement
  - No major vessel involvement

Provider Claims Codes

There are no provider claims codes associated with this policy.

Medical Terms

Sovaldi; sofosbuvir; chronic hepatitis C infection; HCV; HIV co-infection; hepatocellular carcinoma; pharmacy

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

A Technology Assessment

Final Report

April 15, 2014

Completed by:

Institute for Clinical and Economic Review

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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 – develops rigorous 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.

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

Table of Contents

Abbreviations used in this report

AEs:	Adverse events
AST/ALT:	aspartate aminotransferase/alanine aminotransferase
BOC:	Boceprevir
CDC:	Centers for Disease Control and Prevention
CI:	Confidence interval
CMS:	Centers for Medicare & Medicaid Services
CTAF:	California Technology Assessment Forum
DARE:	Database of Abstracts of Reviews of Effects
DAA:	Direct-acting antiviral agent
FDA:	US Food and Drug Administration
HCC:	Hepatocellular carcinoma
HCV:	Hepatitis C virus
HR:	Hazard ratio
IFN	Interferon
NR:	Not reported
NS:	Not significant
OR:	Odds ratio
P:	Pegylated interferon
PBO:	Placebo
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
TVR:	Telaprevir
US:	United States

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				
Treatment-naïve				
PR (48)	47	48 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (≤ 30%)	No
BOC(24) + PR(48)	73	Add Q8 pills	Anemia (≤ 50%), more nausea and dysguesia, drug interactions	No
TVR(12) + PR(48)	74	Add Q8 pills	Anemia (≤ 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
Treatment-experienced				No
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 (≤ 50%), more nausea and dysguesia, drug interactions	No
TVR(12) + PR(48)	70	Add Q8 pills	Anemia (≤ 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				
Treatment-naïve				
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
Treatment-experienced				
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				
Treatment-naïve				
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
Treatment-experienced				
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),[118] alternative regimens of PR versus standard PR therapy ($17,000-$24,000),[119] and even highly active antiretroviral therapy in HIV patients ($1,000-$79,000).[120]

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.[112] Of note, however, telaprevir costs have increased substantially over the past 1.5 years, even as its use has declined to near zero.[97] 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, a patient advocate, payer representatives, and a representative from a manufacturer of one of the new agents. This discussion was distilled into nine specific recommendations that are described on pages 92-97 of this report. Among the key themes are:

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. Informed, shared decision-making about the timing of treatment should be encouraged. Given the circumstances, it is reasonable to consider prioritizing treatment with the new drugs for patients who need urgent treatment and have some evidence of liver fibrosis but do not have advanced liver disease.
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.

Introduction

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 (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 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.

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 in 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) and will not be considered further in this review. Knowledge of the viral genotype is important because response to therapy varies by genotype.

The acute phase of hepatitis C infection is asymptomatic for most patients. The Centers for Disease Control and Prevention (CDC) estimates that among 100 people infected with hepatitis C, only 20 to 30 will develop symptoms (see Table 1 below).[121] The symptoms are primarily fatigue, decreased appetite, nausea, and jaundice. Of 100 people infected with hepatitis C, 70 to 80 will not have any symptoms, and 75 to 85 will remain chronically infected with hepatitis C. [19-21] Between 60 and 70 of these individuals will develop chronic liver disease, and 5 to 20 will develop cirrhosis over 20 years.[22,23] 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.

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 over 20-30 years	5-20
Die from cirrhosis or liver cancer	1-5

The development of chronic hepatitis is partly dependent on an individual's genetics. Variants in interleukin 28 (IL28) predict clearance of the virus. Approximately half of patients with the IL28 CC variant spontaneously clear the virus while only 16 to 20% of those with the IL28 TT variant clear the virus.[24-26] This will be important to consider in treatment trials as patients carrying the IL28B CC virus are more likely to respond to treatment with interferon.[27,28]

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.[9,29,30] The majority of Americans infected with the hepatitis C virus or HCV (~76%) were born between the years of 1945 and 1965.[30] Both the CDC and the US Preventive Services Task Force (USPSTF) now recommend hepatitis C screening for all Americans born during that time frame.[31,32]

Chronic hepatitis C is a slowly progressive disease. Between 20 and 30% of patients develop cirrhosis over 20 to 30 years of infection.[22,23] The median time from infection to cirrhosis is estimated to be about 40 years, which means that approximately half of patients infected 40 years ago will have developed cirrhosis. Once bridging fibrosis or cirrhosis develops, patients with chronic HCV infection are at risk for the development of hepatocellular carcinoma. Factors associated with progression to cirrhosis include male sex, alcohol intake, elevated aspartate aminotransferase/ alanine aminotransferase (AST/ALT) ratio, elevated total bilirubin, low albumin, low platelets, and higher fibrosis scores.[22,23,33-36]

1.2 Definitions

- *Cirrhosis*: progressive scarring of liver tissue that may affect performance 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 6 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 1 $\log_{10}$ in HCV RNA during prior treatment.
- *Partial response:* greater than a 1 $\log_{10}$ 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 been the backbone of treatment for patients infected with HCV. Treatment is guided by genotype. Patients infected with genotype 1 tend to have a poor response to PR. As noted earlier, the first generation direct-acting antiviral agents (DAAs) – the protease inhibitors boceprevir and telaprevir – were approved for treatment of genotype 1 in 2011. The cure rate with triple therapy (a DAA plus PR) is approximately double the cure rate of the combination of interferon and ribavirin alone. New DAAs have been developed that are effective for multiple genotypes and offer the promise of interferon-free therapy. 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. In recent trials, the FDA has allowed the SVR 12 weeks after the completion of treatment (SVR12) to be the primary outcome.

SVR is a reasonable, but imperfect measure of cure, and it varies somewhat based on when it is measured. For example, the recent PILLAR trial,[37] 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. In a meta-analysis of long-term outcomes, the percent of patients with long-term cure following SVR24 ranged from 98% to 100%.[38]

A number of factors have been identified that predict a poor response to treatment. Patients with genotype 1 have a lower SVR24 than patients with the other genotypes. Among patients infected with genotype 1, the subtype 1a has a lower response rate than subtype 1b. Patients with the IL28B CC genotype respond better than patients with the CT or TT genotype. Other poor prognostic factors include a higher HCV RNA viral load, higher levels of fibrosis of the liver, older age, black race, obesity, and metabolic syndrome. Among patients who have been treated in the past, those who had a relapse after SVR respond better to new treatment than those with only a partial response to initial therapy, and patients with an initial null response to therapy are the least likely to respond to new treatment.

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.[39-41] 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%).[42] Other common side effects of PR include anemia (hemoglobin < 10 g/dL) in up to 30% of patients, generalized pruritis (25% to 30%), and psychiatric symptoms such as depression (up to 25%), insomnia, and anxiety (15% to 25%).[42] 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. Since their approval in 2011, the standard of care for the treatment of genotype 1 has been PR in combination with either boceprevir or telaprevir.[43-45] Among treatment-naïve patients, PR plus boceprevir or telaprevir has a SVR24 between 70% and 75%. Patients with the IL28B CC genotype respond well to interferon. In this group, the response to PR plus either boceprevir or telaprevir is between 80% and 90%.

The length of treatment is guided by the patient's liver histology, response to prior treatment, and the change in viral load during the first weeks of treatment. The treatment algorithm for boceprevir starts with four weeks of PR. Among treatment-naïve patients, this is followed by 24 weeks of PR plus boceprevir with no additional treatment if the patient has an undetectable HCV RNA during weeks 8 to 24 (so-called response guided therapy). Those with detectable RNA at week 8 receive an additional 8 weeks of PR + boceprevir (32 weeks total) followed by an additional 12 weeks of PR alone. Among treatment-experienced patients, the four weeks of PR is followed by 32 weeks of PR plus boceprevir with no additional treatment if the patient has an undetectable HCV RNA during weeks 8 to 24. Treatment-experienced patients with detectable RNA at week 8 receive 32 weeks of PR plus boceprevir and then an additional 12 weeks of PR alone. For both treatment-naïve and experienced patients, if the HCV RNA level is ≥ 100 IU per ml at week 12 or detectable at week 24,

treatment is stopped. Patients with cirrhosis, a prior null response, or less than a one log decrease in HCV RNA during the 4 week PR run in (i.e., a period of therapy with PR before initiating boceprevir) should also be considered for 48 weeks of treatment.

The treatment algorithm for telaprevir is somewhat simpler. Everyone starts with 12 weeks of PR plus telaprevir. Patients who are treatment-naïve or relapsed following prior SVR receive an additional 12 weeks of PR. Those who have HCV RNA > 1000 IU per ml at week 4 or 12 should stop therapy at that time. Prior partial responders and null responders and those who are treatment-naïve but who have detectable HCV RNA at weeks 4 and / or 12 receive an additional 36 weeks of PR. All patients with cirrhosis should be considered for an additional 36 weeks of PR therapy rather than 12 weeks, even if their HCV RNA level is less than 25 IU per ml.

Challenges with boceprevir and telaprevir therapy

The marked improvement in SVR24 with the addition of boceprevir or telaprevir to PR comes with significant practical and clinical trade-offs. Patients must take either 6 or 12 pills per day spaced every 7 to 9 hours, and the pills must be taken with at least 20 grams of fat. Both medications increase the risk for severe anemia that is already common with PR treatment (increased from 30% with PR to 50% with either boceprevir or telaprevir).[42] Boceprevir causes a bitter or metallic taste (40% versus 20% with PR), and telaprevir causes rashes and pruritus (20% more than PR alone).[42] The combination of PR plus boceprevir or telaprevir is associated with serious adverse event rates between approximately 40% and 50%.[42,46,47] Neither can be used as monotherapy because resistance develops quickly.[48,49] 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.

Treatment of Genotypes 2 and 3

Pegylated interferon plus ribavirin

Neither boceprevir nor telaprevir is approved for treatment of genotypes 2 and 3 and therefore the standard of care for these patients has been 24 weeks of PR. The duration of treatment is half that for genotype 1, but the response rate is significantly higher. The SVR24 of patients with genotypes 2 or 3 in clinical trials ranged from 75% to 85%, although the real world experience is again somewhat lower.

Newly-Approved Treatment Regimens

Boceprevir and telaprevir were the first two DAAs approved by the FDA. Since then, more than 30 additional DAAs have entered 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 goals of the new therapies include simpler dosing regimens (fewer pills, shorter duration), fewer side effects, fewer drug interactions, and higher cure rates. Two new DAAs were approved in late 2013: simeprevir and sofosbuvir. At least two additional DAAs, faldaprevir and daclatasvir, are likely to be approved in 2014.[50] Many physicians are monitoring patients with chronic HCV infections but not treating them while waiting for new medical therapies (sometimes referred to as warehousing). Physicians expect that these new therapies will provide high cure rates without the severe side effects of current therapies, which require the use of interferon.

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 considered a second-generation protease inhibitor (boceprevir and telaprevir were first generation protease inhibitors). A major improvement of simeprevir compared with earlier protease inhibitors is the dosing schedule. It may be taken once a day rather than six to twelve pills divided into doses taken every eight hours. A second major improvement is that it does not appear to increase the risk for anemia, which has been a major problem with the first generation protease inhibitors. Simeprevir must be used in combination with PR because viral resistance develops rapidly with monotherapy. Significant new adverse reactions associated with simeprevir include photosensitivity reactions, some of which have required hospitalization, and pruritus. The FDA indication for simeprevir is for genotype 1 only: simeprevir 150 mg 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 2 below).

Table 2. FDA Indications for Simeprevir and Sofosbuvir.

Drug	Genotype	Treatment
Simeprevir	1	• 150 mg daily with PR x 12 weeks plus PR for an additional 12 to 36 weeks
Sofosbuvir	1, 4	• 400 mg daily with PR x 12 weeks • Alternate if interferon (IFN)-ineligible: 400 mg daily with R x 24 weeks
Sofosbuvir	2	• 400 mg daily with R x 12 weeks
Sofosbuvir	3	• 400 mg daily with R x 24 weeks
Sofosbuvir	HIV co-infected	• Same as above based on genotype

Sofosbuvir is the first drug in the class of HCV NS5B nucleotide analog polymerase inhibitors to be approved. Sofosbuvir is the third approved drug given breakthrough designation by the FDA. The goal of the breakthrough therapy program is to speed up the development and review of drugs that have substantial benefits over available therapy for serious or life-threatening conditions. The FDA requires substantially less evidence to support the approval of drugs with breakthrough designation. 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. Unlike simeprevir, sofosbuvir is also approved to treat genotypes 2, 3, and 4 in addition to genotype 1 (see Table 2 on previous page). 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. The FDA indication for patients with genotype 2 is sofosbuvir 400 mg daily with R for 12 weeks. The FDA indication for patients with genotype 3 is sofosbuvir 400 mg daily with R for 24 weeks. For patients who are HIV co-infected, the treatment varies by genotype but is the same as for patients who are not HIV co-infected.

2. Clinical Guidelines

The 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 took the unusual step of jointly creating and updating an online guideline for the treatment of chronic hepatitis C because of the rapidly evolving treatment environment: the FDA is expected to approve an array of new drugs over the next few years. For genotype 1, they recommend sofosbuvir plus PR or sofosbuvir plus simeprevir (in interferon-intolerant patients). They recommend simeprevir + PR as an alternative therapy for patients with genotype 1 without the Q80K polymorphism. For genotypes 2 and 3, they recommend sofosbuvir plus ribavirin.

The Department of Veterans Affairs (VA)
http://www.hepatitis.va.gov/provider/guidelines/2012HCV

The 2012 VA guidelines recommend PR plus either boceprevir or telaprevir for treating genotype 1 infections and PR alone for treating genotype 2 and 3 infections. An updated version of these guidelines following FDA approval of simeprevir and sofosbuvir is expected in Spring 2014.

National Institute for Health and Care Excellence (NICE)
http://cks.nice.org.uk/hepatitis-c

Current treatment guidelines at NICE recommend treatment with PR as the initial therapy for all genotypes but were last revised in March 2010. NICE is currently reviewing the new DAA drugs.

European Association for the Study of the Liver (EASL)
http://www.easl.eu/2013HCVguideline

In December 2013, EASL updated its HCV treatment guidelines. They recommend that treatment should not be deferred for patients with significant fibrosis (METAVIR F3 or F4). They recommend PR plus either boceprevir or telaprevir for treating genotype 1 infections and PR alone for treating genotype 2 and 3 infections.

The Canadian Association for the Study of the Liver (CASL)
http://www.hepatology.ca

Current CASL recommendations (from June 2012) are to use PR plus either boceprevir or telaprevir for treating genotype 1 infections and PR alone for treating genotype 2 and 3 infections. No recommendations including the new DAA therapies have been made to date.

The Japan Society of Hepatology (JSH)
http://JSH2014HCVguidelines

In January 2014, the JSH updated their guidelines for the management of genotype 1. They recommend simeprevir plus PR as the primary therapy for most patients with telaprevir plus PR as an alternative. They do not comment on sofosbuvir as it is not approved for use in Japan.

3. Coverage Policies

Coverage policies of a variety of public and private payers for simeprevir and sofosbuvir were reviewed in February 2014 and are described below.

3.1 Simeprevir

Medicare & Medicaid

No publicly-available coverage policies, prior authorization protocols, or formulary designations for simeprevir were available from the Centers for Medicare & Medicaid Services (CMS) or Medi-Cal, California's Medicaid agency.

Regional Private Payers

HealthNet
https://www.healthnet.com/static/general/unprotected/html/national/pa_guidelines/olysio_natl.html

HealthNet has published an interim prior authorization protocol that provides coverage for simeprevir + PR for chronic hepatitis C patients with genotype 1 but without the Q80K polymorphism. Coverage is *not* authorized for monotherapy with simeprevir, in patients who have failed prior treatment with any protease inhibitor (including simeprevir), or in patients with any known contraindication to interferon (e.g., decompensated liver disease, uncontrolled autoimmune hepatitis).

National Private Payers/Pharmacy Benefit Managers

Aetna
http://www.aetna.com/products/rxnonmedicare/data/2014/GI/hepatitis_c.html

Coverage is limited to patients with chronic hepatitis C virus genotype 1 with compensated liver disease who receive concurrent therapy with PR. Use of simeprevir is not covered in combination with any other protease inhibitor therapy (including sofosbuvir), in genotype 1 patients with the Q80K polymorphism, or in those who have failed previous therapy with protease inhibitors.

Anthem/Express Scripts
http://www.anthem.com/provider/noapplication/f0/s0/t0/pw_e210962.pdf?na=pharminfo

Simeprevir + PR is covered in adult genotype 1 patients with chronic hepatitis C *and* compensated liver disease who are negative for the Q80K polymorphism.

CVS-Caremark
http://www.caremark.com/portal/asset/FEP_Criteria_Olysio.pdf

CVS-Caremark has published prior authorization criteria stating that simeprevir + PR is approved for use in patients with genotype 1 chronic hepatitis C who have compensated liver disease, have not been previously treated with any protease inhibitor, have not had a liver transplant, and do not expect to reduce or interrupt simeprevir dosing. Monotherapy with simeprevir is not approved.

Humana
http://apps.humana.com/tad/tad_new/Search.aspx?criteria=simeprevir&searchtype=freetext&policyType=both

Humana limits coverage to adult patients who have a diagnosis of genotype 1 hepatitis C *with* evidence of compensated liver disease and concurrent therapy with PR. Simeprevir is not covered in combination with other protease inhibitors or sofosbuvir, in combination with medications that are either potent CYP3A4/5 inducers or CYP3A4/5 inhibitors, in patients with the Q80K polymorphism, or in those who have previously received a treatment with a protease inhibitor.

3.2 Sofosbuvir

Medicare & Medicaid

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

Regional Private Payers

HealthNet
https://www.healthnet.com/static/general/unprotected/html/national/pa_guidelines/sovaldi_natl.html

HealthNet has published an interim prior authorization protocol that ties coverage for sofosbuvir to the FDA-approved indications and therapy durations. Monotherapy with sofosbuvir (i.e., without ribavirin) is not covered.

National Private Payers/Pharmacy Benefit Managers

Aetna:
http://www.aetna.com/products/rxnonmedicare/data/2014/GI/hepatitis_c.html

Aetna provides coverage for sofosbuvir + PR in patients with genotypes 1 or 4, and coverage for sofosbuvir + R in genotypes 2 and 3. Additionally, sofosbuvir + R may be used in genotype 1 patients who are ineligible for interferon, defined by Aetna as including: recent suicide attempt, severe depression, or previous interferon-related adverse events. Combination therapy with simeprevir is not covered.

Anthem/Express Scripts
http://www.anthem.com/provider/noapplication/f0/s0/t0/pw_e210963.pdf?na=pharminfo

Sofosbuvir is generally covered in adult patients with chronic hepatitis C who have evidence of compensated liver disease (including cirrhosis). Coverage is tied to FDA-approved indications and therapy durations. Sofosbuvir + R may be used in genotype 1 patients who are ineligible for interferon, defined by Anthem as including: autoimmune hepatitis, Child-Pugh liver function score >6, or known hypersensitivity to interferon.

CVS-Caremark
http://www.caremark.com/portal/asset/FEP_Criteria_Sovaldi.pdf

CVS-Caremark has published prior authorization criteria stating that sofosbuvir + PR (genotypes 1 and 4) or sofosbuvir + R (genotypes 2 and 3 as well as genotype 1 patients ineligible for interferon) must be used only in adults with chronic hepatitis C who do not have renal impairment, decompensated cirrhosis, liver cancer awaiting transplant, or significant or unstable cardiac disease. Sofosbuvir monotherapy is not allowed in any situation. The occurrence of liver transplant is a trigger for discontinuation of sofosbuvir.

Humana:

http://apps.humana.com/tad/tad_new/Search.aspx?criteria=sofosbuvir&searchtype=freetext&policyType=both

Humana limits coverage of sofosbuvir to adult patients who have a diagnosis of chronic hepatitis C *with* evidence of compensated liver disease. Additionally, coverage for genotype 1 patients is limited to those who have failed to achieve SVR with a prior regimen containing a protease inhibitor or who have documented contraindications to interferon therapy (e.g., hypersensitivity to interferon, hepatic decompensation, hemiglobinopathies). Coverage for genotypes 2, 3, and 4 is not restricted other than based on the general criteria above and FDA-approved treatment regimens. Use of sofosbuvir as monotherapy or in combination with any other protease inhibitor (including simeprevir) is not considered medically necessary and is not covered.

4. Previous Systematic Reviews and Technology Assessments

We were unable to identify any technology assessments of the new DAAs. Four systematic reviews used network meta-analysis to evaluate the efficacy of boceprevir and telaprevir because there are no head-to-head comparisons of treatment regimens including the two drugs. There were no systematic reviews evaluating simeprevir or sofosbuvir.

4.1 Formal Health Technology Assessments

No formal health technology assessments were identified. However, the Canadian Agency for Drugs and Technologies in Health (CADTH) is currently undertaking a review of new DAA agents (among patients with genotype 1 chronic hepatitis C only), and NICE is undertaking individual technology assessments of sofosbuvir and simeprevir according to their labeled indications in Europe (i.e., all genotypes for sofosbuvir, genotypes 1 and 4 for simeprevir).

4.2 Systematic Reviews

Cure 2012

Cure S, Diels J, Gavart S, Bianic F, Jones E. Efficacy of telaprevir and boceprevir in treatment-naïve and treatment-experienced genotype 1 chronic hepatitis C patients: an indirect comparison using Bayesian network meta-analysis. *Current medical research and opinion.* Nov 2012;28(11):1841-1856.

This systematic review and Bayesian network meta-analysis of 11 studies found that both boceprevir and telaprevir combined with PR were better than PR alone in treatment-naïve and treatment-experienced patients. The authors highlighted a trend towards better outcomes with telaprevir.

Cooper 2013

Cooper C, Lester R, Thorlund K, et al. Direct-acting antiviral therapies for hepatitis C genotype 1 infection: a multiple treatment comparison meta-analysis. *QJM : monthly journal of the Association of Physicians.* Feb 2013;106(2):153-163.

This systematic review and Bayesian network meta-analysis of 11 studies found that both boceprevir and telaprevir combined with PR were better than PR alone. In the treatment-naïve,

telaprevir had lower rates of anemia and neutropenia but higher rates of rash and pruritus. In the treatment-naïve, telaprevir had higher rates of all adverse events compared with boceprevir.

Kieran 2013

Kieran J, Schmitz S, O'Leary A, et al. The relative efficacy of boceprevir and telaprevir in the treatment of hepatitis C virus genotype 1. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Jan 2013;56(2):228-235.

This systematic review and Bayesian network meta-analysis of 10 studies found that both boceprevir and telaprevir combined with PR were better than PR alone. In the subgroup of patients who had relapsed following SVR, telaprevir-based treatments were more effective than boceprevir-based treatments.

Sitole 2013

Sitole M, Silva M, Spooner L, Comee MK, Malloy M. Telaprevir versus boceprevir in chronic hepatitis C: a meta-analysis of data from phase II and III trials. *Clinical therapeutics.* Feb 2013;35(2):190-197.

This systematic review and Bayesian network meta-analysis of eight studies found that both boceprevir and telaprevir combined with PR had higher SVR than PR alone, but with an increase in drug-related adverse events. They highlighted the lack of data on long-term outcomes such as hospitalization for liver disease, HCC, and mortality.

5. Ongoing Studies

We did not include studies focusing exclusively on the treatment of HCV genotypes 4, 5, or 6 nor did we include combinations with drugs that are not yet FDA approved.

Two of the ongoing studies of simeprevir stand out as likely to answer key open questions. The first (NCT01485991) is a randomized trial comparing simeprevir to telaprevir in treatment-experienced patients. This will be the first study to compare the new DAAs to the previous standard of care for treating HCV genotype 1. The second (NCT01349465) is the three-year follow-up of patients in the phase 2 and 3 trials: this should give at least preliminary information on the impact of treatment on disease progression. The list of studies below does not include several ongoing studies of interferon-free combinations of simeprevir with DAAs that do not have FDA approval including daclatasvir, IDX-719, TMC-647055, and GSK-23336805.

None of the studies of sofosbuvir listed on clinicaltrials.gov have a PR or PR plus boceprevir or telaprevir control group. There are no trials with primary outcomes beyond SVR12. The list of studies below does not include several ongoing studies of interferon-free combinations of sofosbuvir with DAAs in development that do not yet have FDA approval including daclatasvir, ledipasvir, GS-5885, GS-0938, and GS-5816.

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Simeprevir or SMV (TMC435)					
An Efficacy, Safety and Tolerability Study for TMC435 vs Telaprevir in Combination With PegINFα-2a and Ribavirin in Chronic Hepatitis C Patients Who Were Null or Partial Responders to Prior PegINFα-2a and Ribavirin Therapy (ATTAIN) NCT01485991	RCT Double blind Placebo-controlled Non-inferiority N = 766	SMV 150 + PR TVR 750 mg every 8 hours + PR	• Genotype (GT) 1 • Treatment-experienced	SVR12	March 2014
3-year Follow-up Study in Patients Previously Treated With a TMC435 for the Treatment of Hepatitis C Virus (HCV) Infection NCT01349465	Cohort N = 249	None	• Treated with simeprevir in a phase 2 or phase 3 study	SVR at 3 years	February 2016
An Efficacy, Pharmacokinetics, Safety and Tolerability Study of TMC435 as Part of a Treatment Regimen for Hepatitis C-Infected Patients (Phase 3) NCT01725529	RCT Double-blind Placebo (PBO) controlled N = 457	SMV 150 + PR SMV 100 + PR PBO + PR	• GT 1 • Treatment-naïve	SVR12	October 2014
A Study of TMC435 in Combination With Peginterferon Alfa-2A and Ribavirin for Hepatitis C Virus Genotype-1 Infected Patients Who Participated in a Control Group of a TMC435 Study NCT01323244	Cohort Open-label N = 270	SMV 150 + PR	• GT 1 • Did not achieve SVR in the placebo arm of prior trials of simeprevir	SVR12	January 2015

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
A Study of TMC435 in Combination With PSI-7977 (GS7977) in Chronic Hepatitis C Genotype 1-Infected Prior Null Responders To Peginterferon/Ribavirin Therapy or HCV Treatment-naïve Patients COSMOS Cohorts 1 and 2 NCT01466790	RCT Open-label N = 168	SMV + sofosbuvir (SOF) 12 Weeks SMV + SOF + R 12 Weeks SMV + SOF 24 Weeks SMV + SOF + R 24 Weeks	• GT 1 • Naïve and Experienced • METAVIR F3 or F4	SVR12	January 2014
A Study to Evaluate the Efficacy, Safety and Tolerability of TMC435 in Combination With PegIFN Alfa-2a (Pegasys) and Ribavirin (Copegus) in Treatment-naïve or Treatment-experienced, Chronic Hepatitis C Virus Genotype-4 Infected Patients (RESTORE) Phase 3 NCT01567735	Cohort Open-label N = 107	SMV 150 + PR	• GT 4 • Naïve and Experienced	SVR12	March 2014
A Study to Assess the Safety, Tolerability and Efficacy of TMC435 Along With Pegylated Interferon Alpha-2a (Pegasys) and Ribavirin (Copegus) Triple Therapy in Chronic Hepatitis C Genotype-1 Infected Patients Co-infected With Human Immunodeficiency Virus (HIV)-Type 1 NCT01479868	Cohort Open-label N = 109	SMV 150 + PR	• GT 1 • HIV-1 infection	SVR24	August 2013
A Study of TMC435 Plus Pegylated Interferon Alfa-2a and Ribavirin in Participants With Chronic HCV Infection NCT01846832	Cohort Open label N = 225	SMV 150 + PR	• GT 1 or 4 • Naïve • METAVIR F0-F2	SVR12	October 2014

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Sofosbuvir (GS-7977, PSI-7977)					
Sofosbuvir + R for 16 or 24 Weeks and Sofosbuvir + PR for 12 Weeks in Subjects With Genotype 2 or 3 Chronic HCV Infection NCT01962441	RCT Open label N= 600	SOF 400 + R 16 Weeks SOF 400 + R 24 Weeks SOF 400 + PR 12 Weeks	• GT 2 with cirrhosis or GT 3 • Naïve or experienced	SVR12	December 2014
Open-Label Safety Study of Telaprevir and Sofosbuvir in Chronic Hepatitis C Genotype 1 (STEADFAST) NCT01994486	Cohort Open label N = 20	SOF + TVR 12 Weeks	• GT 1 • Naïve	SVR12	July 2014
Safety and Efficacy Study of Sofosbuvir Plus Ribavirin in Treatment-naïve Adults With Genotype 1 and 3 Chronic HCV Infection. NCT01896193	RCT Open label N= 120	SOF 400 + R 16 Weeks SOF 400 + R 24 Weeks	• GT 1 or 3 • Naïve	SVR12	April 2014
Sofosbuvir Plus Ribavirin in Subjects With HCV Infection and Renal Insufficiency NCT01958281	Non-randomized Open label N = 40	SOF 200 + R 200 24 Weeks SOF 400 + R 200 24 Weeks	• GT 1 or 3 • Naïve • Renal insufficiency	SVR12	July 2016
A Phase 3b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir Plus Ribavirin in Treatment-naïve and Treatment-experienced Japanese Subjects With Chronic Genotype 2 HCV Infection NCT01910636	Cohort Open label N = 134	SOF 400 + R 12 Weeks	• GT 2 • Naïve or experienced	SVR12	April 2014

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Efficacy and Safety of Sofosbuvir Plus Ribavirin in Subjects With Chronic HCV Infection NCT02021643	RCT Open label N=450	SOF 400 + R 12 Weeks SOF 400 + R 16 Weeks SOF 400 + R 24 Weeks	• Naïve with GT 1, 2, 3, or 6 • Experienced with GT 2	SVR12	May 2015
Expanded Access Program of Sofosbuvir With Ribavirin and With or Without Pegylated Interferon-in Aggressive Post-transplant Hepatitis C NCT01779518	Cohort Open label N = not provided	SOF 400 + R or PR 24 Weeks	• Post-liver transplant • Aggressive HCV infection	-	-
A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir Plus Ribavirin in Chronic Genotype 1, 2 and 3 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-infected Subjects NCT01667731	Cohort Open label N = 230	SOF 400 + R 12-24 Weeks	• GT 1, 2, or 3 • HIV-1 infection	SVR12	November 2013
Sofosbuvir (GS-7977) in Combination With P and Ribavirin for 12 Weeks in Treatment-experienced Subjects With Chronic HCV Infection Genotype 2 or 3 NCT01808248	Cohort Open label N = 47	SOF 400 + PR 12 Weeks	• GT 2 or 3 • Experienced	SVR12	September 2013
An Open-Label Study to Explore the Clinical Efficacy of Sofosbuvir With Ribavirin Administered Pre-Transplant in Preventing Hepatitis C Virus (HCV) Recurrence Post-Transplant NCT01559844	Cohort Open label N= 50	SOF 400 + R	• HCV Infection • HCC awaiting liver transplant	Post-transplant virologic response	September 2013

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir Plus Ribavirin in Chronic Genotype 1, 2, 3 and 4 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-infected Subjects NCT01783678	Non-randomized Open label N = 270	SOF 400 + R 12 Weeks SOF 400 + R 24 Weeks	• GT 1, 2, 3, or 4 • HIV-1 infection • Naïve or experienced	SVR12	April 2014
Open-Label Study of Sofosbuvir + Ribavirin With or Without Peginterferon Alfa-2a in Subjects With Chronic HCV Infection Who Participated in Prior Gilead HCV Studies NCT01625338	Non-randomized Open label N = 600	SOF 400 + R 12 Weeks SOF 400 + R 24 Weeks SOF 400 + PR 12 Weeks	• Enrolled in prior sponsored studies of sofosbuvir	SVR12	July 2014
GS-7977 and Ribavirin in Patients With Chronic HCV With Cirrhosis and Portal Hypertension With or Without Liver Decompensation NCT01687257	RCT Open label N = 50	SOF 400 + R 48 Weeks Observe x 24 Weeks then SOF 400 + R 48 Weeks	• HCV infection, any genotype • Cirrhosis with Child-Pugh score < 10 • Esophageal or gastric varices	SVR12	August 2014
Safety of Efficacy of GS-7977 and Ribavirin in Subjects With Recurrent Chronic Hepatitis C Virus (HCV) Post Liver Transplant NCT01687270	Non-randomized Open label N = 40	SOF 400 + R 24 Weeks	• HCV infection, any genotype • Liver transplant 0.5 to 12 years prior to treatment	SVR12	January 2014

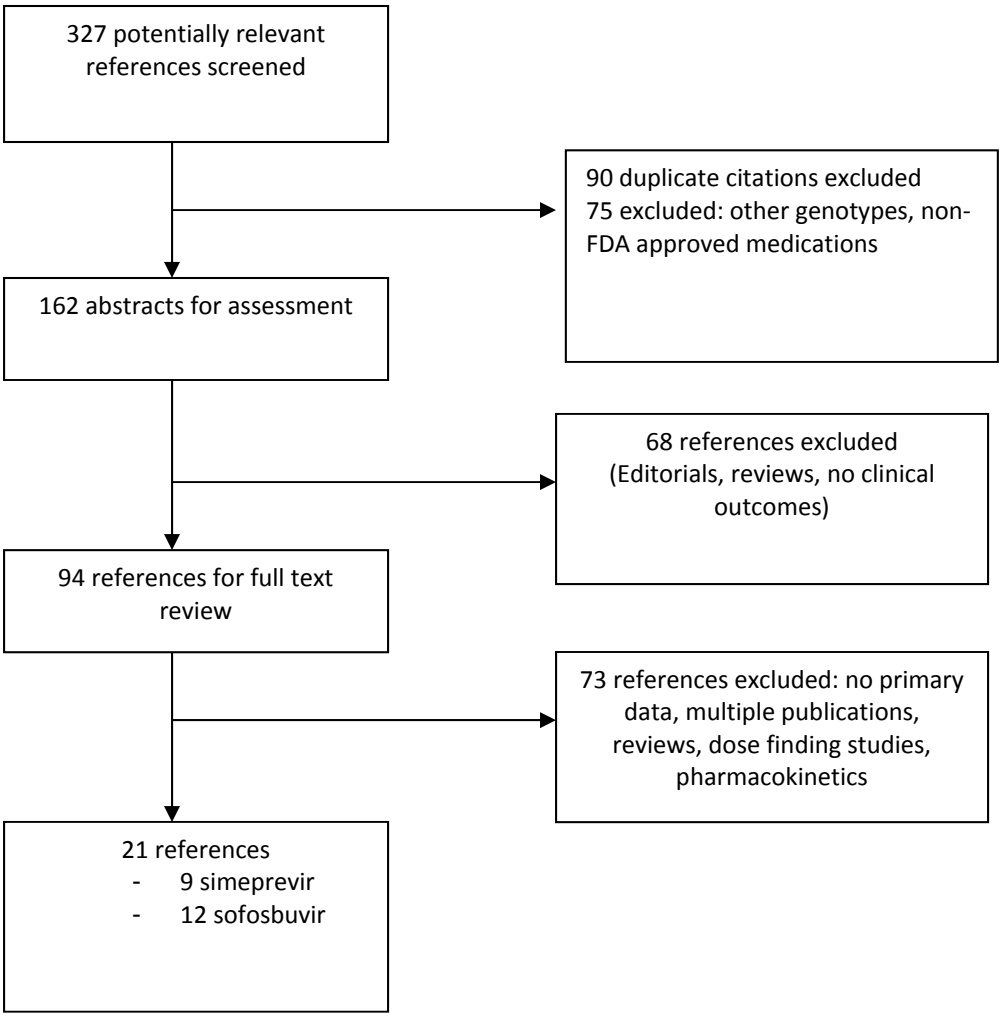
6. Evidence Review (Methods & Results)

The goal of this technology assessment is to evaluate the comparative effectiveness and value of the new DAAs simeprevir and sofosbuvir in the treatment of chronic hepatitis C infection. There were no randomized or other studies that directly compared therapies based on simeprevir to those based on sofosbuvir or to the two first generation protease inhibitors boceprevir and telaprevir. We therefore performed a network meta-analysis to provide indirect evidence about the relative efficacy of the drug combinations available using currently FDA approved therapies.

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." The search was performed for the period from 1945 through January 8, 2014. Full details of the search are in the Appendix. 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. There were peer-reviewed publications for 11 of the 26 studies identified. We included all studies of simeprevir or sofosbuvir for genotypes 1, 2, or 3 that reported SVR12 or SVR24 as an outcome in at least one study arm. For the results of a study to be included in the network meta-analysis, at least one study group must have received a treatment regimen with dosing similar to the final FDA indications. For example, we did not include data from the Japanese studies of simeprevir that used 100 mg rather than 150 mg daily in our analysis, although we have included the studies in our tables. 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 major phase 3 trials of telaprevir and boceprevir were included for the network meta-analysis.[51-58]

The search identified 327 potentially relevant studies (see Figure 1 on the next page). After elimination of duplicate and non-relevant references, the search identified 21 publications and abstracts describing clinical trials of simeprevir[37,59-68] or sofosbuvir.[62,69-79] The primary reasons for study exclusion were (a) early dose finding studies, (b) lack of SVR or other clinical outcomes, or (c) reviews and commentaries.

Figure 1. Selection of Studies for Inclusion in Review.



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 (20-40 years before the development of cirrhosis), large randomized trials with long 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 has accepted recent studies with a primary outcome of SVR 12 weeks after the end of therapy, and SVR12 was the primary outcome for all of the phase 3 studies of simeprevir and sofosbuvir.

The vast majority of patients with SVR at 24 weeks (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.[80-83] Additionally, patients with SVR24 have marked improvements or normalization of their ALT as well as improvements in liver histology.[80-85] More importantly, SVR24 has been associated with improvements in quality of life and a reduction in fatigue within months of treatment.[86,87] Recent studies have demonstrated that SVR24 is associated with decreases in decompensated liver disease, hepatocellular carcinoma, liver transplant, and all-cause mortality.[80,88-92] For example, in the HALT-C trial, the investigators prospectively followed 549 patients with advanced fibrosis who received treatment with PR (140 patients with SVR; 309 patients with non-response to therapy) for a median of approximately 7 years.[89] 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 record, 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.[92] 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.[80,81,83,88,89,93] Thus achieving an SVR24 will not prevent the complications of chronic HCV infection for all patients.

6.1 Overview of the Key Studies of Simeprevir and Sofosbuvir

There are data available from 11 trials of simeprevir (see Table 3 on next page). There are two published phase 2 trials (PILLAR, ASPIRE), three unpublished phase 3 trials (QUEST-1, QUEST-2, PROMISE), one published Japanese trial (DRAGON), and four additional unpublished Japanese trials (CONCERTO 1-4). There are also data presented at conferences on a trial combining simeprevir with sofosbuvir (COSMOS). All 11 trials enrolled only patients with genotype 1 HCV infections who were eligible to receive interferon. Six of the trials enrolled treatment-naïve patients and five enrolled treatment-experienced patients. For completeness, an ongoing trial in HIV co-infected patients is

also listed in the table. None of the trials (except the ongoing trial in HIV co-infected patients) compared simeprevir plus PR to either boceprevir or telaprevir plus PR.

Table 3. Overview of the Clinical Trials of Simeprevir (aka TMC435).

Study	Publication	Treatment	Control	Genotypes	Treatment	IFN Eligible	Prevalence of Cirrhosis (%)
Phase 2							
PILLAR	Fried 2013	SMV + PR	PR	1	Naïve	Yes	0
ASPIRE	Zeuzem 2014	SMV + PR	PR	1	Experienced	Yes	18
Phase 3							
QUEST 1		SMV + PR	PR	1	Naïve	Yes	12
QUEST 2		SMV + PR	PR	1	Naïve	Yes	9
PROMISE		SMV + PR	PR	1	Experienced	Yes	15
Japan							
CONCERTO-1		SMV + PR	PR	1	Naïve	Yes	
CONCERTO-2		SMV + PR		1	Experienced	Yes	
CONCERTO-3		SMV + PR		1	Experienced	Yes	
CONCERTO-4		SMV + PR		1	Naïve/Exp	Yes	
DRAGON	Hayashi 2013	SMV + PR	PR	1	Naïve	Yes	0
Other							
COSMOS	Cohort 1	SOF + SMV ± R	None	1	Experienced	Yes	0
HIV co-infected							
C212		SMV + PR	None	1	Naïve/Exp	Yes	12

The clinical trial data for sofosbuvir are more complex (see Table 4 on the next page). There are data available from 12 trials of sofosbuvir plus one ongoing trial in HIV co-infected patients and one trial in patients awaiting transplant for HCC. There are three published phase 2 trials (PROTON, ELECTRON, ATOMIC), two unpublished phase two trials (P7977-0221, QUANTUM), four published phase 3 trials (FISSION, POSITRON, FUSION, NEUTRINO), one unpublished phase 3 trial (VALENCE), and one published NIH trial (SPARE). The same trial that combines simeprevir with sofosbuvir (COSMOS) is also included in the table. The trials of sofosbuvir enrolled a mix of patients with genotypes 1 through 6 and a mix of treatment-naïve and experienced patients, although they primarily focused on genotypes 2 and 3. One study focused on patients with genotypes 2 and 3 who were unwilling or unable to take interferon or were intolerant of interferon (POSITRON). Three of the 12 trials were randomized trials with PR control groups (P7977-0221, PROTON, FISSION), and one randomized trial had a placebo only control group (POSITRON). The remaining eight trials had *no* control group. None of the trials compared sofosbuvir to PR plus either boceprevir or telaprevir.

Table 4. Overview of the Clinical Trials of Sofosbuvir (GS-7977).

Study	Publication	Treatment	Control	Genotypes	Treatment	IFN Eligible	Prevalence of Cirrhosis (%)
Phase 2							
P7977-O221	-	SOF + PR	PR	1	Naïve	Yes	0
PROTON	Lawitz 2013b	SOF + PR	PR	1, 2, 3	Naïve	Yes	0
ELECTRON	Gane 2013	SOF + PR	None	1, 2, 3	Naïve/Exp	Yes	0
ATOMIC	Kowdley 2013	SOF + PR	None	1, 4, 5, 6	Naïve	Yes	0
QUANTUM	-	SOF + R	None	1, 2, 3, 4, 5, 6	Naïve	Yes	6
Phase 3							
FISSION	Lawitz 2013a	SOF + R	PR	2, 3	Naïve	Yes	20
POSITRON	Jacobson 2013	SOF + R	Placebo	2, 3	Naïve/Exp	Intolerant, unwilling, or ineligible	16
FUSION	Jacobson 2013	SOF + R	None	2, 3	Experienced	Yes	34
NEUTRINO	Lawitz 2013a	SOF + PR	None	1, 4, 5, 6	Naïve	Yes	17
VALENCE		SOF + R	None	2, 3	Naïve/Exp	Yes	
Other							
SPARE	Osinusi 2013	SOF + R	None	1	Naïve	Yes	23
COSMOS		SOF + SMV ± R	None	1	Experienced	Yes	
HIV co-infected							
PHOTON-1		SOF + R	None	1, 2, 3	Naïve GT 1 Exp GT 2/3	Not specified	Up to 20
Pre-transplant							
P7977-2025		SOF + R	None	Any	Naïve/Exp	Yes	100% HCC

Several key differences between the studies of simeprevir and sofosbuvir emerge when looking at Tables 3 and 4. First, simeprevir has only been studied in patients infected with genotype 1, while sofosbuvir has been studies across all genotypes. Second, all three of the phase 3 studies of simeprevir were randomized trials with PR as the control. Only one of the phase 3 trials of

sofosbuvir was a randomized trial with PR as a control (FISSION), and one trial had a placebo control (POSITRON). The phase 3 randomized, placebo controlled trials for sofosbuvir were all in patients infected with HCV genotypes 2 or 3. Third, seven of the sofosbuvir trials are interferon-free. The only interferon-free regimen that includes simeprevir is a regimen in which simeprevir is combined with sofosbuvir (COSMOS). Finally, none of the trials in patients with HCV genotype 1 were randomized trials comparing a new regimen to the previous standard of care for the treatment of genotype 1: boceprevir or telaprevir plus PR.

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

Table 5 on the following page summarizes the results of the major studies of the two new DAAs in treatment-naïve patients with genotype 1. All of the studies excluded patients with HIV, hepatitis B, decompensated cirrhosis, or other significant illnesses. The treatment dosing regimens that match the FDA indication are highlighted and in bold. The primary outcome for most studies was SVR12, but some of the early studies were designed to look at SVR24 and some studies report both. No studies report long-term outcomes.

Interferon-eligible Patients

The PILLAR study was a randomized, double-blind, placebo controlled dose finding study comparing four different dosing regimens for simeprevir to standard PR therapy. The primary outcome was SVR24, which ranged from 75% to 86% compared to 65% for PR. The SVR12 results were slightly higher. The DRAGON study performed in Japan used a similar design with slightly lower doses of simeprevir and found similar results.

The two phase 3 trials, QUEST-1 and QUEST-2, randomized almost 400 patients 2:1 to 12 weeks of simeprevir 150 mg daily plus PR or to a placebo plus PR. The studies had almost identical results: the SVR12 was 80% for simeprevir plus PR versus 50% for PR alone. Subgroup analyses that pooled the results for these two studies showed expected differences by risk factors for poor response to PR. In the IL28B CC genotype subgroup, the SVR12 was 95% for simeprevir plus PR and 80% for PR alone; in the less favorable IL28B TT genotype, the SVR12 was 61% for simeprevir plus PR and 21% for PR alone. The findings were similar in subgroups defined by the METAVIR fibrosis score and by genotype 1a and 1b: outcomes were worse across all poor prognosis subgroups, but the SVR12 of simeprevir plus PR was significantly greater than that of PR alone.

Table 5. HCV Genotype 1 Treatment-naïve Patients.

Study	Treatment Arm	N	SVR12	SVR24
IFN-eligible				
PILLAR	SMV 75 12 Weeks + PR	78	83%	82%
	SMV 75 24 Weeks + PR	75	76%	75%
	SMV 150 12 Weeks + PR	77	80%	80%
	SMV 150 24 Weeks + PR	79	86%	86%
	PBO + PR	77	66%	65%
QUEST 1	**SMV 150 12 Weeks + PR**	264	80%	
	PBO + PR	130	50%	
QUEST 2	**SMV 150 12 Weeks + PR**	257	81%	
	PBO + PR	134	50%	
DRAGON	SMV 50 12 Weeks + PR	27	78%	
	SMV 50 24 Weeks + PR	13	77%	
	SMV 100 12 Weeks + PR	26	77%	
	SMV 100 24 Weeks + PR	13	92%	
	PR	13	46%	
CONCERTO-1	SMV 100 12 Weeks + PR	123	89%	
	PBO + PR	60	62%	
CONCERTO-4	SMV 100 12 Weeks + PR	24	92%	
P7977-0221	SOF 100 4 Weeks + PR	16		56%
	SOF 200 4 Weeks + PR	18		83%
	SOF 400 4 Weeks + PR	15		80%
	PBO + PR	14		21%
PROTON	SOF 200 12 Weeks + PR	48	90%	85%
	SOF 400 12 Weeks + PR	47	91%	89%
	PBO + PR	26	58%	58%
ELECTRON	SOF 400 + R 12 Weeks	25	84%	84%
ATOMIC	**SOF 400 12 Weeks + PR**	52	90%	89%
	SOF 400 24 Weeks + PR	109	93%	89%
	SOF 400 36 Weeks + PR	155	91%	87%
QUANTUM	SOF 400 + R 12 Weeks	19	53%	
	SOF 400 + R 24 Weeks	19	47%	
NEUTRINO	**SOF 400 12 Weeks + PR**	292	89%	
SPARE	SOF 400 12W + Wt R	10	90%	
	SOF 400 12W + Wt R	25	68%	
	SOF 400 12W + low R	25	48%	
IFN-ineligible				
- No studies				

Note: The treatment dosing regimens that match the FDA indication are highlighted and in bold.

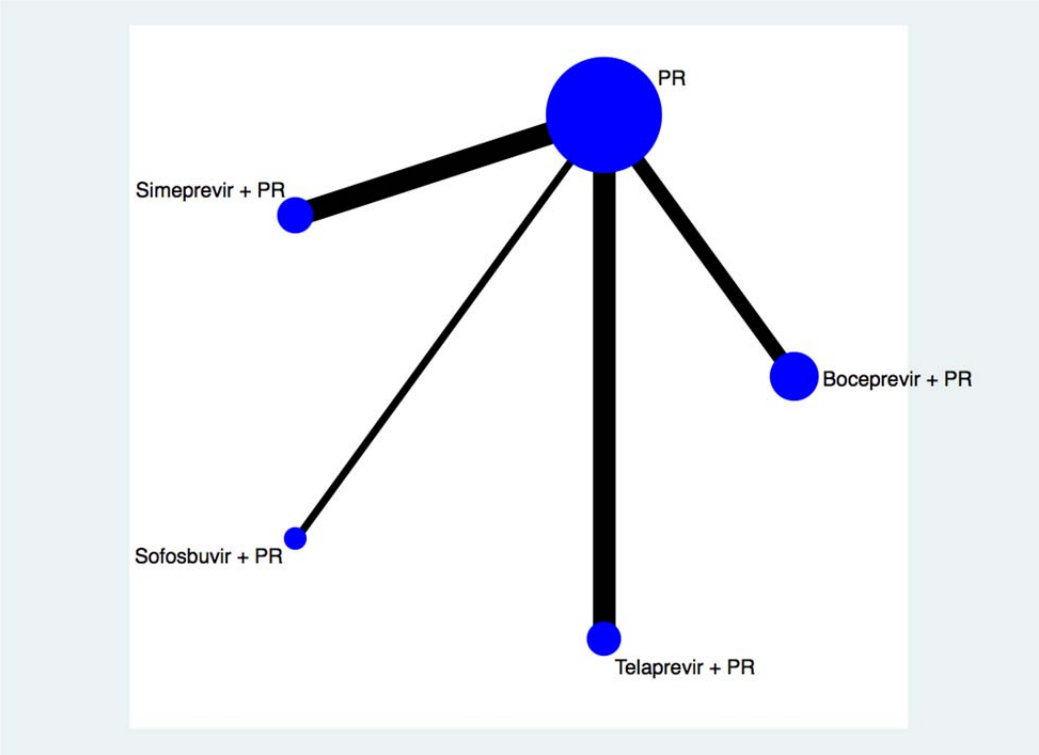
The one exception was for patients with the Q80K polymorphism. The prevalence of the Q80K polymorphism was 16%, and it occurred almost exclusively in HCV genotype 1a. Among the 128 patients with the Q80K polymorphism, the SVR12 was only 58% for simeprevir and 52% for PR (difference NS). However, among the 648 patients without the Q80K polymorphism, the SVR12 was 85% for simeprevir and 49% for PR (difference NS). Most coverage policies and guidelines recommend using simeprevir in patients without the Q80K polymorphism.

The studies of sofosbuvir in treatment-naïve patients infected with genotype 1 were primarily dose finding studies. The largest was the ATOMIC study, which compared 12, 24, and 36 weeks of sofosbuvir in conjunction with PR but had no control group without sofosbuvir. The SVR12 ranged from 90% to 93%. The NEUTRINO study was an open-label, single group study of sofosbuvir plus PR for 12 weeks that had the largest group of participants receiving the FDA indication dosing. The SVR12 in NEUTRINO was 89%. As with simeprevir, the SVR12 of sofosbuvir + PR varied by subgroups defined by known predictors of response to PR therapy. In the NEUTRINO study, the SVR12 for the IL28B CC genotype subgroup was 98% and in the less favorable non-CC genotype, the SVR12 was 87%. There was no control group for comparison. The SVR12 was 92% in patients with no cirrhosis and 80% in those with cirrhosis. Similarly, the SVR12 was 92% in patients with genotype 1a and 82% in those with genotype 1b.

Network Meta-Analysis Comparing Drug Regimens for Genotype 1 Treatment-naïve Patients

The lack of head-to-head trials makes it difficult to assess the relative efficacy of the different drug regimens for treatment-naïve patients infected with HCV genotype 1. Boceprevir + PR, telaprevir + PR, simeprevir + PR, and sofosbuvir + PR have all been compared to PR alone, but not to each other. Since the mix of patients with risk factors that influence response to therapy (IL28B genotype, fibrosis score, genotype 1a versus 1b, viral load, sex, race, age, etc.) vary from study to study, the SVR12 for any treatment group is not a fair assessment of the overall effectiveness of a treatment regimen. To assess the relative efficacy of the five 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 that compare multiple interventions for the same indication.[125-127] 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. We used frequentist estimation procedures implemented in Stata version 13.1 (College Station, Texas) to perform the network meta-analysis; a random-effects approach was employed to account for inconsistency in SVR estimates across trials.[125,128] The structure of our network meta-analysis is depicted graphically in Figure 2 on the following page.

Figure 2. Network Plot for Clinical Trials of Treatment-naïve Patients with HCV Genotype 1.



The size of each node represents the number of participants receiving that treatment. The thickness of the line connecting them represents the number of patients in the comparison.

For the studies of simeprevir, we excluded subjects with the Q80K polymorphism. Three of the four trials of sofosbuvir in treatment-naïve patients with genotype 1 infections did not have a PR control group. Because these three trials (ELECTRON, ATOMIC, NEUTRINO) represent 93% of the patients treated with sofosbuvir, we think it is important to include them in the network meta-analysis. For each of the three trials, we assumed that there was a control group with an equal number of participants as the sofosbuvir + PR treatment group and assumed that the SVR12 in the control group would be the same as that observed in the control group of the PROTON trial (57.7%). Under those assumptions, the results of the network meta-analysis are shown in Table 6 on the following page.

Table 6. Summary Estimates from the Network Meta-Analysis for SVR12 Among Treatment-naïve Patients Infected with HCV Genotype 1.

Treatment	SVR12	95% CI	P versus PR
PR	47%	41% to 52%	-
Boceprevir + PR	73%	68% to 77%	<0.001
Telaprevir + PR	74%	69% to 79%	<0.001
Simeprevir + PR*	84%	78% to 88%	<0.001
Sofosbuvir + PR	83%	79% to 87%	<0.001

*Excludes patients with the Q80K polymorphism

The summary estimates suggest that both the simeprevir and sofosbuvir regimens have similar SVR12 results and that both are superior to triple therapy using either boceprevir or telaprevir. Although the confidence intervals look similar, it is important to remember that the sofosbuvir + PR estimate is based on extrapolations from uncontrolled trials and should be considered to have greater uncertainty than the confidence interval suggests.

The summary estimates for simeprevir and sofosbuvir from the network meta-analysis are lower than those observed in the clinical trials. This is because the meta-analysis estimates are based on the relative improvement in SVR compared to the SVR for the PR control group. The summary SVR estimate from the meta-analyses for PR was 47%, which is similar to accepted estimates from the literature (40% to 50%).[39-41] However, the PR control groups in the trials of simeprevir and sofosbuvir had higher SVRs (50% to 65% for simeprevir and 57.7% for sofosbuvir). These differences in the SVR for the PR control groups likely reflect the underlying distribution of risk factors for response to therapy, with patients enrolling in the trials of simeprevir and sofosbuvir having a higher prevalence of favorable risk factors (or fewer unfavorable risk factors). For instance, the prevalence of cirrhosis was relatively low among patients in the trials of simeprevir and sofosbuvir (see Tables 3 and 4 above). The trials of the newer drugs may also have more patients with the favorable IL28B CC genotype and more patients with 1a rather than 1b genotype. One of the advantages of the network meta-analysis is that it partially accounts for the differences in the response rates for the control groups across all of the studies.

Interferon-ineligible Patients

There were no studies for interferon-ineligible patients in this population. However, the COSMOS trial evaluated four interferon-free regimens in treatment-experienced patients and had a high SVR12. Treatment-naïve patients usually have higher SVR12s than similar patients who are treatment-experienced, so it is likely that the combination of simeprevir plus sofosbuvir would results in an SVR12 > 90% in treatment-naïve, interferon-ineligible patients.

In addition, there were 19 treatment-naïve patients treated with the FDA-approved alternate regimen of sofosbuvir plus ribavirin for 24 weeks. The SVR12 in that patient subset was 47%.

In summary, for treatment-naïve patients infected with HCV genotype 1, simeprevir + PR and sofosbuvir + PR have greater SVR12 than both PR alone and either boceprevir or telaprevir + PR. Simeprevir plus PR in patients without the Q80K polymorphism and sofosbuvir plus PR appear to have similar response rates, but most of the data for sofosbuvir come from uncontrolled studies. We did not identify any studies with SVR12 data on treatment-naïve patients who are interferon-ineligible, but the COSMOS study results, while uncontrolled, suggest that the combination of simeprevir plus sofosbuvir is promising.

6.3 SVR Outcomes of Treatment of HCV Genotype 1 in Treatment-experienced Patients

Table 7 on the following page summarizes the results of the major studies of simeprevir and sofosbuvir in treatment-experienced patients with genotype 1. All of the studies excluded patients with HIV, hepatitis B, decompensated cirrhosis, or other significant illnesses. The treatment dosing regiments that match the FDA indication are highlighted and in bold. The primary outcome for most studies was SVR12, but some of the early studies were designed to look at SVR24, and some studies report both. No studies report long-term outcomes.

Interferon-eligible Patients

The ASPIRE study was a randomized, double-blind, placebo controlled dose finding study comparing six different dosing regimens for simeprevir + PR to standard PR therapy. The primary outcome was SVR24, which ranged from 61% to 80% compared to 23% for PR. The SVR24 for the FDA approved dosing for simeprevir + PR was 67%. As expected, the results in this study are somewhat lower than those observed in the similar PILLAR study, which was performed in a treatment-naïve population.

Table 7. Clinical Trial Results for HCV Genotype 1 Treatment-experienced Patients.

Study	Treatment Arm	N	SVR12	SVR24
IFN-eligible				
ASPIRE	SMV 100 12 Weeks + PR	66		70%
	SMV 100 24 Weeks + PR	65		66%
	SMV 100 48 Weeks + PR	66		61%
	SMV 150 12 Weeks + PR	66		67%
	SMV 150 24 Weeks + PR	68		72%
	SMV 150 48 Weeks + PR	65		80%
	PBO + PR	66		23%
PROMISE	**SMV 150 12 Weeks + PR**	260	79%	
	PBO + PR	133	37%	
CONCERTO-2	SMV 100 12 Weeks + PR	53	53%	
	SMV 100 24 Weeks + PR	53	36%	
CONCERTO-3	SMV 100 12 Weeks + PR	49	96%	
CONCERTO-4	SMV 100 12 Weeks + PR	55	71%	
ELECTRON	SOF 400 + R 12 Weeks	10	10%	10%
COSMOS	SOF + SMV 12 Weeks	14	93%	
	SOF + SMV + R 12 Weeks	27	96%	
	SOF + SMV 24 Weeks	15	93%	
	SOF + SMV + R 24 Weeks	24	79%	
IFN-ineligible				
- No studies				

The phase 3 trial, PROMISE, randomized 400 patients 2:1 to 12 weeks of simeprevir 150 mg daily plus PR or to a placebo plus PR. It is worth noting that the participants were all patients who had relapsed following prior treatment and not partial or null responders. This group tends to have a better response to retreatment than patients who never achieved complete viral suppression during prior therapy. In the PROMISE trial, the SVR12 was 79% for simeprevir + PR and was 37% for PR alone. Subgroup analyses in PROMISE showed expected differences by risk factors for poor response to PR. For example, in the less favorable genotype 1a subgroup, the SVR12 was 70% for simeprevir + PR and 28% for PR alone; in the genotype 1b subgroup, the SVR12 was 86% for simeprevir + PR and 43% for PR alone. Among the 341 patients without the Q80K polymorphism, the SVR12 was 83% for simeprevir + PR and 38% for PR alone.

There is only one small, uncontrolled study of sofosbuvir in treatment-experienced patients infected with HCV genotype 1: a single arm of the ELECTRON study with 10 participants. These 10 individuals were treated with 400 mg of sofosbuvir and ribavirin for 12 weeks: only one participant achieved a sustained virologic response (SVR12 = 10%). This was an interferon-free regimen that does not correspond to the FDA-approved dosing. Because there were essentially no data on sofosbuvir in treatment-experienced patients, the manufacturer's application to the FDA extrapolated from the outcomes of the treatment-naïve patients in the NEUTRINO study who had

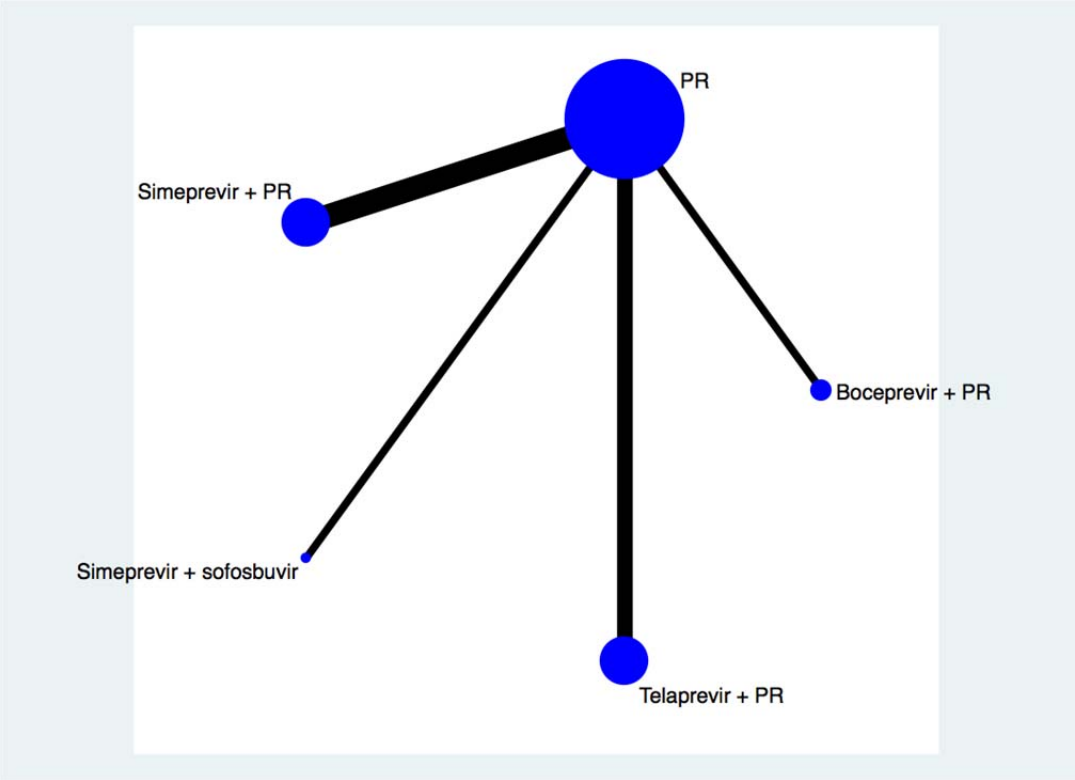
poor prognostic factors. Based on prior FDA publications,[94-96] the manufacturer argued, and the FDA accepted, that this would be a reasonable estimate for the SVR12 for treatment-experienced patients retreated with sofosbuvir + PR. The SVR12 for the 52 patients in NEUTRINO with "poor prognostic factors" was 71%.

Finally, there is one small study (COSMOS) that evaluated the combination of simeprevir and sofosbuvir with and without ribavirin for 12 or 24 weeks in 80 treatment-experienced genotype 1 patients with METAVIR F0 to F2 scores. There was no control arm for the study. Three of the four arms had remarkable 93% to 96% SVR12 outcomes. The fourth arm was the most intense (24 weeks of the combination plus ribavirin) but had the lowest SVR12 (79%). This appears to be due to participants lost to follow-up, although the data have only been presented in abstract form, so the details are not clear. Of note, there is a second part of the COSMOS trial in patients with METAVIR F3 or F4 fibrosis scores that has not yet announced its SVR12 results.

Network Meta-Analysis Comparing Drug Regimens for Genotype 1 Treatment-experienced Patients

The lack of head-to-head trials makes it difficult to assess the relative efficacy of the different treatments for treatment-experienced patients infected with HCV genotype 1. To estimate the relative efficacy of the five treatment options, we performed a network meta-analysis (see Figure 3 on the following page).

Figure 3. Network Plot for Clinical Trials of Treatment-experienced Patients with HCV Genotype 1.



The size of each node represents the number of participants receiving that treatment. The thickness of the line connecting them represents the number of patients in the comparison.

As in the prior network meta-analysis, we excluded patients with the Q80K polymorphism from the simeprevir results. We did not include sofosbuvir + PR regimens because of the lack of data. However, we did include data on sofosbuvir plus simeprevir from the COSMOS trial. We pooled the results from the four arms of this study because the results were similar, and we wanted to increase the power to evaluate the combination therapy (72/80 = 90% SVR12). We had to assume that there was a control group with an equal number of participants as the simeprevir + sofosbuvir treatment group and assumed that the SVR12 in the control group would be the same as the summary estimate for the control group of the other trials (22%). Under those assumptions, the results of the network meta-analysis are shown in Table 8 on the following page.

Table 8. Summary Estimates for the Network Meta-Analysis for SVR12 Among Treatment-experienced Patients Infected with HCV Genotype 1.

Treatment	SVR12	95% CI	P versus PR
PR	22%	15% to 29%	-
Boceprevir + PR	64%	49% to 76%	<0.001
Telaprevir + PR	70%	61% to 77%	<0.001
Simeprevir + PR*	70%	58% to 79%	<0.001
Sofosbuvir + PR	?	?	?
Simeprevir + sofosbuvir	90%	78% to 96%	<0.001

* Excludes patients with the Q80K polymorphism

The summary estimates for the treatment-experienced population suggest that the SVR12 for simeprevir-based therapy is about the same as that for triple therapy with boceprevir and telaprevir with broadly overlapping confidence intervals. The combination of simeprevir plus sofosbuvir has the highest estimated SVR12, although it is important to remember that this estimate is based on extrapolations from one uncontrolled trial and should be considered to have greater uncertainty than the confidence interval suggests. There are no data for sofosbuvir + PR, and the small subgroup of 10 patients in the ELECTRON trial treated with sofosbuvir plus R only had an SVR of 10%.

It is worth noting that the summary estimate for the combination of simeprevir plus sofosbuvir from the network meta-analysis is identical to the SVR12 derived from the COSMOS study. This is because there was only one study for that combination, and the estimate that we used for the PR control group was assumed to be identical to the summary estimate (22%) for the PR control group across all studies of treatment-experienced patients. If the true SVR12 for the 80 control patients enrolled in the COSMOS trial is higher than 22%, then our estimate for simeprevir plus sofosbuvir would be too high. Conversely, if the true SVR12 for the patients enrolled in the COSMOS trial is lower than 22%, then our estimate for simeprevir plus sofosbuvir would be too low.

Interferon-ineligible Patients

There were no studies for interferon-ineligible patients in this population. However, the COSMOS trial evaluated four interferon-free regimens in treatment-experienced patients and had a high SVR12, which suggests that it could be considered for use in this population.

In summary, for treatment-experienced patients infected with HCV genotype 1, simeprevir + PR has a greater SVR12 than PR alone and appears to have similar response rates to boceprevir or telaprevir. The combination of simeprevir plus sofosbuvir may have the greatest SVR12, but the data are sparse, and it is not clear whether ribavirin is needed, although it appears that 12 weeks of treatment is about equivalent to 24 weeks of treatment. Finally there are insufficient data to evaluate sofosbuvir plus ribavirin and no data on sofosbuvir plus PR.

6.4 SVR Outcomes of Treatment of HCV Genotype 2 in Treatment-naïve Patients

The assessment of SVR outcomes is more straightforward for genotypes 2 and 3 because simeprevir, telaprevir, and boceprevir have not been evaluated or approved for genotypes 2 and 3. However, since the SVR24 for PR alone is between 75% and 85% in this population, there is less room for improvement. Table 9 on the following page summarizes the results of the major studies of sofosbuvir in treatment-naïve patients with genotype 2. Again, all of the studies excluded patients with HIV, hepatitis B, or other significant illnesses. The treatment dosing regimens that match the FDA indication are highlighted and in bold. The primary outcome for most studies was SVR12, but some of the early studies were designed to look at SVR24, and some studies report both. No studies report long-term outcomes.

Interferon-eligible Patients

The ELECTRON study was a randomized, double-blind, dose finding study comparing six different dosing regimens for sofosbuvir. The study did not include a control arm with standard PR therapy. It also included a mix of both genotype 2 and 3 patients. Five of the six arms of the study had 100% SVR24, and two of them were interferon-free. The sofosbuvir-only arm had a lower 60% SVR24. Several other relatively small studies had similar findings.

Table 9. Clinical Trial Results for HCV Genotype 2 Treatment-naïve Patients.

Study	Treatment Arm	N	SVR12	SVR24
IFN-eligible				
ELECTRON	SOF 400 + R 12 Weeks + P 0 Weeks	10*	100%*	100%*
	SOF 400 + R 12 Weeks + P 4 Weeks	9*	100%*	100%*
	SOF 400 + R 12 Weeks + P 8 Weeks	10*	100%*	100%*
	SOF 400 + R 12 Weeks + P 12 Weeks	11*	100%*	100%*
	SOF 400 12 Weeks	10*	60%*	60%*
	SOF 400 + PR 8 Weeks	10*	100%*	100%*
PROTON	SOF 400 12 Weeks + PR	25*	92%*	92%*
QUANTUM	**SOF 400 + R 12 Weeks**	6*	67%*	
	SOF 400 + R 24 Weeks	6*	67%*	
FISSION	**SOF 400 + R 12 Weeks**	70	97%	
	PR 24 Weeks	67	78%	
VALENCE	**SOF 400 + R 12 Weeks**	32	97%	
IFN-ineligible				
POSITRON**	SOF 400 + R 12 Weeks	109**	93%**	
	PBO	34**	0%**	

*Mix of GT 2 and 3: the results were not presented separately

** Mix of treatment-naïve and experienced, but ~ 81% were treatment-naïve

Note: The treatment dosing regimens that match the FDA indication are highlighted and in bold.

The phase 3 trial, FISSION, was an open-label study that randomized 137 treatment-naïve genotype 2 patients to 12 weeks of sofosbuvir plus ribavirin or 24 weeks of PR. In the FISSION trial, the SVR12 was 97% for sofosbuvir plus ribavirin and was 37% for PR. Subgroup analyses in FISSION showed expected differences by risk factors for poor response to PR (see Table 10 on the following page).

Table 10. SVR12 for Key Subgroups of Patients with Genotype 2 in the FISSION Study.

Risk factor	Sofosbuvir + ribavirin	PR
Cirrhosis		
Yes	98%	81%
No	91%	62%
IL28B genotype		
CC	100%	82%
Non-CC	95%	72%
HCV RNA viral load		
< 6 $\log_{10}$ IU/ml	100%	74%
≥ 6 $\log_{10}$ IU/ml	96%	80%
Race		
Black	75%	50%
Non-black	98%	78%
Body mass index		
< 30 kg/m2	100%	78%
≥ 30 kg/m2	90%	77%

Interferon-ineligible Patients

The POSITRON trial was a double-blind, placebo-controlled trial that randomized interferon-unwilling (47%), interferon-ineligible (44%) and interferon-intolerant (9%) patients to 12 weeks of sofosbuvir plus ribavirin or 12 weeks of identical placebos. It is the only trial addressing this group of patients. Because the majority of these patients (91%) were treatment-naïve, the results primarily apply to treatment-naïve patients. As expected, the SVR12 was higher in the active treatment group (93% versus 0%) and similar to the SVR12 observed in the VALENCE and FUSION trials.

In summary, for treatment-naïve patients with genotype 2, sofosbuvir is a clear improvement over the previous standard of care. This is in fact the only treatment group for which there is randomized trial evidence documenting a clinically and statistically significant improvement of a sofosbuvir-based regimen compared to standard treatment. In addition, the treatment time is decreased from 24 to 12 weeks, and interferon is no longer needed, so the burden of injections and the side effects of interferon are avoided. All patients with genotype 2 can be treated with this regimen including those unwilling, unable, or intolerant of interferon.

6.5 SVR Outcomes of Treatment of HCV Genotype 2 in Treatment-experienced Patients

Interferon-eligible Patients

There are fewer data for treatment-experienced patients with genotype 2 (see Table 11 below), and neither of the trials had a control group without sofosbuvir. In the FUSION trial, 36 treatment-experienced patients were treated with 12 weeks of sofosbuvir plus ribavirin. The SVR12 was 86% (95% CI 71% to 95%). Similarly, in the VALENCE trial, the SVR12 was 90% (95% CI 77% to 97%). Because both studies were uncontrolled, it is unclear how much better these results are than those that would have been obtained with retreatment with PR. In one recent published study, retreating treatment-experienced patients with genotypes 2 or 3 with PR led to SVRs ranging from 53% to 81%.[97] However, a treatment regimen of sofosbuvir plus ribavirin has the advantage of being both shorter and interferon-free.

Table 11. Clinical Trial Results for HCV Genotype 2 Treatment-experienced Patients.

Study	Treatment Arm	N	SVR12	SVR24
IFN-eligible				
FUSION	**SOF 400 + R 12 Weeks** SOF 400 + R 16 Weeks	36 32	86% 94%	
VALENCE	**SOF 400 + R 12 Weeks**	41	90%	
IFN-ineligible				
POSITRON*	SOF 400 + R 12 Weeks PBO	17* 8*	76%* 0%*	

*Mix of GT 2 and 3: the results were not presented separately
Note: The treatment dosing regimens that match the FDA indication are highlighted and in bold.

Interferon-ineligible Patients

The POSITRON trial was a double-blind, placebo-controlled trial that randomized 25 interferon-intolerant patients to 12 weeks of sofosbuvir plus ribavirin or 12 weeks of identical placebos. The interferon-intolerant by definition must be treatment-experienced. The investigators did not present the data in this subgroup separately for genotype 2 and genotype 3. In the combined group, the SVR12 in the sofosbuvir + R group was 76.5% (95% CI 50% to 93%). It is the only trial addressing this group of patients.

6.6 SVR Outcomes of Treatment of HCV Genotype 3 in Treatment-naïve Patients

In contrast to findings for patients with genotype 2 infection, the clinical trial results for genotype 3 are a bit more complex (see Table 12 below). It should be noted that there are no randomized trial data demonstrating the superiority of sofosbuvir + PR to PR in interferon-eligible patients. The results from the dose-finding ELECTRON study were encouraging as described above. However, 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%. The uncontrolled VALENCE trial tested a longer 24 week regimen of sofosbuvir and ribavirin. In this cohort of patients infected with HCV genotype 3, the SVR12 was 93% (95% CI 87% to 97%). These results should be confirmed in a second trial, but they formed the basis for the FDA recommended dose. Again, this treatment has the advantage of being interferon-free, but for genotype 3, it is not shorter than PR retreatment.

Table 12. Clinical Trial Results for HCV Genotype 3 Treatment-naïve Patients.

Study	Treatment Arm	N	SVR12	SVR24
IFN-eligible				
ELECTRON	SOF + R 12 Weeks + P 0 Weeks SOF + R 12 Weeks + P 4 Weeks SOF + R 12 Weeks + P 8 Weeks SOF + R 12 Weeks + P 12 Weeks SOF 12 Weeks SOF + R 8 Weeks	10* 9* 10* 11* 10* 10*	100%* 100%* 100%* 100%* 60%* 100%*	100%* 100%* 100%* 100%* 60%* 100%*
PROTON	SOF 400 12 Weeks + PR	25*	92%*	92%*
QUANTUM	SOF + R 12 Weeks **SOF + R 24 Weeks**	6* 6*	67%* 67%*	
FISSION	SOF + R 12 Weeks PR 24 Weeks	183 176	56% 62%	
VALENCE	**SOF 400 + R 24 Weeks**	105	93%	
IFN-ineligible				
POSITRON**	SOF + R 12 Weeks PBO	98** 37**	61%** 0%**	

*Mix of GT 2 and 3: the results were not presented separately

** Mix of treatment-naïve and experienced, but ~ 81% were treatment-naïve

6.7 SVR Outcomes of Treatment of HCV Genotype 3 in Treatment-experienced Patients

The story is similar for treatment-experienced patients with genotype 3 (see Table 13 on the next page). In the uncontrolled FUSION and VALENCE trials, the SVR12 increased from 30% to 62% to

77% as the length of treatment increased from 12 weeks to 16 weeks to 24 weeks. Because neither of these studies randomized patients to a PR arm, it is unclear if this represents an improvement over results potentially achieved with retreatment. However, it is interferon-free.

Table 13. Clinical Trial Results for HCV Genotype 3 Treatment-experienced Patients.

Study	Treatment Arm	N	SVR12	SVR24
IFN-eligible				
FUSION	SOF 400 + R 12 Weeks SOF 400 + R 16 Weeks	64 63	30% 62%	
VALENCE	**SOF 400 + R 24 Weeks**	145	77%	
IFN-ineligible				
POSITRON*	SOF 400 + R 12 Weeks PBO	17* 8*	76%* 0%*	

*Mix of GT 2 and 3: the results were not presented separately

Interferon-ineligible Patients

As noted for genotype 2 treatment-experienced patients, the POSITRON trial randomized 25 interferon-intolerant patients to 12 weeks of sofosbuvir plus ribavirin or 12 weeks of identical placebos. In the combined group of genotype 2 and 3 treatment-experienced patients, the SVR12 in the sofosbuvir + R group was 76.5% (95% CI 50% to 93%). This is much higher than the SVR12 reported in the other trials of 12 weeks of sofosbuvir + R for genotype 3, which suggests that the majority of the interferon-intolerant patients in the POSITRON study were genotype 2. It would be difficult to recommend 12 weeks of therapy for interferon-ineligible patients with genotype 3 after concluding that 24 weeks of the same therapy is required for both treatment-naïve and treatment-experienced genotype 3 patients.

In summary, for genotype 3 treatment-naïve and experienced patients, 24 weeks of sofosbuvir + R appears to be superior to 12 or 16 weeks of the same therapy. In the one trial comparing 12 weeks of sofosbuvir + R to 24 weeks of PR, the PR group had a nominally higher SVR12. The lack of control groups in the other trials makes it difficult to conclude that the SVR12 with 24 weeks of sofosbuvir + R is greater than that of 24 weeks of PR. The POSITRON data suggest that sofosbuvir + R is effective for interferon-ineligible patients with genotype 3, although the VALENCE trial suggests that 24 weeks of therapy would be more effective than 12 weeks.

6.8 Harms of Treatment

Harms of Treatment with Simeprevir

HCV genotype 1

It is reasonably straightforward to compare the harms of treatment with simeprevir in patients infected with HCV genotype 1 to the harms of treatment with PR because the three phase 3 trials (QUEST-1, QUEST-2, PROMISE) were all randomized comparisons with PR in patients with HCV genotype 1. In order to fairly assess the independent effect of simeprevir, just the first 12 weeks of therapy were compared. The adverse events (AEs) are summarized in Table 14 below.

Table 14. Summary of Adverse Events in the Randomized Trials of Simeprevir.

Adverse Event	Simeprevir + PR (12 weeks) N = 781	Placebo + PR (12 weeks) N = 397
Any Adverse Event	95%	95%
Significant Adverse Events	2.0%	2.5%
Grade 3 or 4 AE	23%	25%
Therapy stopped due to AE	2.6%	4.5%
Common AEs		
Fatigue	36%	40%
Headache	33%	36%
Flu-like illness	26%	21%
Insomnia	17%	17%
Anemia (hemoglobin < 10 g/dL)	12%	10%
Likely associated with SMV		
Pruritus	21%	14%
Nausea	22%	18%
Rash	14%	11%
Photosensitivity	3.3%	0.5%
Elevated bilirubin	2.0%	0.5%

Adverse events, significant adverse events, grade 3 or 4 AEs, and adverse events leading to treatment discontinuation were not more common with simeprevir. There was clearly more pruritis, photosensitivity-induced rashes, and hyperbilirubinemia due to simeprevir, but these were generally not severe and were easily managed. They did not result in the discontinuation of therapy. Importantly, there was no significant increase in anemia with the addition of simeprevir. As described in the background section above, the earlier protease inhibitors boceprevir and telaprevir nearly doubled the incidence of significant anemia.[42] Overall, the addition of simeprevir to PR did not markedly increase the risk for adverse events.

Harms of Treatment with Sofosbuvir

HCV genotype 1

It is more difficult to carefully assess the relative impact of sofosbuvir on adverse events because few of the trials randomized patients to a regimen based on sofosbuvir versus a regimen without sofosbuvir. For patients infected with genotype 1, the relevant comparison is between patients on sofosbuvir plus PR and PR alone (see Table 15 below). Sofosbuvir plus PR was used in the NEUTRINO study and PR in the FISSION study. Since these are different studies and non-randomized comparisons, the comparisons may be between patients sampled from different populations.

Table 15. Summary of Adverse Events for Sofosbuvir + PR and PR Alone.

Adverse Event	Sofosbuvir + PR (12 weeks) N = 327	PR (24 weeks) N = 243
Any Adverse Event	95%	96%
Significant Adverse Events	1%	1%
Grade 3 or 4 AE	15%	19%
Therapy stopped due to AE	2%	11%
Common AEs		
Fatigue	59%	55%
Headache	36%	44%
Flu-like illness	16%	18%
Insomnia	25%	29%
Anemia (hemoglobin < 10 g/dL)	23%	14%
Pruritus	17%	17%
Nausea	34%	29%
Rash	18%	18%

HCV genotypes 2 and 3

For patients with genotype 2 and 3 infections, the relevant comparison is between patients on sofosbuvir plus R and PR alone. Sofosbuvir plus R was used in the FISSION, FUSION, and POSITRON studies and PR in the FISSION study. These adverse events are summarized in Table 16 on the next page. Since these are different studies and non-randomized comparisons, the comparisons may be between patients sampled from different populations.

Table 16. Summary of Adverse Events for Sofosbuvir + R and PR Alone.

Adverse Event	Sofosbuvir + R (12 weeks) N = 566	PR (24 weeks) N = 243
Any Adverse Event	88%	96%
Significant Adverse Events	4.0%	1%
Grade 3 or 4 AE	7.2%	19%
Therapy stopped due to AE	1.4%	11%
Common AEs		
Fatigue	40%	55%
Headache	23%	44%
Flu-like illness	2.8%	18%
Insomnia	16%	29%
Anemia (hemoglobin < 10 g/dL)	9%	14%
Pruritus	9%	17%
Nausea	20%	29%
Rash	8%	18%

It is evident here that the elimination of interferon from the treatment regimen markedly decreases the risk for most adverse events including fatigue, headache, flu-like illness, anemia, pruritis, nausea, and rashes. There were also significantly fewer grade 3 or 4 adverse events. This translates into a marked eight-fold reduction in discontinuation of therapy due to adverse events (from 11% with PR to 1.4% with sofosbuvir + R).

Harms of Treatment with the Combination of Simeprevir and Sofosbuvir with or without Ribavirin for 12 or 24 Weeks in Genotype 1 (COSMOS trial)

The harms of treatment are incompletely reported in the COSMOS trial. In Cohort 1, 100% of patients completed the 12 week regimen and 87% completed the 24 week regimen (three stopped, one due to an adverse event). No serious AEs were observed for either Cohort 1 or Cohort 2 during the 12 week regimens, but four patients treated for 24 weeks discontinued because of AEs. The most common AEs were fatigue, headache, nausea, and insomnia with more anemia and elevations in bilirubin observed in the treatment arms that included ribavirin.

6.9 Summary

Genotype 1

Table 17 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 increased the SVR12 from the 40% range with PR to the 70% range. The improved SVR was somewhat offset by an

increase in the complexity of the drug therapy. A large number of pills had to be taken about every 8 hours. In addition, there were burdensome new side effects added to the flu-like symptoms of interferon and the anemia and teratogenicity of ribavirin. These included a marked increase in anemia and nausea for both drugs, 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 the previous standard of care for treatment of genotype 1.

Table 17. 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				
Treatment-naïve				
PR (48)	47	48 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (≤ 30%)	No
BOC(24) + PR(48)	73	Add Q8 pills	Anemia (≤ 50%), more nausea and dysguesia, drug interactions	No
TVR(12) + PR(48)	74	Add Q8 pills	Anemia (≤ 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
Treatment-experienced				No
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 (≤ 50%), more nausea and dysguesia, drug interactions	No
TVR(12) + PR(48)	70	Add Q8 pills	Anemia (≤ 50%), more nausea and pruritus, drug interactions	No
SMV(12) + PR(24-48)	67	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)

Simeprevir improves the SVR12 compared with triple therapy when used in patients without the Q80K polymorphism. The primary benefits of simeprevir are the reduced incidence of anemia and

the reduced pill burden: it only requires taking one pill a day. Adverse events specifically associated with simeprevir include pruritus, photosensitivity-induced rashes, and hyperbilirubinemia, but these were uncommon, generally not severe, and easily managed. The increase in pruritus compared to PR was less than that seen with telaprevir. One important finding specific to simeprevir is that its effectiveness is markedly diminished in patients with the Q80K genetic polymorphism in HCV genotype 1. If the Q80K polymorphism is present, simeprevir should not be used. Simeprevir requires PR and cannot be used to treat interferon-ineligible patients. The primary weakness in the data is the lack of head-to-head trials comparing simeprevir and one of the first generation protease inhibitors. As noted in section 5 above, there is a large (n=766) randomized trial comparing simeprevir to telaprevir that was expected to complete data collection for its primary outcome in March 2014. In addition, there are no data on the impact of treatment on long term outcomes such as the incidence of cirrhosis, liver decompensation, HCC, transplant, or death.

Sofosbuvir plus PR also appears to have less anemia and certainly has 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 protease inhibitors. There are less robust comparative data on sofosbuvir + PR compared to PR alone than for simeprevir, and there are no data comparing it to PR plus simeprevir, boceprevir, or telaprevir. 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 the combination of simeprevir plus sofosbuvir (an off-label use not indicated by the FDA) with or without ribavirin are encouraging. The available SVR12 data from treatment-experienced patients averaged 90%; the SVR12 of treatment-naïve patients should be even better. It is interferon-free, so can be used in interferon-ineligible patients. Since it is interferon-free (and perhaps ribavirin-free), it should have markedly lower adverse event rates than PR based treatment. The data come from four different regimens in one small study, none of which are FDA approved, and there are no detailed published results, so the findings should be considered preliminary at this point.

Genotype 2

The story is more straightforward for genotype 2 (see Table 18 on the next page). There is adequate evidence that the combination of sofosbuvir plus ribavirin improves SVR12 and is less burdensome compared to PR therapy. Among treatment-naïve patients, there was a large increase in SVR12 seen in the randomized FISSION trial and supported by the VALENCE trial, although that was not randomized. The SVR12 for treatment-experienced patients was 86% and 90% in the two

uncontrolled studies, but this 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 18. 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				
Treatment-naïve				
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
Treatment-experienced				
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 19 on the next page). The combination of sofosbuvir plus ribavirin for 12 weeks did not increase SVR12 compared to PR among treatment-naïve patients in the FISSION trial. However, the SVR12 consistently increased with increasing lengths of therapy to 16 and 24 weeks (56% to 93% in the uncontrolled VALENCE trial). The SVR12 for treatment-experienced patients increased from 30% (12 weeks) to 62% (16 weeks) to 77% (24 weeks). The sofosbuvir-based regimen is interferon-free, which as noted above, 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 has a lower incidence of anemia than PR in the phase 3 trials. The treatment course is the same 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.

The quality of the evidence is much weaker for sofosbuvir in genotype 3 than in genotype 2. The randomized phase 3 trial (FISSION) reported a modestly lower SVR12 for sofosbuvir + R compared to PR. There is only one arm of an uncontrolled study (VALENCE) that reports SVR12 data on the FDA approved 24 week regiment of sofosbuvir + R. While the VALENCE study results are promising, they may overestimate the effectiveness of sofosbuvir + R for patients infected with genotype 3. Careful attention should be paid to the results of additional studies of this regimen for genotype 3.

Table 19. 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				
Treatment-naïve				
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
Treatment-experienced				
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

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 a cohort model to compare the possible clinical and economic outcomes from the use of sofosbuvir and simeprevir in multiple patient populations.

For comparison purposes, we also identified published studies of the cost-effectiveness of both existing and proposed treatment options for hepatitis C treatment, which are summarized in the section immediately following. We limited our summary to those studies published from 2011 onwards as representative of current costs of hepatitis C management. However, we also report on any available studies that used a "cost per treatment success" measure of cost-effectiveness, as that was a central output of our model (see Summary, Section 7.4).

7.1 Prior Published Evidence on Costs and Cost-effectiveness

We identified a number of studies published in the era of direct-acting antiviral agents (i.e., from 2011 to the present) that evaluated the economic impact of hepatitis C therapy, including an in-press publication examining the cost-effectiveness of sofosbuvir.[98] The methods and results of these studies are summarized below by therapeutic approach. As can be seen in these summaries, most model results were highly sensitive to the estimated cost of treatment, and all focused exclusively on improvements in overall or quality-adjusted life expectancy (i.e., impacts on intermediate outcomes such as disease progression and liver transplantation were not described).

Cost-Effectiveness of Sofosbuvir

As noted above, we identified a single study assessing the economic impact of sofosbuvir.[98] This was an industry-funded, lifetime simulation model conducted from the perspective of the Italian National Health Service, and it involved separate comparisons of triple therapy with sofosbuvir versus boceprevir and telaprevir in genotype 1 patients who were naïve to treatment and age 50 years. Strategies with an incremental cost per life-year gained less than €25,000 (~$35,000) were considered to be cost-effective. Costs included those of therapy, management of side effects, and disease-related complications.

On an overall basis, sofosbuvir triple therapy (sofosbuvir + PR) was estimated to increase life expectancy by approximately eight months relative to boceprevir and three months versus telaprevir. Discounted lifetime costs in the sofosbuvir strategy (~$63,000) were 35-40% higher than those in the boceprevir and telaprevir strategies, even after accounting for improved survival with sofosbuvir. 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. Of interest for this analysis, model findings were most sensitive to changes in the price of sofosbuvir, which was assumed to be $4,800 per week in the base case; the current price in the U.S. is $7,000 weekly.

Cost-Effectiveness of All-Oral Hepatitis C Regimens

While all-oral treatment regimens for hepatitis C are not yet available, two simulation models have assessed the potential cost-effectiveness of hypothetical combinations of oral drugs.[4,99] Hagan and colleagues assessed cost-effectiveness of a hypothetical 2-drug regimen over a lifetime versus standard care (i.e., triple therapy or PR) across all genotypes in a 50 year-old treatment-naïve cohort using a societal perspective in an NIH-funded analysis.[4] 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. The base case cost estimate for a course of all-oral therapy was estimated to be $70,000, and such therapy was no longer considered cost-effective in this model (at a $50,000 per QALY threshold) at prices exceeding $75,000. Given that the average wholesale prices for courses of sofosbuvir and simeprevir are already at least $84,000 and $66,000 respectively, the true cost of combination all-oral therapy will likely be much higher. A second, industry-funded analysis produced a lower cost-effectiveness ratio ($15,709 per QALY gained), which appears to be closely tied to the assumption that all-oral drug costs would be equivalent to those of existing triple therapy with telaprevir.[99]

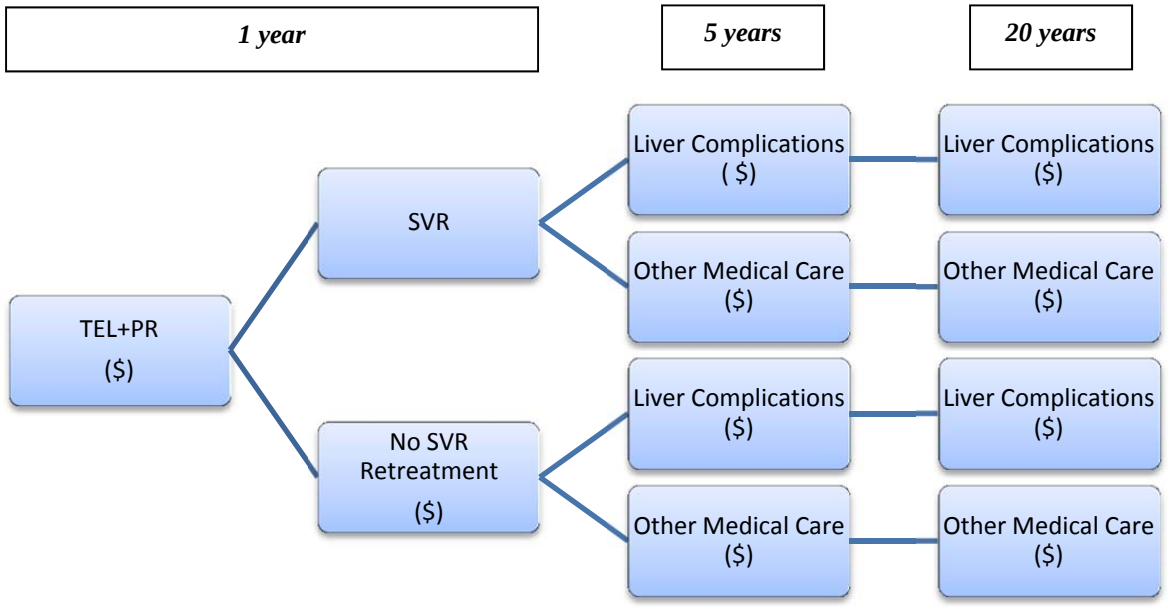
Cost-Effectiveness of Telaprevir and/or Boceprevir

We also identified six recent studies evaluating the cost-effectiveness of telaprevir and boceprevir, all of which used simulation techniques to evaluate outcomes and costs on a lifetime basis.[100-105] Cost-effectiveness ranged widely in these studies, from $11,000-$70,000 per QALY gained. Results were sensitive to whether patients had mild or advanced fibrosis, response to prior PR therapy, and of course, the assumed costs of therapy itself, as many of these studies assumed costs for telaprevir and boceprevir that are markedly less than current average wholesale prices for these agents.

7.2 Model Overview

To examine the potential clinical and economic impact of the introduction of sofosbuvir and simeprevir in California, we 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. Strata were designed to purposely align with those used in the recently published AASLD/IDSA/IAS treatment guidelines.[106] We adopted the perspective of a third-party payer for these analyses. Figure 4 below depicts the model schematic for 1,000 patients receiving telaprevir + PR.

Figure 4. Example of Model Schematic for 1,000 Patients Receiving Telaprevir + PR.



NOTE: "$" indicates model elements with calculated cost
TEL: Telaprevir; PR: Pegylated interferon + ribavirin; SVR: Sustained virologic response

Patient Outcomes

We employed a variety of patient outcome measures for this analysis. The rates of SVR for each treatment strategy were drawn from the network meta-analysis or individual studies as previously described. Because the effectiveness of retreatment with newer regimens is not yet known, estimates of SVR (presented on a per 1,000 basis) were based on the *initial treatment course only*.

Pooled estimates of the percentage of patients discontinuing therapy due to an adverse event were obtained from all available trial reports for each treatment strategy (see Tables 14-16 on pages 47-49), and were also presented on a per 1,000 basis. Note that these estimates are presented for information only and did not affect other model parameters. For example, estimates of SVR already account for early drug discontinuation, as any patient not completing the full regimen due to an adverse event would already be recorded as not achieving SVR.

All patients were assumed to be at risk of downstream liver-related complications (e.g., cirrhosis, liver cancer, transplantation). Relatively little is known about the detailed natural history of hepatitis C infection. However, a systematic review of 57 epidemiologic studies estimated the rate of advanced liver disease/cirrhosis at 20 years to be 24%, and suggested that the rate of progression was reasonably linear.[23] We used this as our estimate of liver-related complications at 20 years across all patients, and derived a 5-year estimate of 6% based on the linear assumption. For patients with advanced liver fibrosis (i.e., METAVIR scores of F3 or F4), we assumed that the rate of progression would be double that of the overall cohort (i.e., 48% and 12% at 20 and five years respectively) based on a comparison of findings in patients with advanced fibrosis versus all patients in a second systematic review of observational studies of hepatitis C complications.[107] These rates were applied to patients who would not achieve SVR with initial therapy. Among patients achieving SVR, rates of liver-related complications were assumed to be reduced by 80% (i.e., rate ratio of 0.2), as multiple observational studies have shown risk reductions of this level or better for a variety of liver-related complications.[90,107,108] Rates of liver-related complications averted were presented per 1,000 patients treated.

The 20-year time horizon employed in this model suggests that many patients followed for such a time period would be at competing risks of morbidity and mortality. We did not estimate these competing risks in the model, as our focus was on outcomes expected to be directly influenced by choice of treatment strategy. For example, inclusion of estimates of mortality would have resulted in patient attrition over 20 years of follow-up, which would have served to lower estimates of liver-related complications experienced and cost offsets. However, the *relative* rates of events and estimates of cost offset between treatment regimens would not have been materially affected, as there are no data directly linking any one treatment regimen to reductions in mortality relative to others.

Treatment Strategies

Treatment strategies varied by cohort and included a "previous standard" regimen prior to the availability of simeprevir and sofosbuvir. Additional treatment strategies were based on those recommended in the 2014 AASLD/IDSA/IAS guidelines. Strategies of interest, along with estimated SVR rates, are presented in Table 20 on the following page. SVR rates were obtained from the network meta-analysis or individual studies as appropriate (see Section 6). The guidelines do not make distinctions regarding interferon eligibility in some cases. We therefore assumed that pooled SVR rates within subpopulations of genotype/prior treatment status were equivalent for those eligible and not eligible for interferon (unless study/meta-analysis data were available within interferon eligibility strata). Also of note, we used triple therapy with first generation protease inhibitors as a "referent" strategy for genotype 1. However, because boceprevir and telaprevir involve markedly different dosing and duration, we opted to focus on triple therapy with telaprevir as the previous standard for our model given that it held a 70% share of the triple therapy market prior to the introduction of the newer DAAs.[109] Impact was assessed during the year of treatment initiation as well as five and 20 years after treatment.

We also assessed the impact of use of newer drug regimens by applying the measures above to the entire California chronic hepatitis C population based on expected numbers of patients within each genotype who would present for treatment; scenarios were employed alternatively for all patients as well as those with advanced liver fibrosis (i.e., fibrosis score of F3 or F4) only (see page 78 for a summary of methods and results of these analyses).

Table 20. Treatment Strategies of Interest, by HCV Genotype, Prior Treatment Status, and Interferon Eligibility.

Prior Treatment Status, IFN eligibility	Genotype 1	*SVR (%)*	Genotype 2	*SVR (%)*	Genotype 3	*SVR (%)*
Treatment-naïve						
IFN-eligible	***TEL + PR (12/24)*** **SMV + PR (12/24)** **SOF + PR (12)**	**74** **84** **83**	***PR (24)*** **SOF + R (12)**	**78** **97**	***PR (24)*** **SOF + R (24)**	**62** **93**
IFN-ineligible	***No Rx*** **SOF + R (24)** **SOF + SMV + R (12)**	**0*** **72** **90**	***No Rx*** **SOF + R (12)**	**0*** **93**	***No Rx*** **SOF + R (24)**	**0*** **63**
Treatment-experienced						
IFN-eligible	***TEL + PR (12/24)*** **SMV + PR (12/24)** **SOF + PR (12)** **SOF + SMV + R (12)**	**70** **70** **71** **90**	***PR (24)*** **SOF + R (12)**	**71** **88**	***PR (24)*** **SOF + R (24)**	**51** **77**
IFN-ineligible	***No Rx*** **SOF + R (24)** **SOF + SMV + R (12)**	**0*** **61** **90**	***No Rx*** **SOF + R (12)**	**0*** **88**	***No Rx*** **SOF + R (24)**	**0*** **63**

NOTES: Duration of therapy in parentheses; "/" indicates situations in which different components have different durations.
SVR rates obtained from ICER network meta-analysis or individual studies as necessary
"Previous standard of care" italicized and highlighted in yellow
TEL: Telaprevir; R: ribavirin; PR: pegylated interferon/ribavirin; SMV: simeprevir; SOF: sofosbuvir; No Rx: no standard treatment available
*Assumed rate of 0 for No Rx category (no assumed spontaneous SVR)

Costs

The model first presents the estimated cost per patient for the initial course of therapy. Based on this cost and the estimated SVR rate, the cost per additional SVR is calculated (also on a per patient basis). We also calculated expected *total* drug costs in the first year, based on an assumption that those not achieving SVR initially would be retreated with the most effective regimen available within each genotype, prior treatment status, and interferon eligibility combination (see Table 20 above for most effective regimens). It is important to note that this was done only to provide an accurate picture of likely drug costs over one year for the cohort, *not* to assess the potential impact of SVR from sequential treatment. Total one-year drug costs are presented for the entire 1,000

patient cohort in order to compare these costs to any cost offsets from prevention of liver-related complications and greater achievement of SVR (see below).

Annual costs of liver-related complications ($25,728) were calculated based on an analysis of median costs among patients with and without advanced liver disease in Florida Medicaid claims.[110] Of note, we did not attempt to model the time course of these events, but rather assigned the full 5- and 20-year costs to any patient experiencing a liver-related complication during these time periods. Annual costs of maintenance care for patients achieving and not achieving SVR were derived from a study comparing post-treatment costs by SVR status among patients treated in the Kaiser health system.[111] In this study, the annual costs of care following hepatitis C treatment were estimated for patients achieving and not achieving SVR, including outpatient care, inpatient care, laboratory, and pharmacy. Costs were approximately $3,800 higher for patients without SVR versus those with successful treatment.

We estimated the costs of medication using published wholesale acquisition costs or average wholesale prices.[112] Of note, however, telaprevir costs have increased substantially over the past 1.5 years, even as its use has declined to near zero.[97] 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 likely artificially-inflated) price.

All costs were expressed in 2013 dollars. Costs incurred in future years were discounted by 3% in accordance with generally-accepted practice for economic evaluations.[113] We did not consider short-term costs of adverse-event management or monitoring during treatment (consistent with the Manos study that focused on costs after treatment was completed). We also based our estimates of treatment success on data from the initial course of treatment only. The cost offsets associated with prevention of liver-related complications and greater achievement of SVR at five and 20 years after treatment are presented on a per 1,000 basis to facilitate comparisons to one-year drug costs (see above). To further illustrate the effects of these cost offsets in patients of differing severity of liver disease, we conducted alternative analyses for genotype 1 in which model outputs were generated assuming all patients alternatively had no-to-mild liver disease or advanced liver disease respectively (see page 65).

All derived costs (such as cost per additional SVR and cost offsets at 5 and 20 years) were rounded to the nearest $1,000 to reflect the uncertainty in these estimates from reliance on published prices and literature-based cost estimates rather than primary data.

Key model estimates are presented in Table 22 on page 62. Key model assumptions, many of which are described above, are also summarized in Table 21 on the following page.

Table 21. Key Assumptions Used in Model Development.

Key Assumption	Rationale
Cost per SVR and downstream cost offsets based on effectiveness of initial course of therapy only	No available data on effectiveness of retreatment with newer regimens
Patients would complete and be fully compliant with therapy	Compliance data not available for all regimens and populations of interest
Clinical benefits limited to SVR and its effects on downstream liver-related complications	Intent was to develop policy-based model rather than to document natural history
Costs limited to drug therapy and downstream management of liver disease and other medical care	Intent was to develop policy-based model rather than to create full accounting of costs
No differential costs assumed for identification and management of side effects and other drug-related harms	Inclusion of such measures would dilute the model focus on differential SVR rates and their impact on downstream events and costs
Costs were measured for assumed retreatment regimens, but effectiveness was not	Focus of model was on clinical impact of initial course of therapy
No inclusion of estimates of competing morbidity and mortality risks	Focus of model was on differential effects between treatment regimens (i.e., SVR status and its sequelae)

Table 22. Estimates for Cohort Model of Hepatitis C Treatment.

Measure	Estimate	Sources
Discontinuation due to adverse events, %		CTAF Evidence Review
PR	8.4	
Telaprevir (+PR)	14.0	
Simeprevir (+PR)	6.4	
Sofosbuvir (+PR)	5.5	
Sofosbuvir (+R)	1.3	
Sofosbuvir + simeprevir (±R)	5.0	
Risk of liver-related complications, %		Freeman, 2001; Singal, 2010
At 5-years		
All patients	6.0	
Advanced fibrosis only	12.0	
At 20-years		
All patients	24.0	
Advanced fibrosis only	48.0	
Hazard ratio for composite liver complications with SVR	0.20	Van der Meer, 2012; Singal, 2010; Pearlman, 2011
Annual costs of care, $		
Patients with liver complications	25,728	Menzin, 2012
Patients without SVR	10,149	Manos, 2013
Patients with SVR	6,301	Manos, 2013
Weekly drug costs, $		Red Book® Online, 2012 & 2014
Ribavirin	348	
Pegylated interferon	691	
Telaprevir	4,920*	
Simeprevir	5,530	
Sofosbuvir	7,000	

PR: Pegylated interferon plus ribavirin

*Price deemed to be representative of period in which telaprevir was the standard of care

7.3 Model Results

Genotype 1, Treatment-naïve, Interferon-eligible

Table 23 on the following page presents model results for all patients with genotype 1 who are treatment-naïve. Among a population of 1,000 interferon-eligible patients, we estimate that SVR will be achieved for 830 treated with sofosbuvir + PR; for 840 treated with simeprevir + PR; and for 740 patients treated with telaprevir + PR. Ten patients would require treatment with simeprevir + PR to obtain one additional SVR when compared with the SVR rates of telaprevir + PR; the corresponding figure is 11 patients per additional SVR for sofosbuvir + PR. The number of patients discontinuing therapy due to adverse events is 2-3 times greater for telaprevir + PR versus the newer regimens.

Drug costs for the initial treatment course are 9% and 15% greater for the newer regimens ($91,296 and $96,468 for simeprevir and sofosbuvir, respectively) than for the first generation DAA triple therapy ($83,976). The cost per additional SVR when looking just at the initial treatment course was estimated to be $73,000 for simeprevir + PR and $139,000 for sofosbuvir + PR. A cost per additional SVR could not be calculated for sofosbuvir + PR versus simeprevir + PR, as the latter was found to be comparable in effectiveness to sofosbuvir + PR and slightly less costly.

Total drug costs over one year were tabulated for an entire 1,000-person cohort under the assumption that all patients who do not achieve SVR with initial therapy are then prescribed simeprevir + PR. These costs were estimated to total $108 million for telaprevir, $106 million for simeprevir, and $112 million for sofosbuvir. The incremental one-year drug costs for the entire 1,000 patient cohort over the costs for telaprevir + PR would be $4.3 million for sofosbuvir + PR. A cohort initially treated with simeprevir + PR would realize a savings of $1.8 million versus telaprevir + PR, as these two agents are closer in price and fewer simeprevir + PR patients would require retreatment.

Over five years, the simeprevir and sofosbuvir regimens would reduce the number of liver-related complications per 1,000 when compared with telaprevir + PR by five and four patients, respectively. The cost offset over five years per 1,000 patients that is created by savings from fewer liver complications and greater number of patients achieving SVR is estimated to be approximately $2.4 million for simeprevir + PR and $2.1 million for sofosbuvir + PR. Over a 20-year time horizon, simeprevir and sofosbuvir regimens would result in 19 and 17 fewer liver-related complications per 1,000, respectively. At 20 years, the cost offset for simeprevir + PR would be approximately $7.7 million (or a total of $9.5 million including savings in one-year drug costs), while the offset for sofosbuvir + PR would be approximately $7 million, which would completely offset the initial incremental drug cost and result in net savings.

Table 23. Clinical and Economic Impact of Treatment Options Among 1,000 60 year-old Patients with Hepatitis C Genotype 1 Who Are New to Treatment (Treatment-naïve).

	Evidence Review Data					*Modeled 1-Year Drug Costs*		*Modeled Long-Term Effects of Achieving SVR*			
Population/regimen	**SVR per 1000**	**NNT for 1 add'l SVR**	**Discontinued due to AE (per 1000)**	**Cost for initial Rx (per patient)**	**Cost per add'l SVR**	**Total Drug Costs (per 1000)**	**Incremental (vs. pre-DAA)**	**Liver Events Averted (per 1000)**		**Total Estimated Cost Offset (per 1000, vs. pre-DAA)**	
								5 years	**20 years**	**5 years**	**20 years**
IFN-eligible											
TEL + PR (12/24) (pre-DAA)*	740	---	140	$83,976	---	$107,712,960	---	---	---	---	---
SMV + PR (12/24)*	840	10	64	$91,296	$73,000	$105,903,360	($1,810,000)	(5)	(19)	($2,393,000)	($7,730,000)
SOF + PR (12)*	830	11	55	$96,468	$139,000	$111,988,320	$4,275,000	(4)	(17)	($2,154,000)	($6,957,000)
IFN-ineligible											
No Rx (pre-DAA)	0	---	0	$0	---	$0	---	---	---	---	---
SOF + R (24)†	720	1	13	$176,352	$245,000	$219,622,080	$219,622,000	(35)	(138)	($17,233,000)	($55,653,000)
SOF + SMV + R (12)‡	900	1	0	$154,536	$172,000	$169,989,600	$169,990,000	(43)	(173)	($21,541,000)	($69,566,000)

*ICER network meta-analysis

†Pooled data from PHOTON-1 and QUANTUM

‡Pooled data from COSMOS treatment arms

Total drug costs Include initial therapy and retreatment with most effective regimen available for those not achieving SVR initially

Total estimated cost offset includes cost savings from liver events averted and reduced annual costs from greater numbers of patients achieving SVR

SVR: sustained virologic response; NNT: number needed to treat; DAA: direct-acting antivirals

Genotype 1, Treatment-naïve, Interferon-ineligible

Among interferon-ineligible patients, comparisons were made between sofosbuvir + R (24 weeks), sofosbuvir + simeprevir + R (12 weeks), and no drug therapy (as these patients previously had no treatment options). The combination of sofosbuvir + simeprevir + R was most effective (900 achieving SVR per 1,000 versus 710 for sofosbuvir + R) and resulted in little to no discontinuation due to adverse events. Both regimens are very expensive: ~$176,000 for 24 weeks of sofosbuvir + R and ~$155,000 for 12 weeks of sofosbuvir + simeprevir + R. Assuming retreatment of patients failing to achieve SVR with sofosbuvir + simeprevir + R, one-year drug costs for 1,000 patients treated with sofosbuvir + R for 24 weeks would total $220 million, while sofosbuvir + simeprevir + R for 12 weeks would generate $170 million in drug costs per 1,000 patients.

At five years, cost offsets per 1,000 patients due to averted liver complications and greater achievement of SVR would total approximately $17 million for sofosbuvir + R and $22 million for sofosbuvir + simeprevir + R, or about 10% of incremental drug costs for these regimens; even at 20 years, cost offsets relative to no drug treatment would represent 40% of these totals at most (for sofosbuvir + simeprevir + R).

Alternative Analysis Based on Severity of Liver Disease

Primary analyses focused on the effects of preventing liver-related complications among patients at *all* stages of liver disease. For the genotype 1, treatment-naïve population, we also explored the number of liver-related complications averted if all 1,000 patients alternatively had no-to-mild liver disease (i.e., METAVIR F0-F2) and if all patients had advanced liver disease (METAVIR F3-F4). The full set of findings is presented in Tables A1 and A2 in the Appendix. A summary of the key clinical findings at 20 years is presented in Table 24 on the following page.

Table 24. Effects of Treatment on Liver-related Complications at 20 Years, Among 1,000 Genotype 1 Treatment-naïve Patients at Varying Levels of Liver Disease.

Regimen	All Patients		METAVIR F0-F2 Only		METAVIR F3-F4 Only	
	Events Averted (per 1,000)	NNT	Events Averted (per 1,000)	NNT	Events Averted (per 1,000)	NNT
IFN-eligible (vs. TEL + PR)						
SMV + PR	19	52	10	103	38	26
SOF + PR	17	58	9	115	35	29
IFN-ineligible (vs. No Rx)						
SOF + R	138	7	70	14	276	4
SOF + SMV + R	173	6	87	11	346	3

NNT: Number needed to treat

Among interferon-eligible patients, simeprevir + PR and sofosbuvir + PR would avoid 19 and 17 liver-related complications per 1,000 over 20 years when compared to telaprevir + PR when all stages of liver disease are considered; corresponding numbers needed to treat to avoid one liver-related complication were 52 and 58 respectively. If all 1,000 patients had no-to-mild liver disease only, the number of events averted would be approximately 50% of the estimates for patients at all stages of liver disease, and the number needed to treat would approximately double. In the scenario assuming that all patients had advanced liver disease, simeprevir + PR and sofosbuvir + PR would avoid 38 and 35 liver-related complications per 1,000 over 20 years respectively, with corresponding NNT figures of 26 and 29 to avoid one liver-related complication.

Absolute differences between regimens were greater among interferon-ineligible patients, given the lack of a prior standard of care. Sofosbuvir + R and sofosbuvir + simeprevir + R would avoid 138 and 173 liver-related complications per 1,000 over 20 years respectively when all stages of liver disease are considered, resulting in relatively low NNT figures (7 and 6, respectively). These figures are again halved when only patients with no-to-mild liver disease are considered but still result in relatively low numbers needed to treat (14 and 11, respectively). When all 1,000 patients are assumed to have advanced liver disease, approximately 28% and 35% of patients treated with sofosbuvir + R and sofosbuvir + simeprevir + R respectively would avoid liver-related complications, with corresponding NNT figures of 4 and 3 to avoid one liver-related complication.

Data on cost offsets are also presented in the Appendix. In comparison to primary analyses involving patients at all stages of liver disease, cost offsets would decline by approximately 25% if all 1,000 patients had no-to-mild liver disease and would increase by roughly the same percentage if all patients had advanced liver disease.

Genotype 1, Treatment-experienced, Interferon-eligible

Findings for genotype 1 patients who have been treated previously can be found in Table 25 on the following page. Among patients eligible for interferon therapy, comparisons were made for simeprevir + PR, sofosbuvir + PR, and sofosbuvir + simeprevir + R versus a previous standard of telaprevir + PR. Based on the network meta-analysis findings as well as data derived from an FDA algorithm for sofosbuvir, both simeprevir + PR and sofosbuvir + PR were as effective but more expensive than the first generation DAA triple therapy. Based on data from the COSMOS trial, sofosbuvir + simeprevir + R was the most effective therapy (900 SVR per 1,000 patients versus 710 and 700 for sofosbuvir + PR and telaprevir + PR, respectively). Five patients would need to be treated with sofosbuvir + simeprevir + R to achieve one additional SVR over the other available regimens.

Table 25. Clinical and Economic Impact of Treatment Options Among 1,000 60 year-old Patients with Hepatitis C Genotype 1 Who Have Been Treated Previously (Treatment-experienced).

	Evidence Review Data					*Modeled 1-Year Drug Costs*		*Modeled Long-Term Effects of Achieving SVR*			
Population/regimen	**SVR per 1000**	**NNT for 1 add'l SVR**	**Discontinued due to AE (per 1000)**	**Cost for initial Rx (per patient)**	**Cost per add'l SVR**	**Total Drug Costs (per 1000)**	**Incremental (vs. pre-DAA)**	**Liver Events Averted (per 1000)**		**Total Estimated Cost Offset (per 1000, vs. pre-DAA)**	
								5 years	**20 years**	**5 years**	**20 years**
IFN-eligible											
TEL + PR (12/24) (pre-DAA)*	700	---	140	$83,976	---	$130,336,800	---	---	---	---	---
SMV + PR (12/24)*	700	N/C	64	$91,296	N/C	$137,656,800	$7,320,000	0	0	$0	$0
SOF + PR (12)†	710	100	55	$96,468	$1,249,000	$141,283,440	$10,947,000	(0)	(2)	($239,000)	($773,000)
SOF + SMV + R (12)‡	900	5	0	$154,536	$353,000	$169,989,600	$39,653,000	(10)	(38)	($4,787,000)	($15,459,000)
IFN-ineligible											
No Rx (pre-DAA)	0	---	0	$0	---	$0	---	---	---	---	---
SOF + R (24)Ω	610	2	13	$176,352	$289,000	$236,621,040	$236,621,000	(29)	(117)	($14,600,000)	($47,150,000)
SOF + SMV + R (12)‡	900	1	0	$154,536	$172,000	$169,989,600	$169,990,000	(43)	(173)	($21,541,000)	($69,566,000)

*ICER network meta-analysis

†FDA estimate based on data from NEUTRINO among patients with "poor prognostic factors"

‡Pooled data from COSMOS treatment arms

ΩNo available data. Data pooled from PHOTON-1 and QUANTUM and adjusted downward based on decrement from Rx-naïve to Rx-experienced with SOF+PR (83% vs. 71%)

Total drug costs Include initial therapy and retreatment with most effective regimen available for those not achieving SVR initially

Total estimated cost offset includes cost savings from liver events averted and reduced annual costs from greater numbers of patients achieving SVR

N/C: Not calculable

SVR: sustained virologic response; NNT: number needed to treat; DAA: direct-acting antivirals

The cost per additional SVR could not be calculated for simeprevir + PR because it was equally effective in comparison to telaprevir + PR. The cost per additional SVR for sofosbuvir + PR was very high ($1.2 million) given the small difference in effectiveness (SVR achieved in 710 per 1,000 versus 700 for telaprevir + PR). The cost per additional SVR for sofosbuvir + simeprevir + R was $353,000, as the treatment cost is nearly twice that of telaprevir + PR (~$155,000 versus ~$84,000). When the sofosbuvir regimens were compared to each other, the cost per SVR of sofosbuvir + simeprevir + R was estimated to be $306,000 (data not shown).

Over one year, the use of simeprevir + PR and sofosbuvir + PR is projected to increase overall drug costs per 1,000 patients by approximately $7.3 and $11 million respectively relative to telaprevir + PR, but almost none of these costs would be offset due to the similarity in effectiveness between regimens. The sofosbuvir + simeprevir + R treatment regimen would increase drug spending by approximately $40 million per every 1,000 treated patients relative to first generation DAA triple therapy. While liver-related complications would be substantially reduced at both five and 20 years (by 10 and 38 patients per 1,000 respectively), cost offsets would total at most 39% of drug costs.

Genotype 1, Treatment-experienced, Interferon-ineligible

Among treatment-experienced patients with genotype 1 not eligible for interferon, no active treatment was previously available for these patients. Newer regimens examined included sofosbuvir + simeprevir + R for 12 weeks as described above as well as a 24-week regimen of sofosbuvir + R, the identical regimens assessed for treatment-naïve patients. No data on SVR were available for sofosbuvir + R in this population; we therefore derived an estimate based on the difference in effectiveness for sofosbuvir regimens between treatment-naïve and treatment-experienced interferon-eligible patients (i.e., 83% versus 71%). Based on this assumption, the incremental drug costs at one year for 1,000 patients receiving this regimen would be $237 million. The effectiveness of sofosbuvir + simeprevir + R was assumed to be identical to that among treatment-naïve patients, resulting in an incremental cost of $170 million. Even at 20 years, cost offsets relative to no drug treatment would represent at most 40% of these totals.

Genotype 1: Considerations of Duration of PR Therapy

Because telaprevir therapy is response-guided, some patients will require 48 weeks of PR therapy rather than the 24 weeks assumed for these analyses. Similarly, simeprevir requires 48 weeks of PR for the proportion of treatment-experienced patients who are null or partial responders. For telaprevir, assumption of PR therapy duration consistent with the Phase III clinical trials (~60% for 24 weeks, ~40% for 48 weeks) yields a blended cost estimate of $93,950 (versus $83,976 in the base case). Among treatment-naïve patients, this does not materially affect the direction of model results, as simeprevir + PR would continue to produce cost savings at 1 year, and sofosbuvir + PR remains more expensive than telaprevir + PR. While the proportion of prior partial or null

responders to telaprevir + PR who would be candidates for simeprevir + PR is unknown, it is likely that extending the duration of PR therapy for some proportion of treatment-experienced simeprevir + PR patients would make this regimen more expensive than all other regimens except for sofosbuvir + simeprevir + R.

Genotype 2, Treatment-naïve, Interferon-eligible

Table 26 on the following page presents results for patients with genotype 2 who are new to hepatitis C treatment. Among interferon-eligible patients, a regimen of 12 weeks of sofosbuvir + R was compared to the previous standard of 24 weeks of PR alone. Based on pooled data from the VALENCE and FISSION trials, sofosbuvir + R was highly effective in this population (970 per 1,000 achieving SVR initially), but PR is also relatively effective in genotype 2 patients (780 per 1,000). The number needed to treat to achieve an additional SVR for sofosbuvir + R was 5. Rates of discontinuation due to adverse events was very low in the sofosbuvir + R group (13 versus 84 per 1,000 for PR). The costs of sofosbuvir + R are nearly four times that of PR (~$88,000 versus ~$25,000), resulting in a cost per additional SVR of $333,000.

Over one year, sofosbuvir + R would be expected to generate an additional $46 million in drug costs per 1,000 patients treated. The newer regimen would prevent nine and 36 liver-related complications per 1,000 over five and 20 years respectively, and it would generate cost offsets of approximately $4.5 and $15 million during these periods. These offsets represent 10% of the incremental drug costs for sofosbuvir at five years and 32% of drug costs at 20 years.

Genotype 2, Treatment-naïve, Interferon-ineligible

Among patients with genotype 2 not eligible for interferon, 12 weeks of sofosbuvir + R is estimated to be slightly less effective than in interferon-eligible patients, resulting in achievement of SVR by 930 patients per 1,000 treated (based on data from the POSITRON trial). Use of this regimen would generate approximately $94 million in drug costs per 1,000 patients treated over one year in a population without any historical treatment options. Sofosbuvir + R would prevent 45 and 179 liver-related complications per 1,000 over five and 20 years, respectively; because of the relatively low cost of sofosbuvir + R (~$88,000) versus other sofosbuvir-based regimens, cost offsets at these time points ($22 million and $72 million, respectively) represented a higher percentage of drug expenditures (24% and 76%).

Table 26. Clinical and Economic Impact of Treatment Options Among 1,000 60 year-old Patients with Hepatitis C Genotype 2 Who Are New to Treatment (Treatment-naïve).

	Evidence Review Data					*Modeled 1-Year Drug Costs*		*Modeled Long-Term Effects of Achieving SVR*			
Population/regimen	**SVR per 1000**	**NNT for 1 add'l SVR**	**Discontinued due to AE (per 1000)**	**Cost for initial Rx (per patient)**	**Cost per add'l SVR**	**Total Drug Costs (per 1000)**	**Incremental (vs. pre-DAA)**	**Liver Events Averted (per 1000) 5 years**	**20 years**	**Total Estimated Cost Offset (per 1000, vs. pre-DAA) 5 years**	**20 years**
IFN-eligible											
PR (24) (pre-DAA)*	780	---	84	$24,936	---	$44,334,720	---	---	---	---	---
SOF + R (12)*	970	5	13	$88,176	$333,000	$90,821,280	$46,487,000	(9)	(36)	($4,547,000)	($14,686,000)
IFN-ineligible											
No Rx (pre-DAA)	0	---	---	$0	---	$0	---	---	---	---	---
SOF + R (12)†	930	1	13	$88,176	$95,000	$94,348,320	$94,348,000	(45)	(179)	($22,259,000)	($71,885,000)

*Pooled data from VALENCE and FISSION

†Based on data from POSITRON

Total drug costs Include initial therapy and retreatment with most effective regimen available for those not achieving SVR initially

Total estimated cost offset includes cost savings from liver events averted and reduced annual costs from greater numbers of patients achieving SVR

SVR: sustained virologic response; NNT: number needed to treat; DAA: direct-acting antivirals

Genotype 2, Treatment-experienced, Interferon-eligible

Table 27 on the following page presents model findings for 1,000 genotype 2 patients previously treated for hepatitis C. For interferon-eligible patients, the previous standard is 24 weeks of PR, and newer options include 12 weeks of sofosbuvir + R (note: sofosbuvir + PR is also recommended in treatment guidelines, but we assumed that such therapy would be unlikely in a group of patients that may have already failed prior PR therapy). Sofosbuvir + R resulted in SVR in 880 of 1,000 patients (based on pooled data from VALENCE and FUSION), versus 710 for PR therapy [no available data; based on an estimate of 78% for treatment-naïve patients adjusted downward based on the difference in effectiveness between treatment-naïve and treatment-experienced patients for sofosbuvir + R (97% versus 88%)]. The resulting number needed to treat for sofosbuvir + R to achieve one additional SVR over PR was 13. The number of patients discontinuing therapy due to adverse events was six times greater for PR (84 versus 13 for sofosbuvir + R). The cost per additional SVR was approximately $372,000 for sofosbuvir + R, owing to a therapy cost over three times higher for sofosbuvir + R relative to the previous standard.

Over one year, sofosbuvir + R would be expected to add nearly $50 million in drug costs for a 1,000-patient cohort, and would prevent liver-related complications in eight and 33 patients per 1,000 at five and 20 years, respectively. Cost offsets at five years were modest ($4.1 million, or 8% of incremental drug costs), as the incremental reductions in liver complications compared to treatment with PR were smaller in this population. At 20 years, cost offsets were estimated to be $13.1 (27% of incremental drug costs).

Genotype 2, Treatment-experienced, Interferon-ineligible

Among genotype 2 patients previously-treated for hepatitis C who are not eligible for interferon, there has been no standard effective treatment. Sofosbuvir + R for 12 weeks is now recommended by the 2014 AASLD/IDSA/IAS guidelines and would be expected to achieve SVR in 880 patients per 1,000 treated (note: data were only available from a small arm of the POSITRON study [n=17]; we therefore assumed the same SVR rate as observed for interferon-eligible patients receiving this treatment). Over one year, use of this regimen would generate approximately $99 million in drug costs for the 1,000-patient cohort. Because a large number of liver-related complications would be averted relative to no treatment (42 and 169 per 1,000 at five and 20 years), potential cost offsets are relatively high. At five years, cost offsets would total $21 million (20% of drug costs). At 20 years, these offsets would total approximately $68 million (70% of drug costs).

Table 27. Clinical and Economic Impact of Treatment Options Among 1,000 60 year-old Patients with Hepatitis C Genotype 2 Who Have Been Treated Previously (Treatment-experienced).

	Evidence Review Data					*Modeled 1-Year Drug Costs*		*Modeled Long-Term Effects of Achieving SVR*			
Population/regimen	**SVR per 1000**	**NNT for 1 add'l SVR**	**Discontinued due to AE (per 1000)**	**Cost for initial Rx (per patient)**	**Cost per add'l SVR**	**Total Drug Costs (per 1000)**	**Incremental (vs. pre-DAA)**	**Liver Events Averted (per 1000) 5 years**	**20 years**	**Total Estimated Cost Offset (per 1000, vs. pre-DAA) 5 years**	**20 years**
IFN-eligible											
PR (24) (pre-DAA)*	710	---	84	$24,936	---	$50,507,040	---	---	---	---	---
SOF + R (12)†	880	6	13	$88,176	$372,000	$98,757,120	$48,250,000	(8)	(33)	($4,069,000)	($13,140,000)
IFN-ineligible											
No Rx (pre-DAA)	0	---	0	$0	---	$0	---	---	---	---	---
SOF + R (12)‡	880	1	13	$88,176	$100,000	$98,757,120	$98,757,000	(42)	(169)	($21,062,000)	($68,020,000)

*No available data. Data pooled from VALENCE and FISSION and adjusted downward based on decrement from Rx-naïve to Rx-experienced with SOF+R (97% vs. 88%)

†Pooled data from VALENCE and FUSION

‡Data only available from small arm of POSITRON study (n=17). Rate assumed to be equivalent to that among IFN-eligible patients

Total drug costs Include initial therapy and retreatment with most effective regimen available for those not achieving SVR initially

Total estimated cost offset includes cost savings from liver events averted and reduced annual costs from greater numbers of patients achieving SVR

SVR: sustained virologic response; NNT: number needed to treat; DAA: direct-acting antivirals

Genotype 3, Treatment-naïve, Interferon-eligible

For the genotype 3 population, the previous standard of care was PR therapy for 24 weeks. Newer regimens available for comparison included sofosbuvir + R for 24 weeks (note: sofosbuvir + PR is also recommended in treatment guidelines, but as with genotype 2, we assumed that patients would opt for an interferon-free regimen if available). The numbers of patients per 1,000 achieving SVR were estimated to be 620 for PR therapy (based on data from FISSION) and 930 for sofosbuvir + R (based on data from VALENCE), resulting in a number needed to treat of 3 to obtain an additional SVR (see Table 28 on the following page). As with prior comparisons, PR therapy would result in a greater rate of discontinuation due to adverse events per 1,000 (84) compared with sofosbuvir + R (13). However, the estimated cost of the 24-week sofosbuvir + R regimen ($176,352) is over seven times the cost of PR alone, resulting in a high cost per additional SVR ($488,000) for sofosbuvir + R.

Under the assumption that all patients failing to achieve SVR would receive the sofosbuvir + R regimen, the 24-week sofosbuvir + R regimen would increase drug costs by approximately $97 million in this 1,000-person cohort. The numbers of patients avoiding liver-related complications at five and 20 years with sofosbuvir + R were 15 and 60 per 1,000 respectively. Cost offsets are estimated to total approximately $7 million and $24 million at five and 20 years respectively, which represent 8% and 25% of incremental drug costs for sofosbuvir + R.

Genotype 3, Treatment-naïve, Interferon-ineligible

Among patients with genotype 3 not eligible for interferon therapy, there has been no standard effective treatment. The 24-week sofosbuvir + R regimen has now been recommended in the 2014 AASLD/IDSA/IAS treatment guidelines. The effectiveness of this regimen is lower among patients not eligible for interferon, however, with SVR achieved in only 630 per 1,000 (based on pooled data from the treatment-naïve and treatment-experienced arms of the POSITRON study) versus 930 per 1,000 among interferon-eligible patients. As a result, the use of this regimen, including retreatment for those not achieving SVR initially, would add $242 million in drug costs per 1,000 patients treated. While use of sofosbuvir + R would reduce liver-related complications per 1,000 by 30 at five years and 121 at 20 years, cost offsets at these time points would be $15 million and $49 million, respectively, or just 6% and 20% of one-year incremental drug costs.

Table 28. Clinical and Economic Impact of Treatment Options Among 1,000 60 year-old Patients with Hepatitis C Genotype 3 Who Are New to Treatment (Treatment-naïve).

	Evidence Review Data					*Modeled 1-Year Drug Costs*		*Modeled Long-Term Effects of Achieving SVR*			
Population/regimen	**SVR per 1000**	**NNT for 1 add'l SVR**	**Discontinued due to AE (per 1000)**	**Cost for initial Rx (per patient)**	**Cost per add'l SVR**	**Total Drug Costs (per 1000)**	**Incremental (vs. pre-DAA)**	**Liver Events Averted (per 1000) 5 years**	**20 years**	**Total Estimated Cost Offset (per 1000, vs. pre-DAA) 5 years**	**20 years**
IFN-eligible											
PR (24) (pre-DAA)*	620	---	84	$24,936	---	$91,949,760	---	---	---	---	---
SOF + R (24)†	930	3	13	$176,352	$488,000	$188,696,640	$96,747,000	(15)	(60)	($7,420,000)	($23,962,000)
IFN-ineligible											
No Rx (pre-DAA)	0	---	---	$0	---	$0	---	---	---	---	---
SOF + R (24)‡	630	2	13	$176,352	$280,000	$241,602,240	$241,602,000	(30)	(121)	($15,079,000)	($48,696,000)

*Based on data from FISSION

†Based on data from VALENCE

‡Based on overall data from POSITRON (Rx-naïve and Rx-experienced)

Total drug costs Include initial therapy and retreatment with most effective regimen available for those not achieving SVR initially

Total estimated cost offset includes cost savings from liver events averted and reduced annual costs from greater numbers of patients achieving SVR

SVR: sustained virologic response; NNT: number needed to treat; DAA: direct-acting antivirals

Genotype 3, Treatment-experienced, Interferon-eligible

Outcomes and costs for patients with genotype 3 who have received prior hepatitis C therapy are presented in Table 29 on the following page. The previous standard of care has been PR for 24 weeks. As with treatment-naïve genotype 3 patients, sofosbuvir + R for 24 weeks is recommended, but the incremental effectiveness is less than that seen among treatment-naïve patients. Among treatment-experienced patients eligible for interferon, PR for 24 weeks is still estimated to produce SVR in 510 patients per 1,000 treated (no available data; estimated based on data from FISSION downgraded to reflect the difference in effectiveness for sofosbuvir + R for treatment-naïve versus treatment-experienced patients). The 24-week sofosbuvir + R regimen would achieve SVR in 770 patients per 1,000 (based on data from VALENCE). The number needed to treat to obtain an additional SVR was four for sofosbuvir + R. Because cost differences were the same as for treatment-naïve patients but incremental effectiveness was lower, the cost per additional SVR for sofosbuvir + R is higher in this population ($582,000 versus $488,000 for treatment-naïve patients).

Over one year, sofosbuvir + R would be expected to add $106 million in drug costs per 1,000 treated. The numbers of liver-related complications averted would total 12 and 50 per 1,000 at five and 20 years respectively, which would translate into cost offsets of $6 million and $20 million at these time points (representing 6% and 19% of drug costs).

Genotype 3, Treatment-experienced, Interferon-ineligible

Because there were no studies evaluating the effectiveness of sofosbuvir + R in genotype 3 who had received prior hepatitis C therapy and were ineligible for interferon, we assumed the same effectiveness for this regimen as among patients who were treatment-naïve (630 achieving SVR per 1,000 treated). Use of this regimen would increase drug costs by $242 million per 1,000 treated, would prevent 30 and 121 liver-related complications per 1,000 at five and 20 years respectively, and would result in offsets to this cost of approximately $15 million (6%) and $49 million (20%) at five and 20 years.

Table 29. Clinical and Economic Impact of Treatment Options Among 1,000 60 year-old Patients with Hepatitis C Genotype 3 Who Have Been Treated Previously (Treatment-experienced).

	Evidence Review Data					*Modeled 1-Year Drug Costs*		*Modeled Long-Term Effects of Achieving SVR*			
Population/regimen	**SVR per 1000**	**NNT for 1 add'l SVR**	**Discontinued due to AE (per 1000)**	**Cost for initial Rx (per patient)**	**Cost per add'l SVR**	**Total Drug Costs (per 1000)**	**Incremental (vs. pre-DAA)**	**Liver Events Averted (per 1000)**		**Total Estimated Cost Offset (per 1000, vs. pre-DAA)**	
								5 years	**20 years**	**5 years**	**20 years**
IFN-eligible											
PR (24) (pre-DAA)*	510	---	84	$24,936	---	$111,348,480	---	---	---	---	---
SOF + R (24)†	770	4	13	$176,352	$582,000	$216,912,960	$105,564,000	(12)	(50)	($6,223,000)	($20,097,000)
IFN-ineligible											
No Rx (pre-DAA)	0	---	---	$0	---	$0	---	---	---	---	---
SOF + R (24)‡	630	2	13	$176,352	$280,000	$241,602,240	$241,602,000	(30)	(121)	($15,079,000)	($48,696,000)

*No available data. Based on data from FISSION and adjusted downward based on decrement from Rx-naïve to Rx-experienced with SOF+R (93% vs. 77%)

†Based on data from VALENCE

‡Based on overall data from POSITRON (Rx-naïve and Rx-experienced)

Total drug costs Include initial therapy and retreatment with most effective regimen available for those not achieving SVR initially

Total estimated cost offset includes cost savings from liver events averted and reduced annual costs from greater numbers of patients achieving SVR

SVR: sustained virologic response; NNT: number needed to treat; DAA: direct-acting antivirals

Estimates of Budget Impact in California for Different Treatment Scenarios

As mentioned above, we also applied estimates of the budgetary impact as well as 5- and 20-year clinical benefits and cost offsets to the California hepatitis C population. In this case, the budgetary impact over one year was compared for the previous standard of care and the most effective regimen in each genotype/prior treatment status/interferon eligibility stratum based on the estimated drug costs for *initial therapy* with these regimens—we did not assume any retreatment for population-based analyses. We estimated liver complication rates and related costs as well as annual costs for patients achieving and not achieving SVR for each patient subgroup of interest. We also discounted future costs in this analysis.

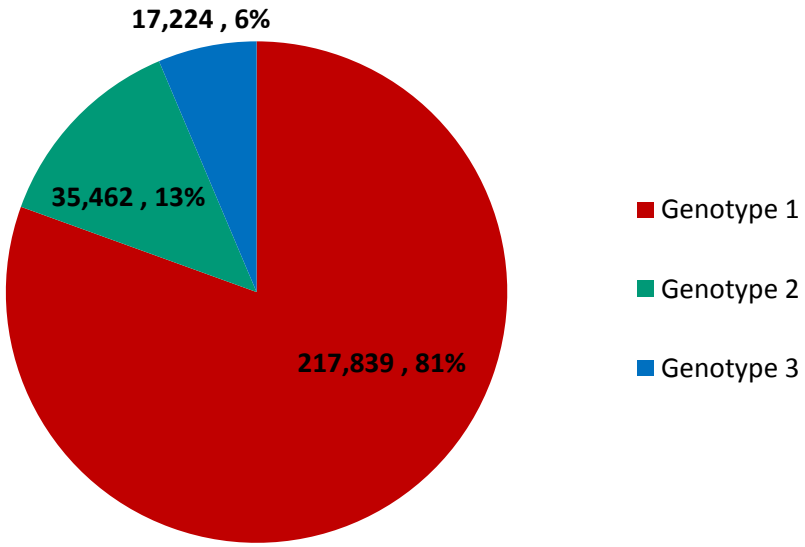
We estimated the size of the chronic hepatitis C population in California to be approximately 560,000 based on information from the 1999-2002 screening round of the National Health and Nutrition Examination Survey (NHANES)[7] as well as estimates of the numbers of incarcerated and homeless individuals living with the disease.[114,115] Of these patients, approximately 540,000 (97%) would be infected with genotypes 1, 2, or 3.[17]

It is commonly recognized, however, that a substantial percentage of patients do not know they are infected. This proportion has been historically reported to be approximately 50% of infected patients,[29] but in recent years more patients may have become aware of their status due to efforts to increase awareness of the disease and expand screening efforts. We therefore alternatively evaluated budgetary impact based on assumptions that either 50% (~270,000) or 75% (~405,000) of infected individuals would know they were infected and would be considered for treatment.

Figure 5 on the following page shows the estimated distribution of the California hepatitis C population by genotype using the assumption that 50% of infected individuals know they are infected. The distribution of patients by genotype was obtained from an analysis of 275 NHANES participants with laboratory-confirmed hepatitis C.[17]

As described previously in this report, genotype 1 is dominant, representing over 80% of the 270,000 Californians who have chronic hepatitis C and are aware of the infection, followed by genotypes 2 (13%) and 3 (6%) respectively.

Figure 5. Estimated Numbers of Californians with Chronic Hepatitis C, by Genotype (Based on Assumption of Awareness of Infection by 50% of Infected Individuals).



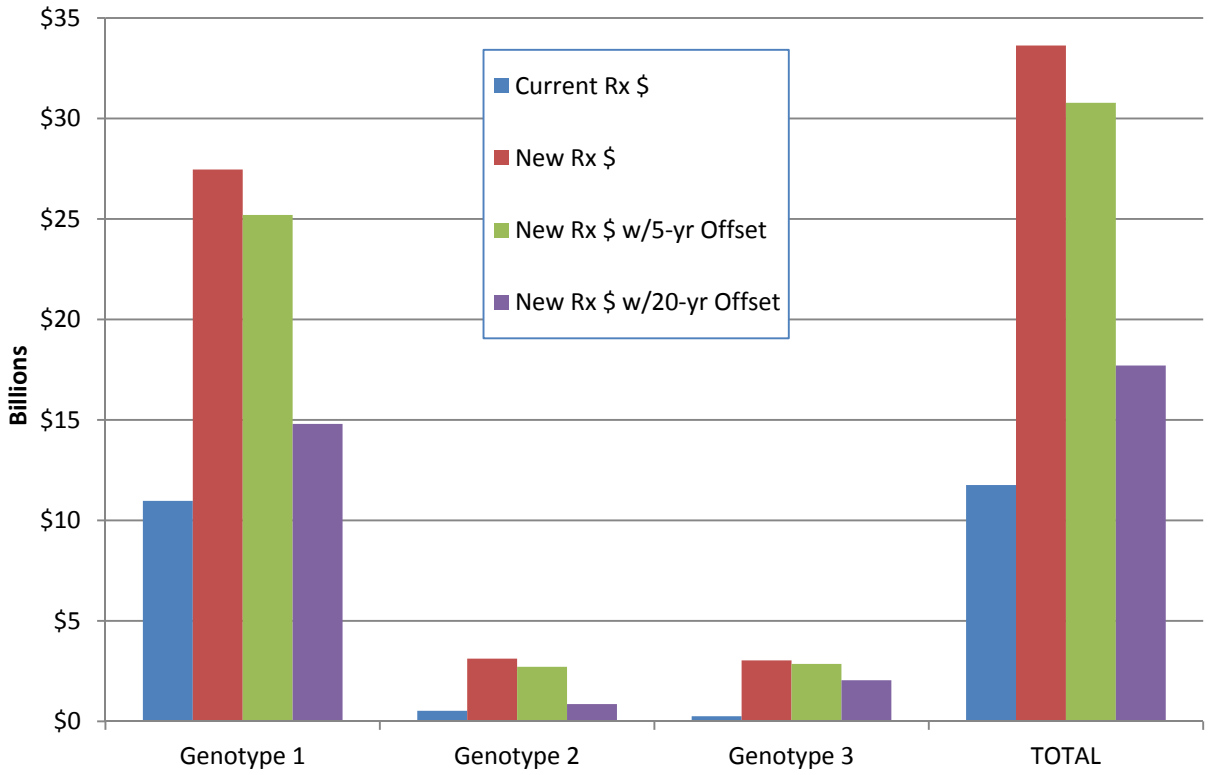
Within each genotype, we also estimated the number of patients who would be treatment-naïve versus previously treated, as well as the number who would be expected to be eligible for interferon therapy versus not. We estimated that 75% of patients would be naïve to treatment based on the proportion of previously-treated patients in a large VA patient registry.[92] Estimates of ineligibility for interferon therapy vary greatly and have been reported to be as high as 60% at the VA.[116] We used a more conservative estimate of 40% based on expert opinion regarding the proportion of patients in broader insured populations who know they are infected and have contraindications to interferon therapy such as significant psychiatric disorders, autoimmune disease, and severe cardiovascular or pulmonary disease (personal communication, Lisa M. Nyberg, MD).

For the California population of hepatitis C patients, we evaluated two different treatment scenarios. In Scenario 1, all patients with known hepatitis C infection are treated. In Scenario 2, only those patients with advanced liver fibrosis (METAVIR scores of F3 or F4) receive treatment. The proportion of infected patients with F3 or F4 scores was estimated to be 33.1% based on a multicenter study of the natural history of fibrosis progression.[117] Within each genotype, analyses of clinical and economic outcomes were based on a change from the previous standard of care to the most effective therapeutic regimen within each of the strata defined by prior treatment status and interferon eligibility.

Results of California-based Analyses

Figure 6 below depicts the budgetary impact and potential cost offsets if 50% of the estimated total California chronic hepatitis C population were to be treated (n=217,839). Drug costs to treat all these patients with the previous standard of care are estimated to total approximately $12 billion across all genotypes. Were these patients all treated instead with the most effective new regimen, treatment costs would grow by $22 billion to a total of $34 billion. Over five years, our model estimates that only approximately 15% of the $22 billion in additional costs would be offset by reductions in the cost of treating liver-related complications and other medical care for patients not achieving SVR. By 20 years, however, cost offsets would grow to $16 billion, or nearly three-quarters of the additional drug expenditures incurred initially.

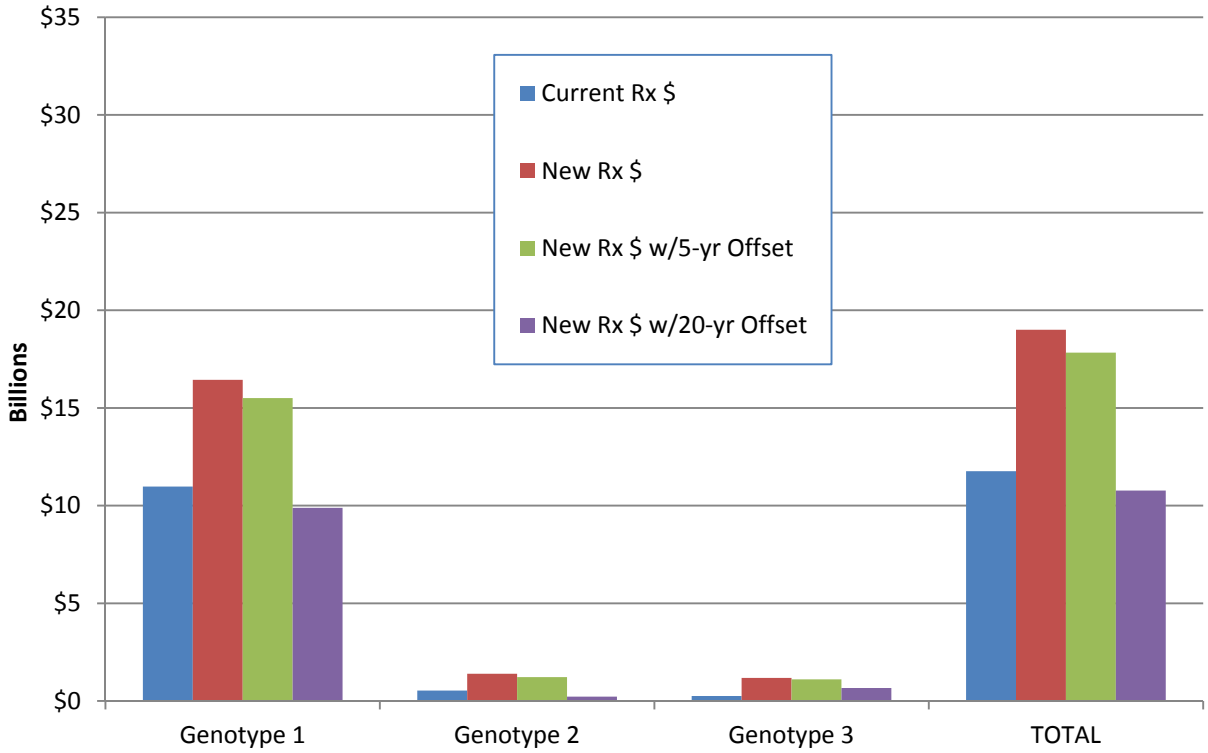
Figure 6. Total Budgetary Impact and Potential Cost Offsets from Use of Newer Drug Regimens in the Chronic Hepatitis C Population in California: 50% of Infected Patients Are Treated (n=270,525).



In our second scenario, we measured the impact of a switch to the most effective new treatment regimens only for patients with evidence of advanced liver fibrosis (i.e., METAVIR scores F3 or F4). As shown in Figure 7 on the following page, treating this smaller group resulted in an increase in drug expenditures of approximately $7 billion in the first year, only one-third of the extra amount needed to treat all infected patients. Costs saved by reducing liver-related complications in this

subgroup would total approximately $1.2 billion (17% of added drug costs) at five years. But at 20 years, estimated cost offsets of $8 billion would exceed the initial incremental drug expenditures of $7 billion, producing a net savings of approximately $1 billion.

Figure 7. Total Budgetary Impact and Potential Cost Offsets from Use of Newer Drug Regimens in the Chronic Hepatitis C Population with Advanced Fibrosis in California: 50% of Infected Patients Are Treated (n=89,544).



We repeated all these different treatment scenarios under the alternative assumption that 75% of the chronic hepatitis C population in California would be aware of their infection and present for treatment. Figures 8 and 9 on the following page depict the increases in drug expenditures and potential cost offsets at five and 20 years if all patients were treated and if only those with advanced fibrosis were treated. The budget impact of initial treatment is obviously higher with more patients treated, but the relation of potential downstream cost offsets remains the same, with relatively little cost offset over the initial five years and an estimated net savings after 20 years if only those patients with advanced liver fibrosis are treated.

Figure 8. Total Budgetary Impact and Potential Cost Offsets from Use of Newer Drug Regimens in the Chronic Hepatitis C Population in California: 75% of infected Patients Are Treated (n=405,788).

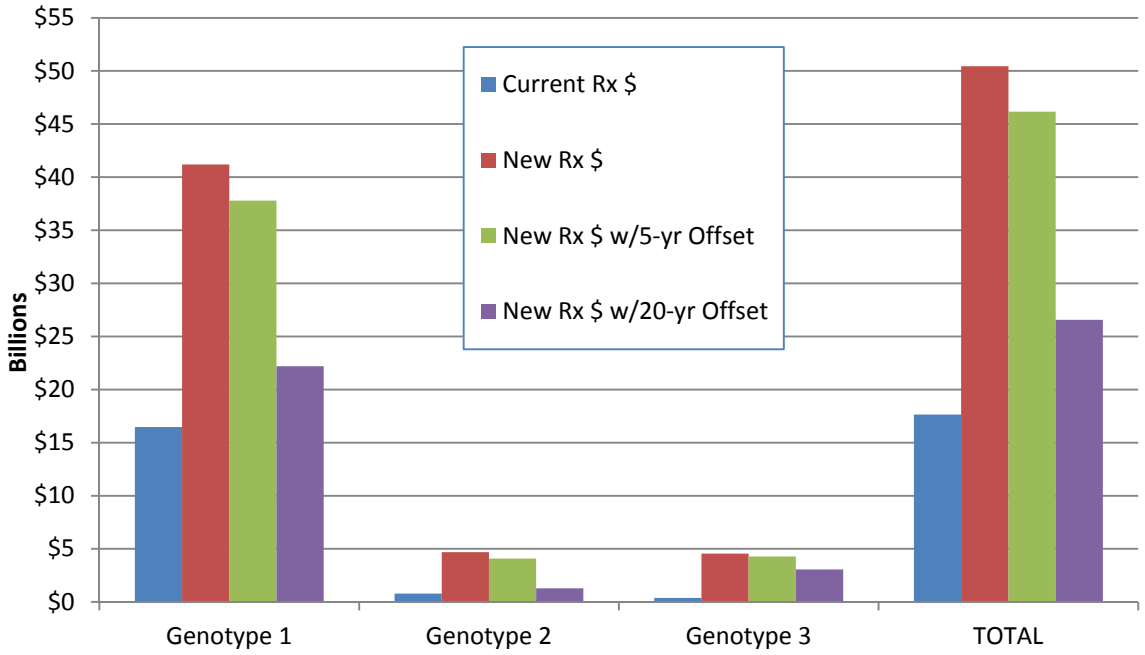
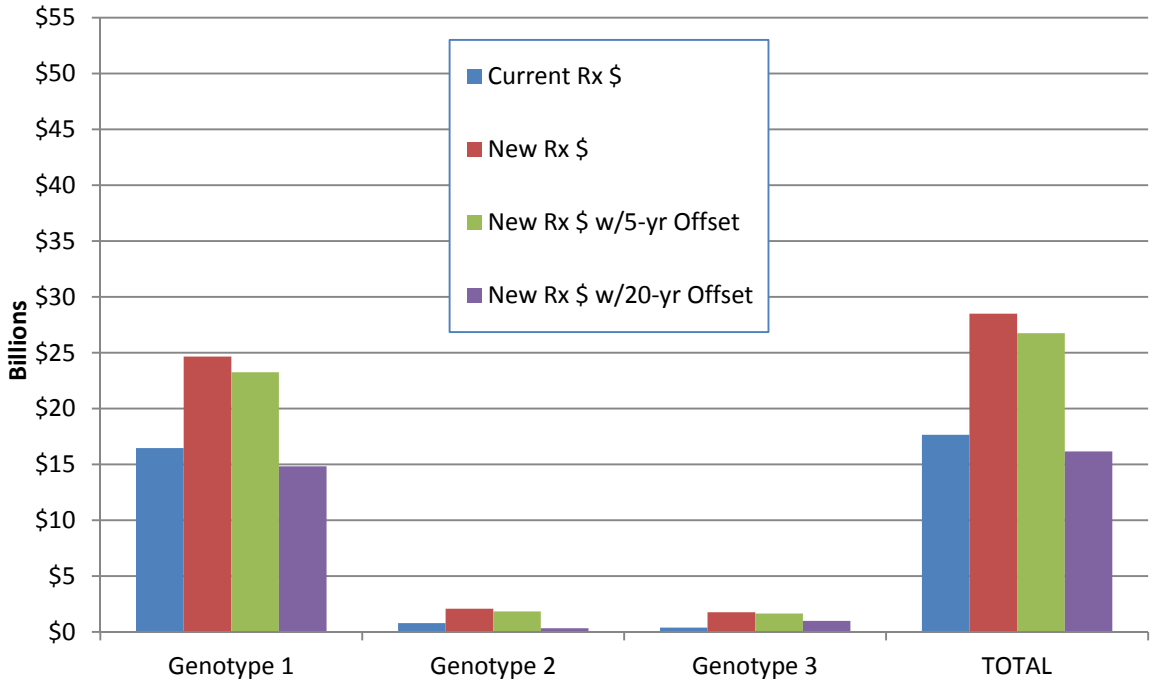


Figure 9. Total Budgetary Impact and Potential Cost Offsets from Use of Newer Drug Regimens in the Chronic Hepatitis C Population with Advanced Fibrosis in California: 75% of Infected Patients Are Treated (n=134,316).



The proportion of hepatitis C patients who are aware of their infection and are actually treated has historically been much lower than these estimates. Rates as low as 7-11% of those estimated to have chronic hepatitis C have been reported,[9] which may be due in part to a prior lack of palatable treatment options as well as system challenges in referring appropriate candidates for therapy. With the advent of interferon-free regimens and efforts to increase hepatitis C screening, treatment rates are likely to increase, however. To explore these possible countervailing effects, we conducted a third scenario (presented in Figures A1 and A2 in the Appendix) in which an assumed 25% of the chronic hepatitis C population in California received treatment. Under this scenario, drug costs would increase by approximately $11 billion. After inclusion of 20-year cost offsets, the increase in drug costs would be reduced by approximately 75%, to $3 billion. If only patients with advanced liver disease are treated, drug costs would increase by approximately $3.5 billion, a difference that would be completely eliminated with inclusion of 20-year cost offsets.

7.4 Summary

Consistent with the findings of the systematic review, our model demonstrates that therapeutic regimens containing sofosbuvir or simeprevir have the potential to substantially increase the number of patients achieving SVR relative to previous therapeutic options; for sofosbuvir, there is the added potential to provide the first effective interferon-free option to patients ineligible or intolerant to interferon. These advantages are considerable.

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 be expected to be retreated, adding further to the estimated treatment costs over a one-year time frame.

Among treatment-naïve patients with genotype 1 who are eligible for interferon and are candidates for newer regimens (i.e., without Q80k polymorphism for simeprevir), the findings of our model suggest that the increased costs of simeprevir and sofosbuvir are offset by downstream savings from reductions in liver-related complications and greater numbers of patients achieving SVR. However, for many other comparisons with the previous standard of care, 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),[118] alternative regimens of PR versus standard PR therapy ($17,000-$24,000),[119] and even highly active antiretroviral therapy in HIV patients ($1,000-$79,000).[120]

The clinical advantages of newer treatment regimens would 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 of the number of infected individuals in California who 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 $22-33 billion in a single year, assuming 50-75% of infected individuals were aware of their infection and presented for treatment. 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. At a 5-year time horizon, however, cost offsets would 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 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 “only” $7 billion 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.

Some of the public comments received suggested that our estimate of the costs of liver-related complications was overly conservative, and that cost offsets would be more fully realized if other data had been used. In fact, one might consider our approach to be less than conservative, as we applied the annual cost of liver-related complications to ***each*** year of the 5- or 20-year time horizon; in many cases, these events will occur toward the end of the timeframe, and increased costs will only be realized for a portion of that time.

We nevertheless explored the effects of using one of the suggested estimates, a comparison of costs among patients with hepatitis C in the Henry Ford Health System.[129] The comparison of mean monthly costs among those with end-stage liver disease ($4,931) versus those with non-cirrhotic liver disease ($1,420) yields a net cost of $3,511, or $42,132 on an annual basis. This estimate is 64% higher than our base case estimate of $25,728. However, when applied to the genotype 1 analysis, total cost offsets at five and 20 years rise by only 15%. For example, the cost offset at 20 years for SOF + SMV + R versus no therapy among interferon-ineligible patients is $69.6 million using the base case liver complication cost and rises to $80.3 million using the Gordon et al (2012) estimate. This is because liver-related events only occurred for a proportion of the treated cohort, and because this increase does not affect the other source of cost offset—the reduction in annual maintenance care costs from greater achievement of SVR. In any event, the results do not change the overall picture of the model—the incremental cost of newer regimens is completely offset at 20 years versus the previous standard of care among interferon-eligible patients, but only a portion of these costs are offset for the interferon-ineligible subgroup.

We must emphasize several limitations of our analysis. 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 therefore 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 and having greater numbers of patients achieve SVR. 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, and we did not assume additional costs from management of specific side effects such as anemia (which may be more pronounced with some regimens than with others). These assumptions may not adequately reflect the drawbacks associated with the previous standard of care or the potential benefits of newer regimens, particularly those free of interferon. However, as noted previously, use of SVR as our primary measure of effectiveness already takes therapy compliance into account, as any patient not completing a full course of therapy is recorded as not having achieved SVR.

Finally, our analysis 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. Regarding the former, however, analyses of quality-of-life data from the sofosbuvir trials suggest that any differential effects between regimens are temporary, as quality of life reverts to baseline levels once treatment is complete for all regimens.[130] In any event, 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 simulation models that approximate the natural history of hepatitis C and its treatment.

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This is the first review of this technology by the California Technology Assessment Forum.

8. Questions and Discussion

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. At the March 10, 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 new treatments for hepatitis C. The key questions are developed by the 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.

Following the evidence presentation and public comments, the CTAF Panel voted on questions concerning the comparative clinical effectiveness and comparative value of new treatments for hepatitis C. The voting results are presented below, along with comments reflecting considerations mentioned by CTAF Panel members during the voting process.

When voting on comparative value, the CTAF Panel was asked to assume the perspective of Medi-Cal (the state Medicaid program) or a public payer that must make resource decisions within a relatively fixed budget for care. The CTAF Panel is not given prescribed boundaries or thresholds for budget impact or incremental cost-effectiveness ratios to guide its judgment of low, reasonable/comparable, or high value. However, the CTAF Panel did make use of a value framework designed for the CTAF process with different categories of evidence on effectiveness and cost to assist the CTAF Panel in assigning an overall value rating of low, reasonable/comparable, or high value (see Figure 10 on the following page).

Figure 10. Evidence Categories for Ratings of Low, Reasonable/Comparable, and High Value.

Low Value	Reasonable/ Comparable Value*	High Value
1. Worse outcomes; Higher or equivalent cost	5. Worse outcomes; Lower cost	9. Comparable outcomes; Lower cost
2. Comparable outcomes; Higher cost	6. Comparable outcomes; Comparable cost	10. Promising but inconclusive evidence of better outcomes; Lower cost
3. Promising but inconclusive evidence of better outcomes; Higher cost	7. Promising but inconclusive evidence of better outcomes; Comparable cost	11. Better outcomes; Lower or comparable cost
4. Better outcomes; Too high a cost	8. Better outcomes; Reasonable higher cost	12. Better outcomes; Slightly higher cost

* For comparisons of one drug or a set of drugs to another drug or set of drugs, the term "comparable" is used in the value assessment; for comparisons of one drug or a set of drugs to no treatment, the term "reasonable" is used in the value assessment.

8.1 Summary of the Votes and Considerations for Policy

I. Genotype 1: treatment-naïve, interferon eligible

1. Do you agree that SMV + PR and SOF + PR are superior to TEL + PR because of adequate evidence of equal to better SVR and fewer side effects?

   CTAF Panel Vote: 14 yes 1 no

   Comment: The CTAF Panel member who voted no stated that there were too many uncertainties remaining about the comparative effectiveness of these drug regimens because the evidence base is composed largely of uncontrolled studies using surrogate endpoints.

   a. *If yes, what is the comparative value of SMV + PR vs. TEL + PR?*

      CTAF Panel Vote: 8 low 3 comparable 3 high

      Comment: One of the CTAF Panel members who voted high value said that the model results indicating that simeprevir would cost less than telaprevir at one year were persuasive, and that there were even more savings when a longer time frame was considered. One of the CTAF Panel members who voted low value stated that interferon was still a required part of treatment for simeprevir, and as a result, a number of patients would not complete treatment, thereby diminishing its comparative value.

b. *If yes, what is the comparative value of SOF + PR vs. TEL + PR?*
CTAF Panel Vote: 11 low 1 comparable 2 high
Comment: The same value considerations came into play for the voting on sofosbuvir, emphasizing its high upfront costs.

2. Do you agree that the evidence is inadequate to distinguish between the clinical effectiveness of SOF + PR and SMV + PR?
CTAF Panel Vote: 15 yes

II. Genotype 1: treatment-naïve, interferon ineligible

3. Do you agree that SOF + R is superior to no treatment?
CTAF Panel Vote: 12 yes 3 no
Comment: It was noted prior to the vote that patients who are interferon ineligible currently have no other FDA-approved options. One of the CTAF Panel members who voted no justified the vote by noting that there were only two small studies and no controlled trials in this population.

a. *If yes, what is the comparative value of SOF + R vs. no treatment?*
CTAF Panel Vote: 10 low 2 reasonable

4. Is the evidence adequate to demonstrate that SOF + SMV + R is superior to no treatment?
CTAF Panel Vote: 8 yes 7 no
Comment: One CTAF Panel member justified voting yes by highlighting the excellent outcomes in the COSMOS trial among "treatment-experienced" patients. If these data are extrapolated to treatment-naïve patients, results should be even better. One of the CTAF Panel members who voted no expressed concerns about the very small sample size of the COSMOS trial and the lack of long-term outcomes, leaving this Panel member hesitant to give full credence to a limited evidence base given the large size of the patient population that could be treated with this regimen.

a. *If yes, what is the comparative value of SOF + SMV + R vs. no treatment?*
CTAF Panel Vote: 6 low 2 reasonable

5. Is the evidence adequate to demonstrate that SOF + SMV + R is equivalent or superior to SOF + R?
CTAF Panel Vote: 6 yes 9 no

III. Genotype 1: treatment-experienced, interferon eligible

6. Do you agree that SMV + PR is superior to TEL + PR because of adequate evidence of equivalent SVR and fewer side effects?
   CTAF Panel Vote: 13 yes 2 no

   a. *If yes, what is the comparative value of SMV + PR vs. TEL + PR?*
      CTAF Panel Vote: 6 low 5 comparable 2 high
      Comment: One of the CTAF Panel members who voted high value noted the reduced side effects with simeprevir.

7. Is the evidence adequate to demonstrate that SOF + PR is superior to TEL + PR?
   CTAF Panel Vote: 11 yes 4 no

   a. *If yes, what is the comparative value of SOF + PR vs. TEL + PR?*
      CTAF Panel Vote: 7 low 2 comparable 2 high

8. Is the evidence adequate to demonstrate that SOF + SMV + R is superior to TEL + PR?
   CTAF Panel Vote: 10 yes 5 no

   a. *If yes, what is the comparative value of SOF + SMV + R vs. TEL + PR?*
      CTAF Panel Vote: 6 low 4 comparable

9. Is the evidence adequate to demonstrate that SOF + SMV + R is superior to SMV + PR?
   CTAF Panel Vote: 8 yes 7 no

   a. *If yes, what is the comparative value of SOF + SMV + R vs. SMV + PR?*
      CTAF Panel Vote: 5 low 3 comparable

IV. Genotype 1: treatment-experienced, interferon ineligible

10. Is the evidence adequate to demonstrate that SOF + R is superior to no treatment?
    CTAF Panel Vote: 10 yes 5 no

    a. *If yes, what is the comparative value of SOF + R vs. no treatment?*
       CTAF Panel Vote: 7 low 3 reasonable

11. Is the evidence adequate to demonstrate that SOF + SMV + R is superior to no treatment?
    CTAF Panel Vote: 11 yes 4 no

    a. *If yes, what is the comparative value of SOF + SMV + R vs. no treatment?*
       CTAF Panel Vote: 6 low 3 reasonable 2 high

12. Is the evidence adequate to demonstrate that SOF + SMV + R is superior to SOF + R?
    CTAF Panel Vote: 7 yes 8 no

V. Genotype 2, treatment-naïve or treatment-experienced

13. Do you agree that SOF + R is superior to PR for interferon eligible patients and that SOF + R is superior to no treatment for interferon ineligible patients?
    CTAF Panel Vote: 14 yes 1 no

    a. *If yes, what is the comparative value of SOF + R vs. PR for interferon eligible patients?*
       CTAF Panel Vote: 6 low 8 comparable

    b. *If yes, what is the comparative value of SOF + R vs. no treatment for interferon ineligible patients?*
       CTAF Panel Vote: 3 low 11 reasonable
       Comment: The shift in value votes toward more "reasonable" votes for sofosbuvir treatment of patients with genotype 2 infections was accompanied by comments noting that the evidence base for this genotype included more patients and the only controlled trial for sofosbuvir. This added strength of evidence on clinical effectiveness, paired with the lack of first-generation anti-viral options, was described as influential in Panel votes.

VI. Genotype 3, treatment-naïve or treatment-experienced

14. Do you agree that SOF + R is superior to PR for interferon eligible patients and that SOF + R is superior to no treatment for interferon ineligible patients?
    CTAF Panel Vote: 15 yes

    a. *If yes, what is the comparative value of SOF + R vs. PR for interferon eligible patients?*
       CTAF Panel Vote: 7 low 8 comparable

    b. *If yes, what is the comparative value of SOF + R vs. no treatment for interferon ineligible patients?*
       CTAF Panel Vote: 7 low 8 reasonable

CTAF Panel members who voted that the evidence was inadequate to demonstrate comparative clinical effectiveness were asked to abstain from voting on the comparative value questions. Some CTAF Panel members mentioned that this resulted in more positive assessments of value than if these panelists had also been asked to vote, since their votes would have likely been for "low" value on the basis of inadequate evidence of comparative clinical effectiveness.

8.2 Roundtable Discussion and Key Policy Implications

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, a patient advocate, payer representatives, and a representative from a manufacturer of one of the new agents. The names of the participants on the Policy Roundtable are shown below.

- Sylvia Carlisle, MD, MBA, Managing Medical Director, Anthem Blue Cross
- Ryan Clary, Executive Director, National Viral Hepatitis Roundtable
- Rena K. Fox, MD, Professor of Clinical Medicine, Division of General Internal Medicine, UCSF
- R. Todd Frederick, MD, Transplant Hepatologist and Fellowship Director of Transplant Hepatology, Department of Transplantation, Division of Hepatology, California Pacific Medical Center
- Amandeep Sahota, MD, MS, Transplant Hepatologist and Southern California Permanente Medical Group Regional Hepatitis C Champion, Kaiser Permanente
- Robert Snediker, Principal Liaison, HECOR, Janssen Pharmaceuticals, Inc.
- John Yao, MD, MBA, MPH, Senior Medical Director, Blue Shield of California

The roundtable discussion explored the implications of CTAF Panel votes for clinical practice and medical policy, considered real life issues critical for developing best practice recommendations in this area, and identified potential avenues for applying the evidence to improve patient care within a value context. The main themes and recommendations from the discussion are summarized below.

1) *Despite having voted that the evidence is adequate to demonstrate the superior clinical effectiveness of the new drugs in most patient subpopulations, the CTAF Panel emphasized in discussion that serious limitations in the evidence base remain.*

During the voting process and the ensuing roundtable discussion, the CTAF Panel noted that their judgments of clinical superiority were influenced strongly by the lower side effect profile of the new drugs, especially when regimens do not include interferon, and upon the relatively consistent large magnitude of difference in SVR between the new drugs and prior treatment options. Several CTAF Panel members expressed strong opinions, however, that small, uncontrolled trials should not be the standard to which new treatments in this clinical area should be held going forward. The evidence was noted as being particularly limited for genotype 1, treatment-experienced patients, and for all genotype 3 patients. The CTAF Panel found the indirect comparisons made through the network meta-analysis quite helpful, but they said that direct head-to-head trials or analyses of observational real-world data should be performed to buttress our understanding of the comparative clinical effectiveness of these drug regimens, particularly since new drug combination options are likely to be introduced over the next 1-2 years. Further research to evaluate the

relationship of short-term SVR outcomes to longer-term patient-centered outcomes of liver-related complications, mortality, and quality of life is also needed.

2) *For most patient subpopulations, the CTAF Panel found the new drug treatments for hepatitis C to represent a "low value" due to the magnitude of the potential impact on health care budgets of treating large numbers of patients with these high-priced drug regimens.*

A consistent consensus was expressed by CTAF Panel members that the new drug treatments for hepatitis C represented a low value from the perspective of a state Medicaid program. A majority continued to judge these drugs as low value across multiple patient subpopulations, even those for which the evidence was deemed adequate to demonstrate clinical superiority to previous options. Only for the smaller populations of patients infected with genotypes 2 and 3 were the votes more split between "low" and "reasonable/comparable" value. For none of the patient subpopulations did a majority of the CTAF Panel vote that the new drug regimens were a "high value."
Among those CTAF Panel members voting for "low value", there was a mix of those who: a) indicated that they judged the evidence on comparative clinical effectiveness to be promising but inconclusive, while costs were higher, and b) those who voted for low value because they felt the evidence demonstrated superior outcomes but at too high a cost. Discussion of the information provided in the report on costs suggested that the CTAF Panel did not consider the additional cost per SVR, a measure of cost-effectiveness, to be as influential in their thinking as was the information on the potential budget impact of new drug regimens. The substantial budget impact figures raised concerns among the Panel about the opportunity cost of the new drugs in the current health care system, as well as concerns about the potential impact on overall health care insurance premiums across the entire insured population.

3) *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.*

Very large numbers of patients could potentially benefit from receiving the new drugs for hepatitis C. However, the prices of the new drugs, highlighted by sofosbuvir's price of $1,000/pill and $84,000 per 12 weeks of treatment, when multiplied by the number of eligible patients, create a financial burden that was considered by the CTAF Panel and several of the Policy Roundtable participants to be untenable. Although mechanisms to lower prices were not a specific focus of the conversation, several of the Policy Roundtable participants expressed that without reductions in price, the only options for the health care system involved prioritizing (i.e., limiting the number of) patients considered for treatment. There was some discussion of the possibility that additional treatment options expected to be available within the next 1-2 years might create market

competition that would lower the price of the current set of new drugs or equally effective options, but some skepticism was also voiced that competition would achieve this goal. Alternative policy mechanisms that have been used in other drug classes include payer contracts that vary the price by subpopulation (i.e., higher prices to treat some patient subpopulations and lower prices for others); risk-sharing contracts in which manufacturers rebate the price paid for patients who do not achieve the desired clinical outcome; reference pricing that involves setting the price for a new treatment at the lowest "reference" price paid for any existing treatment with equivalent effectiveness (note, for example, that the CTAF Panel voted that the evidence cannot distinguish between the effectiveness of simeprevir and sofosbuvir for treatment-experienced patients with genotype 1); and price setting to some external standard, such as the cost per quality-adjusted life year gained. Although these mechanisms were not discussed during the CTAF meeting, the price of the new drug regimens was frequently mentioned as the primary policy issue driving the concerns around their coverage by insurers and their use by clinicians.

4) *In recognition of limitations of the clinical infrastructure for initiating treatment among a very large patient population, patients, physicians, and payers should work together to encourage informed, shared decision-making about whether patients need to initiate treatment immediately or whether they are well enough to postpone treatment.*

During the discussion, several members of the CTAF Panel referenced the information presented earlier in the meeting showing that most patients with chronic hepatitis C infection do not progress to severe liver dysfunction over the course of their lifetimes. While noting that overt symptoms of liver dysfunction are not an appropriate way to monitor for the onset of liver damage, the clinical experts on the Policy Roundtable commented that many patients with hepatitis C, especially those diagnosed through broad screening efforts, will not need immediate treatment, although they should be evaluated thoroughly and monitored closely to assess for worsening liver function. It was acknowledged that the idea of postponing treatment would not come naturally to many patients, but that it was not unreasonable given the current limited number of clinicians with significant experience caring for patients undergoing treatment for hepatitis C, the promise of additional options for interferon-free regimens in the near future, and the uncertain balance of risks and benefits of immediate treatment for patients who show no current signs of liver dysfunction. All Policy Roundtable participants stressed the importance of shared decision-making between an informed patient and clinician as the appropriate goal for considerations of whether to initiate or postpone treatment. Educational resources for patients (and clinicians) are needed that can support a full dialogue based on an objective view of the evidence and full appreciation for the individual patient values surrounding the potential risks and benefits of the various treatment options.

5) *Given the limited number of experienced treating clinicians, the balance of risks and benefits for immediate treatment of patients without significant liver damage, and the financial impact of current high prices, it is reasonable to consider prioritization of treatment by level of liver fibrosis.*

The clinical experts on the Policy Roundtable suggested, and the CTAF Panel agreed, that treating all eligible patients 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 for payers and provider groups to consider prioritizing treatment with the new drugs for patients who have some evidence of liver fibrosis but do not have advanced liver disease (decompensation). The clinical experts on the Policy Roundtable indicated that patients with advanced fibrosis and cirrhosis (METAVIR scores of F3-F4), those who have liver cancer and are awaiting transplant, and those who are post-liver transplant have the greatest chance of benefiting from immediate treatment. It was also noted that the analyses developed for the CTAF report suggested that immediate treatment of only these patient subpopulations would moderate the short-term financial impact on the health care system while offering greater likelihood of long-term clinical benefits and cost-offsets from reduced cases of liver failure.

6) *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 developing prior authorization criteria that a) require patient commitment to and compliance with the treatment regimen, b) utilize "futility rules" that define when a lack of early response should lead to discontinuation of treatment, and c) require that prescriptions of simeprevir and sofosbuvir be written by specialist physicians with experience treating patients with hepatitis C.*

In a discussion about prior authorization criteria, it was noted that the new drugs have fewer side effects and that greater patient compliance is expected. 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, it was suggested that coverage be contingent upon a documented patient commitment to the planned course of treatment, including anticipated blood tests and office visits during and after treatment.

Given that good adherence to the new drugs is extremely likely to result in dramatic reductions in viral load within the first four weeks of treatment if the treatment is going to work at all, another prior authorization option would be to develop "futility rules" that require a check on viral load at 4 weeks and that would lead to cessation of coverage for further pills should the results show inadequate response.

Also discussed during the roundtable was the idea that, at least in the short term, it may make clinical and financial sense to limit prescribing of the new drugs to experienced hepatitis C experts. These clinicians have the knowledge to engage in shared decision-making over initiating treatment; they know well the side effects and adherence issues that are critical components of successful treatment; and they know how to monitor and care for patients who are on regimens combined with interferon and ribavirin. Over time, and with the introduction of more all-oral drug regimens, the care of patients with hepatitis C may be shared on a growing basis with primary care clinicians, but for the short-term it seems wise to consider limiting prescription of the newest drugs to specialists. Provider groups should start working now, however, on mechanisms to coordinate the care between primary care and specialty care, including guidelines for primary care clinicians on the tests that should be ordered at the time a patient is first diagnosed with hepatitis C infection.

Among the approaches that payers may take as part of prior authorization, the Policy Roundtable participants did not support "fail-first" policies that would require patients to try and fail to achieve SVR with one of the first generation anti-viral treatments or interferon and ribavirin alone before receiving coverage for sofosbuvir or simeprevir. Comments made regarding fail-first approaches suggested that the side effect profiles and relative effectiveness of previous treatment options were viewed as so inferior to the newer drugs that a fail-first approach would itself fail to find support within the clinical community.

7) *Although there is very little evidence regarding the off-label use of simeprevir and sofosbuvir in combination to treat interferon-ineligible genotype 1 patients, payers may wish to consider covering these drugs on a limited basis for certain patients needing immediate treatment.*

The CTAF Panel's votes on the comparative clinical effectiveness of the off-label use of 12 weeks of simeprevir and sofosbuvir were divided. A slight majority of the CTAF Panel (8 members) voted that the evidence was adequate to demonstrate that this combination was more effective than no treatment at all for genotype 1 patients who were ineligible for interferon and therefore left with no treatment option before the advent of the new drugs, but only six members of the CTAF Panel voted that the evidence was adequate to show that the off-label combination was better than 24 weeks of sofosbuvir plus ribavirin. Even when compared with no treatment, however, the CTAF Panel rated sofosbuvir plus simeprevir as "low value" on the basis of its potential budget impact. During the discussion, the clinical experts on the Policy Roundtable indicated that for certain select patients who are truly ineligible for interferon and who are also felt to require immediate treatment, it may make sense to consider using sofosbuvir plus simeprevir since it can be used for only 12 weeks instead of 24 for sofosbuvir alone, and is thus likely to be more effective and less expensive.

8) *Specialty society clinical guidelines should be developed using best practices, including ratings of strength of evidence, transparency regarding the role of various organizations involved in guideline development, and full transparency regarding potential conflicts of interest of individual guideline committee members, with limits on the proportion of committee members who receive direct or indirect financial support from manufacturers.*

The Policy Roundtable noted the important role in informing patients and clinicians served by the clinical guidelines for the treatment of hepatitis C developed by the American Association for the Study of Liver Diseases (AASLD), the Infectious Disease Society of America (IDSA), and the International Anti-Viral Society-USA. This coordinated effort has produced online guidelines that recommend use of the new drugs either alone or in combination as the first choice for all subtypes of hepatitis C. It was noted that these guidelines do not attempt to address which patients should (or should not) be treated; nor do the guidelines include consideration of the costs of different treatment options. A concern was raised regarding the difficulty in ascertaining the degree of drug industry support for the organizations involved in guideline development, and concern was also expressed that well over half of individual guideline committee members, including the committee chairmen, had either direct (e.g., consulting) and/or indirect support (for research) from the manufacturers of the new hepatitis C drugs. The CTAF Panel agreed that the process for creating clinical guidelines should be as transparent and conflict-free as possible, especially given how consequential the specialty society guidelines are likely to be. This will allow patients, providers, and other stakeholders to fully trust in the objectiveness and trustworthiness of key clinical guidelines.

9) *Further evidence should be generated to evaluate more fully the comparative clinical effectiveness and value of these new treatment regimens for patients with hepatitis C.*

As noted above, the CTAF Panel discussed the limited evidence available (single arm, open-label, non-randomized studies with small numbers of patients) to assess the comparative clinical effectiveness of the new treatments for hepatitis C. The CTAF Panel stated that more robust studies are needed moving forward, both for the current FDA-approved drugs and for subsequent additions to the range of therapeutic options. During the discussion it was suggested that manufacturers consider engaging with payers and independent review organizations to discuss evidence standards at the same time they are generating evidence for review by the FDA. It was also recommended that payers implement policies to support evidence generation – e.g., provide coverage only if patients are enrolled in a practical clinical trial or an observational registry. The relative paucity of evidence for genotype 1, treatment-experienced patients and for genotype 3 patients in particular were noted as the most significant needs for further evidence at this time.

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APPENDIX

Search Strategies

PubMed (NLM), run date 1/8/14

(sofosbuvir OR simeprevir) AND (randomized controlled trial[pt] OR randomized controlled trials[mh] OR controlled clinical trial[pt] OR controlled clinical trials as topic[mh] OR placebo[tiab] OR drug therapy[sh] OR random*[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]) NOT news[pt]
59 refs (trials)

(sofosbuvir OR simeprevir) AND (systematic[sb] OR meta-analysis[pt] OR systematic[tiab] OR meta-anal*[tiab] OR metaanal*[tiab] OR guideline*) NOT (animals[mh] NOT humans[mh]) NOT news[pt]
4 refs (systematic reviews/guidelines)

Embase (Elsevier), run date 1/8/14

139 (trials)

#2 sofosbuvir OR simeprevir AND ('controlled study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'controlled clinical trial (topic)'/de OR 'controlled clinical trial'/de) OR ('hepatitis c' AND (sofosbuvir OR simeprevir) AND (placebo:ab,ti OR random*:ab,ti OR trial:ab,ti OR groups:ab,ti)) NOT ([animals]/lim NOT [humans]/lim)

23 (systematic reviews/guidelines)

#1 sofosbuvir OR simeprevir AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim OR systematic:ab,ti OR 'meta-analysis' OR metaanaly* OR 'practice guideline') NOT ([animals]/lim NOT [humans]/lim)

The Cochrane Library (Wiley), run date 1/8/14

sofosbuvir or simeprevir (Word variations have been searched)

All Results (10): ☐ Cochrane Reviews (0) ☉ All ☐ Review ☐ Protocol ☐ Other Reviews (0) ☉ **Trials (6)** ☐ Methods Studies (0) ☐ **Technology Assessments (4)** ☐ Economic Evaluations (0) ☐ Cochrane Groups (0)

Cochrane Database of Systematic Reviews: Issue 1 of 12, January 2014
Cochrane Central Register of Controlled Trials (Central): Issue 12 of 12, Dec 2013
Other Reviews (DARE) **Issue 4 of 4, Oct 2013**
Methods Studies **Issue 3 of 4, Jul 2012**
Technology Assessments **Issue 4 of 4 Oct 2013**
Economic Evaluations
Cochrane Groups **Issue 12 of 12, Dec 2013**

BIOSIS Previews & Web of Science (Thomson Reuters), run date 1/8/14; search for meeting abstracts

Final count: 31 from WOS; 18 from BIOSIS = **49 meeting abstracts** (duplicates removed)

BIOSIS Previews

Set	Results	
# 2	41	Topic=(sofosbuvir OR simeprevir) Refined by: Document Types=(MEETING) Databases=BIOSIS Previews Timespan=All years
# 1	67	Topic=(sofosbuvir OR simeprevir) Databases=BIOSIS Previews Timespan=All years

WOS

Set	Results	
# 2	33	Topic=(sofosbuvir OR simeprevir) Refined by: Document Types=(MEETING ABSTRACT) Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=All years
# 1	76	Topic=(sofosbuvir OR simeprevir) Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=All years

Trip Database (http://www.tripdatabase.com/), run date 1/8/14

sofosbuvir OR simeprevir
43 refs

8 Evidence-based Synopses
4 Systematic Reviews
1 Guidelines
5 Key Primary Research
12 Controlled Trials
16 Extended Primary Research

Trip is a clinical search engine designed to allow users to quickly and easily find and use high-quality research evidence to support their practice and/or care.

Table A1. Clinical and Economic Impact of Treatment Options Among 1,000 60 Year-old Patients with Hepatitis C Genotype 1 Who Are New to Treatment (Treatment-naïve) and Have No-To-Mild Liver Disease Only.

	Evidence Review Data					*Modeled 1-Year Drug Costs*		*Modeled Long-Term Effects of Achieving SVR*			
Population/regimen	**SVR per 1000**	**NNT for 1 add'l SVR**	**Discontinued due to AE (per 1000)**	**Cost for initial Rx (per patient)**	**Cost per add'l SVR**	**Total Drug Costs (per 1000)**	**Incremental (vs. pre-DAA)**	**Liver Events Averted (per 1000)** 5 years	20 years	**Total Estimated Cost Offset (per 1000, vs. pre-DAA)** 5 years	20 years
IFN-eligible											
TEL + PR (12/24) (pre-DAA)*	740	---	140	$83,976	---	$107,712,960	---	---	---	---	---
SMV + PR (12/24)*	840	10	64	$91,296	$73,000	$105,903,360	($1,810,000)	(2)	(10)	($2,106,000)	($6,800,000)
SOF + PR (12)*	830	11	55	$96,468	$139,000	$111,988,320	$4,275,000	(2)	(9)	($1,895,000)	($6,120,000)
IFN-ineligible											
No Rx (pre-DAA)	0	---	0	$0	---	$0	---	---	---	---	---
SOF + R (24)†	720	1	13	$176,352	$245,000	$219,622,080	$219,622,000	(17)	(70)	($15,160,000)	($48,960,000)
SOF + SMV + R (12)‡	900	1	50	$154,536	$172,000	$169,989,600	$169,990,000	(22)	(87)	($18,950,000)	($61,200,000)

*ICER network meta-analysis

†Pooled data from PHOTON-1 and QUANTUM

‡Pooled data from COSMOS treatment arms

Total drug costs Include initial therapy and retreatment with most effective regimen available for those not achieving SVR initially

Total estimated cost offset includes cost savings from liver events averted and reduced annual costs from greater numbers of patients achieving SVR

SVR: sustained virologic response; NNT: number needed to treat; DAA: direct-acting antivirals

Table A2. Clinical and Economic Impact of Treatment Options Among 1,000 60 Year-old Patients with Hepatitis C Genotype 1 Who Are New to Treatment (Treatment-naïve) and Have Advanced Liver Disease Only.

	Evidence Review Data					*Modeled 1-Year Drug Costs*		*Modeled Long-Term Effects of Achieving SVR*			
Population/regimen	**SVR per 1000**	**NNT for 1 add'l SVR**	**Discontinued due to AE (per 1000)**	**Cost for initial Rx (per patient)**	**Cost per add'l SVR**	**Total Drug Costs (per 1000)**	**Incremental (vs. pre-DAA)**	**Liver Events Averted (per 1000)** 5 years	20 years	**Total Estimated Cost Offset (per 1000, vs. pre-DAA)** 5 years	20 years
IFN-eligible											
TEL + PR (12/24) (pre-DAA)*	740	---	140	$83,976	---	$107,712,960	---	---	---	---	---
SMV + PR (12/24)*	840	10	64	$91,296	$73,000	$105,903,360	($1,810,000)	(10)	(38)	($2,975,000)	($9,608,000)
SOF + PR (12)*	830	11	55	$96,468	$139,000	$111,988,320	$4,275,000	(9)	(35)	($2,677,000)	($8,647,000)
IFN-ineligible											
No Rx (pre-DAA)	0	---	0	$0	---	$0	---	---	---	---	---
SOF + R (24)†	720	1	13	$176,352	$245,000	$219,622,080	$219,622,000	(69)	(276)	($21,420,000)	($69,174,000)
SOF + SMV + R (12)‡	900	1	50	$154,536	$172,000	$169,989,600	$169,990,000	(86)	(346)	($26,774,000)	($86,468,000)

*ICER network meta-analysis

†Pooled data from PHOTON-1 and QUANTUM

‡Pooled data from COSMOS treatment arms

Total drug costs Include initial therapy and retreatment with most effective regimen available for those not achieving SVR initially

Total estimated cost offset includes cost savings from liver events averted and reduced annual costs from greater numbers of patients achieving SVR

SVR: sustained virologic response; NNT: number needed to treat; DAA: direct-acting antivirals

Figure A1. Total Budgetary Impact and Potential Cost Offsets from Use of Newer Drug Regimens in the Chronic Hepatitis C Population in California: 25% of infected Patients Are Treated (n=135,263).

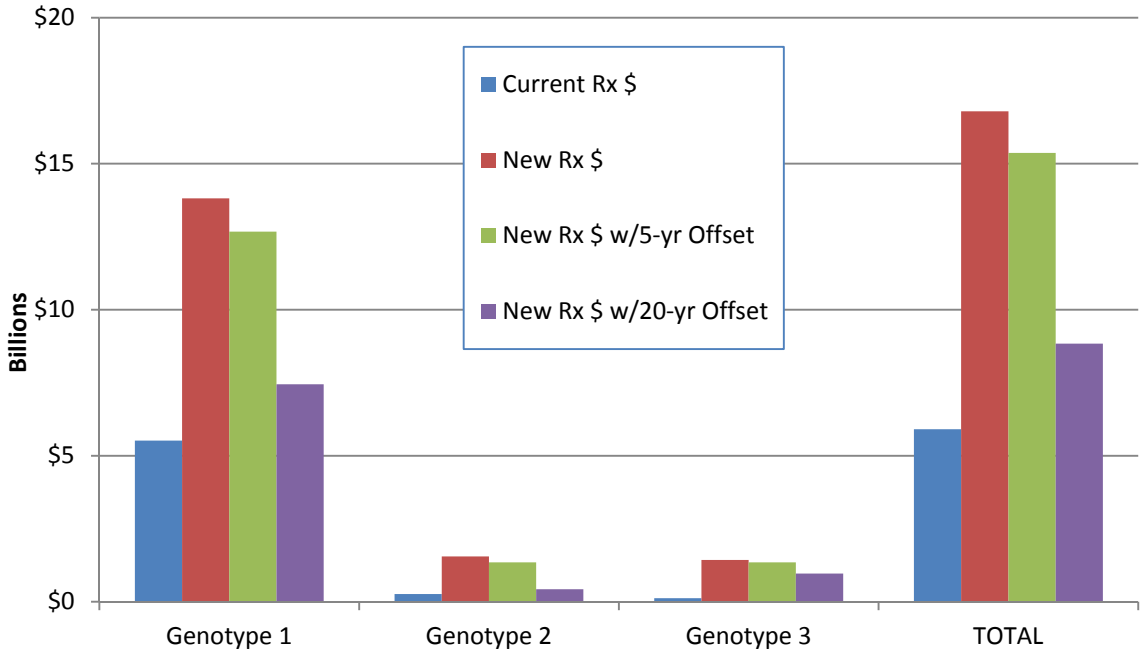
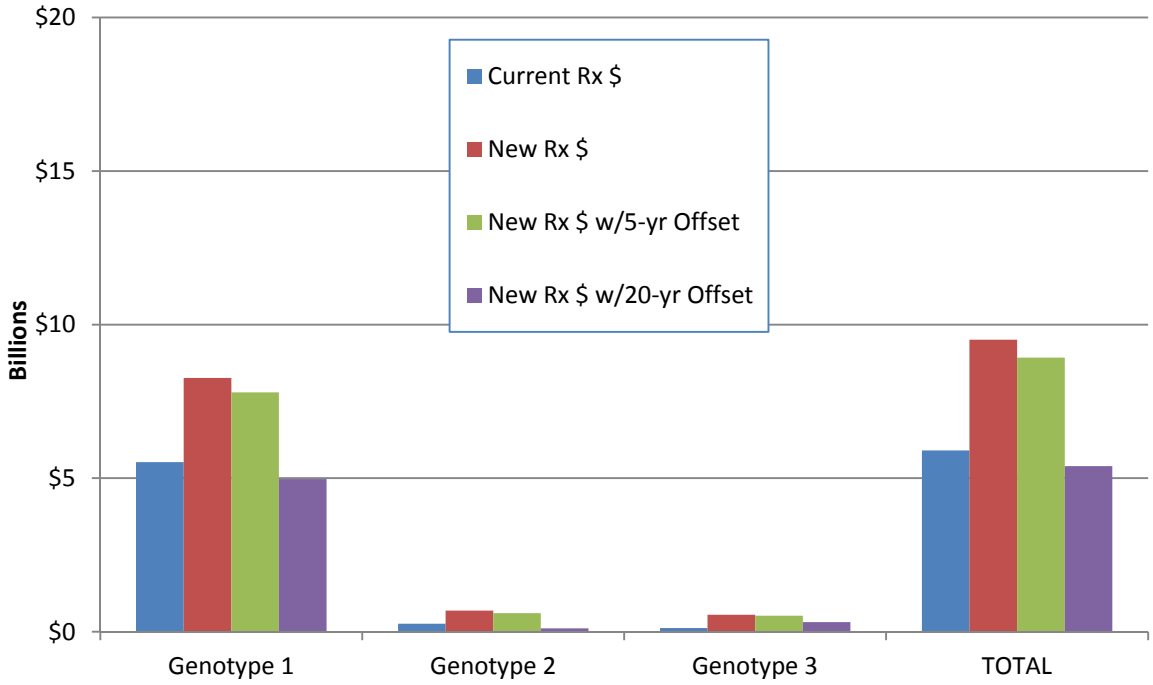


Figure A2. Total Budgetary Impact and Potential Cost Offsets from Use of Newer Drug Regimens in the Chronic Hepatitis C Population with Advanced Fibrosis in California: 25% of Infected Patients Are Treated (n=44,772).



AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AASLD

IDSA

Infectious Diseases Society of America

Recommendations for Testing, Managing, and Treating Hepatitis C

Collaborating Partner

IAS–USA

International Antiviral Society–USA

TABLE OF CONTENTS

INTRODUCTION

The landscape of treatment for hepatitis C virus (HCV) infection has evolved substantially since the introduction of highly effective HCV protease inhibitor therapies in 2011. The pace of change is expected to increase rapidly, as numerous new drugs with different mechanisms of action will likely become available over the next few years. To provide healthcare professionals with timely guidance as new therapies are available and integrated into HCV regimens, the Infectious Diseases Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management. The International Antiviral Society–USA (IAS–USA) provides the structure and assistance to sustain the process that represents the work of leading authorities in hepatitis C prevention, diagnosis, and treatment.

The AASLD/IDSA hepatitis C Guidance addresses management issues ranging from testing and linkage to care, the crucial first steps toward improving health outcomes for HCV-infected persons, to the optimal treatment regimen in particular patient situations. Recommendations are based on evidence and are rapidly updated as new data from peer-reviewed evidence become available. For each treatment option, recommendations reflect the best possible management for a given patient and a given point of disease progression. Recommendations are graded with regard to the level of the evidence and strength of the recommendation. The AASLD/IDSA hepatitis C Guidance is supported by the membership-based societies and not by pharmaceutical companies or other commercial interests. The Boards of Directors of AASLD and IDSA have appointed an oversight panel of 5 co-chairs and have selected panel members from the 2 societies based on their expertise in hepatitis C research and care. Likewise, the Guidance development process is generally consistent with that used by the IAS–USA (https://www.iasusa.org/about/program-development-policy).

This Guidance should be considered a "living document" in that new sections will be added (eg, Who and When to Initiate Treatment, and Monitoring Patients Who are On or Have Completed Therapy are coming soon) and the Guidance will be updated frequently as new information and treatments become available. This continually evolving report provides guidance on FDA-approved regimens. At times, it may also recommend off-label use of certain drugs or tests or provide guidance for regimens not yet approved by FDA. Readers should consult prescribing information and other resources for further information. Of note, the choice of treatment may, in the future, be further guided by data from cost-effectiveness studies.

METHODS

The Guidance was developed by a panel of HCV experts in the fields of hepatology and infectious diseases, using an evidence-based review of information that is largely available to healthcare practitioners. The process and detailed methods for developing the Guidance are detailed in Methods Table 1. Recommendations were graded according to the strength of the recommendation and quality of the supporting evidence (see Methods Table 2). Commonly used abbreviations are expanded in Methods Table 3.

Methods Table 1. Summary of the Process and Methods for the Guidance Development

Topic	Description
Statement of Need	The introduction of direct-acting agents against HCV in 2011 has rapidly changed the treatment of HCV and the timely diagnosis of infection remains essential. This ever increasing pace of change anticipates numerous additional therapies in the next few years, requiring timely guidance on how each new development changes practice for health care professionals.
Goal of the Guidance	The goal of the Guidance is to provide up-to-date recommendations to health care practitioners on the optimal screening, management, and treatment for adults with HCV infection in the United States, considering the best available evidence. The Guidance will be updated regularly, as new data, information, and tools and treatments become available. The initial recommendations address 4 areas of priority: screening, testing, and linkage to care; initial treatment regimens in persons for whom the decision to treat has been made; retreatment regimens and considerations for persons for whom the decision to treat has been made; and treatment in unique patient populations.
Panel members	The Panel members were chosen because of their expertise in the diagnosis, management, and treatment of HCV infection in terms of research and patient care. Members from the fields of hepatology and infectious diseases are included. Members were appointed by the respective Sponsor Societies after vetting by an appointed Sponsor Society committee. At least 1 representative from the hepatitis C community serves on the Panel. The Panel chairs were appointed by the Society boards, 2 each from the Sponsor Societies and 1 representing the Collaborating Partner. All Panel chairs and members serve as volunteers (not compensated) for defined terms (3 years), which may be renewed.
Conflict of interest management	Financial conflict of interest statements, with regard to personal (ie, direct payment to the individual) and institutional financial relationships with commercial entities that have products in the field of hepatitis C, for the prior year of all chairs and members under consideration were reviewed by the Sponsor Societies and Collaborating Partner during the vetting processes. Panel members under consideration were given the opportunity to divest or begin divesting themselves of any nonconforming personal conflicts of interest before being confirmed to the Panel. The Panel is composed of members with personal financial relationships with commercial entities and those with no such personal financial relationships with commercial entities at the time that each Panel member was confirmed. Designation of financial interest was determined based on each Sponsor Society's criteria (eg, limits on annual compensation from any particular commercial entity, absence of employment with a commercial entity, absence of equity or options in the relevant commercial entity, absence of service on company speakers' bureaus and company paid lectureships). More details on the management of conflicts of interest can be found on the organizations' websites. At the first in-person meeting of the full Panel, each chair and member read his or her disclosure statement to the group; members are given the opportunity to recuse themselves (or be recused) from particular topic areas where there is a perceived conflict of interest that cannot be resolved. Panel member direct personal and institutional/general research financial disclosure information was provided at the beginning of this project (October 2013). Financial disclosures for each individual Panel member can be accessed from the Panel members' pages.
Intended Audience	Medical practitioners especially those who provide care to or manage patients with hepatitis C.
Sponsors, funding, and collaborating partner	The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) are the Sponsors of the Guidance and provide financial support. The International Antiviral Society–USA (IAS–USA) is the Collaborating Partner responsible for providing expertise and managing the Panel and the Guidance development process. Centers for Disease Control and Prevention (CDC) provided financial support for the gathering and review of evidence related to hepatitis C screening and testing recommendations and interventions to implement HCV screening in clinical settings.

Evidence identification and collection	The Guidance was developed using an evidence-based review of information that is largely available to health care practitioners. Data from the following sources are considered by Panel members when making recommendations: research published in the peer-reviewed literature or presented at major national or international scientific conferences, safety warnings from FDA or other regulatory agencies or from manufacturers, drug interaction data, prescribing information from FDA-approved products, and registration data for new products under FDA review. Unpublished or presented reports, data on file, and personal communications are generally not considered. Panel members were appointed based on their collective broad knowledge of available data and current research in the field. These experts were responsible for initially identifying and discussing relevant data, including recent reports from scientific conferences. An initial literature search was conducted on November 4, 2013, to ensure that the Panel addressed all relevant published data. A total of 3939 unique citations were retrieved. Medical subject headings and free text terms were combined to maximize retrieval of relevant citations from the PubMed, Scopus, EMBASE, and Web of Science databases. To be considered for inclusion, articles were required to have been published in English from 2010 to the present. Review articles, studies using mice or rats, and in vitro studies were excluded from consideration. The Panel members regularly monitor the field for new evidence, and the literature search is updated as needed.
Grading of the evidence and RECOMMENDATIONS	The Guidance is presented in the form of RECOMMENDATIONS. Each RECOMMENDATION is graded in terms of the level of the evidence and strength of the recommendation, using a scale adapted from the American College of Cardiology and the American Heart Association Practice Guidelines. (American Heart Association, 2014); (Shiffman, 2003) A summary of the supporting (and conflicting) evidence follows each RECOMMENDATION or set of RECOMMENDATIONS.
Data review and synthesis and preparation of RECOMMENDATIONS and supporting information	The Guidance was initially divided into 3 subsections: 1) Testing and Linkage to Care; 2) Choice of Regimen in Treatment-Naive Patients For Whom the Decision to Treat Has Been Made, and 3) Retreatment for Patients in Whom the decision to treat has been made. It was later decided to make treatment for unique patient populations a separate section. Subgroups of the panel were assigned to collect, review, and prepare initial draft RECOMMENDATIONS. Draft RECOMMENDATIONS were reviewed at the first full Panel meeting in October 2013. Subgroups of the Panel then met regularly by conference call and presented their updated RECOMMENDATIONS and supporting evidence at each of 3 full-Panel conference calls. Final approval of all RECOMMENDATIONS was made by full-Panel, general consensus. Initial recommendations and their grades were individually subject to Panel survey; panelists were given the opportunity to agree, disagree, and provide comment. This procedure helped identify any disagreement or inconsistency between Panel members for each recommendation. Sponsor Societies have final review and approval of each recommendation prior to release of the Guidance on the website, www.hcvguidelines.org.
Update Process	The Guidance will be expanded to cover more management issues as needed, and will be updated on an ongoing basis. Panel members will regularly monitor the field for data that may warrant modification of the Guidance. Updates may be prompted by new publications or presentations at major national or international scientific conferences, new drug approvals (or new indications, dosing formulations, or frequency of dosing), new safety warnings, or other information that may have a substantial impact on the clinical care of patients. Updated RECOMMENDATIONS and ratings, once agreed on by the full Panel and approved by the Sponsor Societies, are posted on the Guidance website.
Abbreviations	Commonly used abbreviations in the text with their expansions are listed in Methods Table 3.
Opportunity for Comments	Evidence-based comments may be submitted to the Panel by email hcvguidelines@iasusa.org, or clicking on the “Send a comment to the Panel” button onwww.hcvguidelines.org/contact-us. The Panel considers evidence-based comments about the RECOMMENDATIONS, grades, and evidence summary, but should not be contacted for individual patient management questions.

Methods Table 2. Grading System Used to Rate the Level of the Evidence and Strength of the Recommendation for Each Recommendation

Recommendations are based on scientific evidence and expert opinion. Each recommended statement includes a Roman numeral (**I**, **II**, or **III**) that represents the level of the evidence that supports the recommendation, and a letter (**A**, **B**, or **C**) that represents the strength of the recommendation.

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence and/or opinion is in favor of usefulness and efficacy
Class IIb	Usefulness and efficacy are less well established by evidence and/or opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful
Level of Evidence	**Description**
Level A	Data derived from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Consensus opinion of experts, case studies, or standard of care

Adapted from the American College of Cardiology and the American Heart Association Practice Guidelines. (American Heart Association, 2011); (Shiffman, 2003)

Methods Table 3. Commonly Used Abbreviations and Their Expansions

Abbreviation	Expansion or Notes
HCV	hepatitis C virus. In this Guidance "hepatitis C virus" and HCV refer to the virus. Hepatitis C and HCV infection or HCV disease refer to the resulting disease.
BOC	boceprevir
CrCl	creatinine clearance
CTP	Child Turcotte Pugh
DAA	direct-acting agent
ESRD	end-stage renal disease
IFN	interferon alfa
MELD	model for end-stage liver disease
MSM	men who have sex with men
OATP	organic anion-transporting polypeptide
P-gp	p-glycoprotein
PEG	peginterferon alfa
RAV	resistance-associated variants
RBV	ribavirin
RGT	response-guided therapy
RVR	rapid virologic response
sAg	surface antigen
SMV	simeprevir; used for the treatment of those with genotype 1 of hepatitis C virus (HCV) who have compensated liver disease, including cirrhosis
SOF	sofosbuvir; a nucleoside analog used in combination with other drugs for the treatment of hepatitis C virus (HCV) infection
SVR12 (or 24 or 48, etc)	sustained virologic response at 12 weeks (or at 24 weeks, or at 48 weeks, etc)
TVR	telaprevir; a direct-acting agent (DAA) to treat hepatitis C

Definition of Terms

Child Turcotte Pugh (CTP) classification of the severity of cirrhosis

	Class A	Class B	Class C
Total points	5–6	7–9	10–15
Factor	**1 Point**	**2 Points**	**3 Points**
Total bilirubin (μmol/L)	<34	34–50	>50
Serum albumin (g/L)	>35	28–35	<28
Prothrombin time/international normalized ratio	<1.7	1.71–2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory)

IFN-ineligible

IFN ineligible is defined as one or more of the below:

- Intolerance to IFN
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to PEG or any of its components
- Decompensated hepatic disease
- History of depression, or clinical features consistent with depression
- A baseline neutrophil count below 1500/μL, a baseline platelet count below 90,000/μL or baseline hemoglobin below 10 g/dL
- A history of preexisting cardiac disease

Relapser

a person who has achieved an undetectable level of virus during a prior treatment course of PEG/RBV and relapsed after treatment was stopped

HCV TESTING AND LINKAGE TO CARE

A summary of recommendations for Testing and Linkage to Care is found in the box.

HCV testing is recommended at least once for persons born between 1945 and 1965.

Rating: Class I, Level B

Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.

1. *Risk behaviors*
   - Injection-drug use (current or ever, including those who injected once)
   - Intranasal illicit drug use
2. *Risk exposures*
   - Long-term hemodialysis (ever)
   - Getting a tattoo in an unregulated setting
   - Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-infected blood
   - Children born to HCV-infected women
   - Prior recipients of transfusions or organ transplants, including persons who:
     - were notified that they received blood from a donor who later tested positive for HCV infection
     - received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
     - received clotting factor concentrates produced before 1987
     - were ever incarcerated
3. *Other medical conditions*
   - HIV infection
   - Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels

Rating: Class I, Level B

Of the estimated 2.7 million to 3.9 million persons (1999 to 2008 National Health and Nutrition Examination Survey data [Armstrong, 2006]) chronically infected with HCV in the United States, 45% to 85% are unaware that they are infected. (Smith, 2012) Identification of those with active infection is the first step toward improving health outcomes among persons with HCV infection and preventing transmission. (Smith, 2012); (US Preventive Services Task Force, 2013); (Centers for Disease Control and Prevention, 1998)

HCV testing is recommended in select populations based on demography, prior exposures, high-risk behaviors, and medical conditions. Recommendations for testing are based on HCV prevalence in these populations, proven benefits of care and treatment in reducing the risk of hepatocellular carcinoma and all-cause mortality, and the potential public health benefit of reducing transmission through early treatment, viral clearance, and reduced risk behaviors. (Smith, 2012); (US Preventive Services Task Force, 2013); (Centers for Disease Control and Prevention, 1998)

HCV is primarily transmitted through percutaneous exposure to blood. Other modes of transmission include mother-to-infant and contaminated devices shared for non-injection drug use; sexual transmission also occurs but generally seems to be inefficient except among HIV-infected men who have unprotected sex with men. (Schmidt, 2014) The most important risk for HCV infection is injection-drug use, accounting for at least 60% of acute HCV infections in the United States. Health-care exposures are important sources of transmission, including the receipt of blood products before 1992 (after which routine screening of blood supply was implemented), receipt of clotting factor concentrates before 1987, long-term hemodialysis, needle-stick injuries among healthcare workers, and patient-to-patient transmission resulting from poor infection control practices. Other risk factors include having been born to an HCV-infected mother, having been incarcerated, and having received a tattoo in an unregulated setting. The importance of these risk factors might differ based on geographic location and population. (US Preventive Services Task Force, 2013); (Centers for Disease Control and Prevention, 1998). An estimated 29% of incarcerated persons in North America are anti-HCV positive, supporting the

recommendation to test this population for HCV. (Larney, 2013) Because of shared transmission modes, persons with HIV infection are at risk for HCV; sexual transmission is a particular risk for HIV-infected men who have unprotected sex with men. (Hosein, 2013); (van de Laar, 2010) Recent data also support testing in all cadaveric and living solid-organ donors because of the risk of HCV infection posed to the recipient. (Seem, 2013); (Lai, 2013)

In 2012, CDC expanded its guidelines originally issued in 1998 (Centers for Disease Control and Prevention, 1998) for risk-based HCV testing with a recommendation to offer a 1-time HCV test to all persons born between 1945 and 1965 without prior ascertainment of HCV risk-factors. This recommendation was supported by evidence demonstrating that a risk-based strategy alone failed to identify more than 50% of HCV infections in part due to patient underreporting of their risk and provider limitations in ascertaining risk-factor information. Furthermore, persons in the 1945 to 1965 birth cohort accounted for nearly three-fourths of all HCV infections, with a 5-times higher prevalence (3.25%) than other persons, reflecting a higher incidence of HCV infections in the 1970s and 1980s (peaking at 230,000 versus 15,000 in 2009). A recent retrospective review showed that 68% of persons with HCV infection would have been identified through a birth-cohort testing strategy, whereas only 27% would have been screened with the risk-based approach. (Mahajan, 2013) The cost-effectiveness of 1-time birth cohort testing is comparable to that of current risk-based screening strategies. (Smith, 2012)

CDC and the US Preventive Services Task Force (USPSTF) both recommend a 1-time HCV test in asymptomatic persons belonging to the 1945 to 1965 birth cohort and other persons based on exposures, behaviors, and conditions that increase risk for HCV infection.

Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV.

Rating: Class IIA, Level C

Evidence regarding the frequency of testing in persons at risk for ongoing exposure to HCV is lacking; therefore, clinicians should determine the periodicity of testing based on the risk of reinfection. Because of the high incidence of HCV infection among persons who inject drugs and among HIV-infected MSM who have unprotected sex (Aberg, 2013); (Linas, 2012); (Wandeler, 2012); (Witt, 2013); (Bravo, 2012); (Williams, 2011), at least annual HCV testing is recommended in these subgroups.

An anti-HCV test is recommended for HCV testing, and if the result is positive, current infection should be confirmed by a sensitive RNA test.

Rating: Class I, Level A

Among persons with a negative anti-HCV test who are suspected of having liver disease, testing for HCV RNA or follow-up testing for HCV antibody is recommended if exposure to HCV occurred within the past 6 months; testing for HCV RNA can also be considered in persons who are immunocompromised.

Rating: Class I, Level C

Among persons suspected of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV-RNA testing is recommended because an anti-HCV test is expected to be positive.

Rating: Class I, Level C

Quantitative HCV RNA testing is recommended prior to the initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load).

Rating: Class I, Level A

Testing for HCV genotype is recommended to guide selection of the most appropriate antiviral regimen.

Rating: Class I, Level A

If found to have positive results for anti-HCV test and negative results for HCV RNA by PCR, persons should be informed that they do not have evidence of current (active) HCV infection.

Rating: Class I, Level A

All persons recommended for HCV testing should first be tested for HCV antibody (anti-HCV) (Centers for Disease Control and Prevention [CDC], 2013); (Alter, 2003) using an FDA-approved test. FDA-approved tests include laboratory-based assays and a point-of-care assay (ie, OraQuick HCV Rapid Antibody Test [OraSure Technologies]). (Lee, 2011) The latter is an indirect immunoassay with a sensitivity and specificity similar to those of FDA-approved laboratory-based HCV antibody assays.

A positive test result for anti-HCV indicates either current (active) HCV infection (acute or chronic), past infection that has resolved, or a false-positive test result. (Pawlotsky, 2002) Therefore, an HCV nucleic acid test (NAT) to detect viremia is necessary to confirm current (active) HCV infection and guide clinical management, including initiation of HCV treatment. HCV RNA testing should also be performed in persons with a negative anti-HCV test who are either immunocompromised (eg, persons receiving chronic hemodialysis) (KDIGO, 2008) or who might have been exposed to HCV within the last 6 months (including those who are possibly reinfected after previous spontaneous or treatment-related viral clearance) because these persons may be anti-HCV negative. An FDA-approved quantitative or qualitative NAT with a detection level of 25 IU/mL or lower should be used to detect HCV RNA. Testing and Linkage to Care Table 1 lists FDA-approved, commercially available anti-HCV screening assays. Testing and Linkage to Care Figure 1 shows the CDC-recommended testing algorithm.

Prior to the initiation of HCV therapy, quantitative HCV RNA testing is necessary to document the baseline level of viremia (ie, viral load), because the degree of initial viral decline is a crucial marker of the effectiveness of treatment. Testing for HCV genotype helps to guide selection of the most appropriate treatment regimen. Persons who have positive results for an anti-HCV test and negative results for HCV RNA by PCR should be informed that they do not have laboratory evidence of current (active) HCV infection. Additional HCV testing is typically unnecessary. However, some practitioners or persons may seek additional testing to learn if the HCV antibody test represents a remote HCV infection that has resolved or a false-positive result. For patients with no apparent risk for HCV infection, the likelihood of a false-positive HCV antibody test is directly related to the HCV prevalence in the tested population; false-positive test results for anti-HCV are most common for populations with a low prevalence of HCV infection. (Alter, 2003) If further testing is desired to distinguish between true positivity and biologic false positivity for HCV antibody, testing may be done with a second FDA-approved HCV antibody assay that is different from the assay used for initial antibody testing. A biologic false result should not occur with 2 different tests. (Vermeersch, 2008); (Centers for Disease Control and Prevention [CDC]), 2013) The HCV RNA test can be repeated when there is a high index of suspicion of infection or in patients with prior or ongoing risk factors for HCV infection.

Persons with current (active) HCV infection should receive education and interventions aimed at reducing progression of liver disease and preventing transmission of HCV.

Rating: Class IIa, Level B

1. *Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection.*

   Rating: Class IIa, level B

2. *Evaluation for other conditions that may accelerate liver fibrosis, including HBV and HIV infections, is recommended for all persons with HCV infection.*

   Rating: Class IIb, level B

3. *Evaluation for advanced fibrosis, using liver biopsy, imaging, or non-invasive markers, is recommended in all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy and determine the need for initiating additional screening measures (eg, hepatocellular carcinoma [HCC] screening).*

   Rating: Class I, Level B

4. *Vaccination against hepatitis A and hepatitis B is recommended for all persons with HCV infection who are susceptible to these types of viral hepatitis.*

   Rating: Class IIa, Level C

5. *All persons with HCV infection should be provided education on how to avoid HCV transmission to others.*

   Rating: Class I, level C

In addition to receiving therapy, HCV-infected persons should be educated about how to prevent further damage to their liver. Most important is prevention of the potential deleterious effect of alcohol. Numerous studies have found a strong association between the use of excess alcohol and the development or progression of liver fibrosis and even the development of HCC. (Poynard, 1997); (Harris, 2001); (Wiley, 1998); (Corrao, 1998); (Bellentani, 1999); (Noda, 1996); (Safdar, 2004)

Excess alcohol intake may also cause steatohepatitis. The daily consumption of more than 50 grams of alcohol has a high likelihood of worsening fibrosis. Some studies indicate that daily consumption of smaller amounts of alcohol also have a deleterious effect on the liver; however, these data are controversial. (Westin, 2002) Alcohol screening and brief interventions such as those outlined by the National Institute of Alcohol Abuse and Alcoholism (http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm) have been demonstrated to reduce alcohol consumption and episodes of binge drinking in the general population and among HCV-infected persons who consume alcohol heavily.(Whitlock, 2004); (Dieperink, 2010); (Proeschold-Bell, 2012) Persons identified as abusing alcohol and having alcohol dependence require treatment and consideration for referral to an addiction specialist.

HBV and HIV coinfection have been associated with poorer prognosis of HCV in cohort studies. (Thein, 2008); (Zarski, 1998) Due to overlapping risk factors for these infections and additional benefits of their identification and treatment, persons with HCV should be tested for HIV antibody and HBsAg using standard assays for screening (Moyer, 2013); (Centers for Disease Control and Prevention, 2008) (http://www.aafp.org/afp/2008/0315/p819.html and http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm) and counseled how to reduce their risk of acquiring these infections, including through HBV vaccination (see below).

Patients with obesity and metabolic syndrome having underlying insulin resistance are more prone to have nonalcoholic fatty liver disease, which is a risk factor for fibrosis progression in HCV-infected persons. (Hourigan, 1999); (Ortiz, 2002) Therefore, HCV-infected persons who are overweight or obese (defined by a body mass index 25 kg/m^2 or higher or 30 kg/m^2 or higher, respectively) should be counseled regarding strategies to reduce weight and improve insulin resistance via diet, exercise, and medical therapies. (Musso, 2010); (Shaw, 2006) Patients with HCV infection and hyperlipidemia or cardiovascular comorbidities may also benefit from various hypolipidemic drugs. Prospective studies have demonstrated the safety and efficacy of statins in patients with chronic HCV and others with compensated chronic liver disease. (Lewis, 2007) Therefore, these agents should not be withheld in HCV-infected patients.

The severity of liver disease associated with chronic HCV infection is a key factor in determining the initial and follow-up evaluation of patients. Although patients with more advanced disease generally have a lower response to HCV therapy, they are also most likely to derive the greatest survival benefit. (Ghany, 2011) A liver biopsy can provide objective, semi-quantitative information regarding the amount and pattern of collagen or scar tissue in the liver, which can assist with treatment and monitoring plans. The Metavir fibrosis score (0-4) and Ishak fibrosis score (0-6) are commonly used to score the amount of hepatic collagen. A liver biopsy can also help assess the severity of liver inflammation, or of hepatic steatosis, and help exclude competing causes of liver injury. (Kleiner, 2005) However, the procedure has a low but real risk of complications, and sampling artifact makes its serial use in most patients less desirable. (Regev, 2002) Non-invasive methods frequently used to estimate liver disease severity include a liver-directed physical exam (normal in most patients), routine blood tests (eg, serum alanine transaminase, albumin, bilirubin, international normalized ratio levels, and complete cell blood counts with platelets), serum fibrosis marker panels, liver imaging (eg, ultrasound, computed tomography scan), and liver elastography. Simple blood tests (eg, serum aspartate aminotransferase/platelet ratio index) (Wai, 2003) (http://www.hepatitisc.uw.edu/page/clinical-calculators/apri) and assessment of liver surface nodularity and spleen size by liver ultrasound or other cross-sectional imaging modalities can help determine if patients with HCV have occult portal hypertension, which is associated with a greater likelihood of developing future hepatic complications in untreated patients. (Chou, 2013); (Rockey, 2006) Liver elastography can provide instant information regarding liver stiffness at the point-of-care but can only reliably distinguish cirrhosis from non-cirrhosis. (Castera, 2012) Since persons with known or suspected bridging fibrosis and cirrhosis are at increased risk of developing complications of advanced liver disease, they require more frequent follow up; these persons also should avoid ulcerogenic drugs and receive ongoing imaging surveillance for liver cancer and varices. (Sangiovanni, 2006); (Fontana, 2010)

Exposure to infected blood is the primary mode of HCV transmission. HCV-infected persons must be informed of the precautions needed to avoid exposing others to infected blood. This is particularly important for persons who use injection drugs, given that HCV transmission in this population primarily results from the sharing of needles and other infected implements. Recently, epidemics of acute HCV due to sexual transmission in HIV-infected men who have sex with men have also been described. (van de Laar, 2009); (Urbanus, 2009); (Fierer, 2008) Testing and Linkage Table 2 outlines measures to avoid HCV transmission. HCV is not spread by sneezing, hugging, holding hands, coughing, or sharing eating utensils or drinking glasses, nor is it transmitted through food or water.

Evaluation by a practitioner who is prepared to provide comprehensive management, including consideration of antiviral therapy, is recommended for all persons with current (active) HCV infection.

Rating: Class IIa, level C

The definition of evaluation is: *Patient has attended a medical care visit with a practitioner able to complete a full assessment, the pros and cons of antiviral therapy have been discussed, and the patient has been transitioned into treatment, if appropriate.*

Improvement in identification of current (active) HCV infection and advances in treatment regimens will have limited impact on HCV-related morbidity and mortality without concomitant improvement in linkage to care. All patients with current HCV infection and a positive HCV RNA test result should be evaluated by a practitioner with expertise in assessment of liver disease severity and HCV treatment. Subspecialty care is required for persons with HCV infection who have advanced fibrosis/cirrhosis (stage III or above on METAVIR scale), including possible referral for consideration of liver transplantation. In the United States, only an estimated 13% to 18% of persons chronically infected with HCV receive treatment. (Holmberg, 2013) Lack of appropriate practitioner assessment and delays in linkage to care can result in negative health outcomes. Further, patients who are lost to follow-up fail to benefit from evolving evaluation and treatment options.

Commonly cited patient-related barriers to treatment initiation include contraindications to treatment (eg, medical or psychiatric comorbidities), lack of acceptance of treatment (eg, asymptomatic nature of disease, competing priorities, low treatment efficacy, and long treatment duration and adverse effects), and lack of access to treatment (eg, cost and distance to specialist). (Khokhar, 2007); (Arora, 2011); (Clark, 2012) Common practitioner–related barriers include perceived patient-related barriers (eg, fear of adverse effects, treatment duration, cost, and effectiveness), lack of expertise in HCV treatment, lack of specialty referral resources, resistance to treating persons currently using illicit drugs or alcohol, and concern about cost of HCV treatment. (Morrill, 2005); (Reilley, 2013); (McGowan, 2013) Some possible strategies to address these barriers are listed in Testing and Linkage to Care Table 3. One strategy that addresses several barriers is co-localization of HCV screening, evaluation, and treatment with other medical or social services. Co-localization has already been applied to settings with a high prevalence of HCV infection (eg, correctional facilities and programs providing needle exchange, substance abuse treatment, and methadone maintenance) but is not uniformly available. (Islam, 2012); (Stein, 2012); (Bruggmann, 2013)

A strategy that addresses lack of access to specialists (a primary barrier to hepatitis C care) is participation in models involving close collaboration between primary-care practitioners and subspecialists. (Arora, 2011); (Rossaro, 2013); (Miller, 2012) Such collaborations have used telemedicine and knowledge networks to overcome geographic distances to specialists. (Arora, 2011); (Rossaro, 2013) For example, Project ECHO (Extension for Community Healthcare Outcomes [http://www.echohcvexperts.com]) uses videoconferencing to enhance primary care practitioner capacity in rendering HCV care and treatment to New Mexico's large rural and underserved population. (Rossaro, 2013) Through case-based learning and real-time feedback from a multidisciplinary team of specialists (ie, gastroenterology, infectious diseases, pharmacology, and psychiatry practitioners), Project ECHO has expanded access to HCV infection treatment in populations that might have otherwise remained untreated.

Additional strategies of enhancing linkage to care could be adapted from other fields, such as tuberculosis and HIV, but remain to be evaluated for HCV infection. For example, use of directly observed therapy has enhanced adherence to TB treatment, and use of case managers and patient navigators has reduced loss of follow-up in HIV care. (Govindasamy, 2012) An assessment of efficacy and comparative effectiveness of these strategies is a crucial area of future research for patients with HCV infection. Replication and expansion of best practices and new models for linkage to HCV care will also be crucial to maximize the public health impact of newer treatment paradigms.

Testing and Linkage To Care Box. Summary of Recommendations for Testing and Linkage to Care

HCV testing is recommended at least once for persons born between 1945 and 1965.

Rating: Class I, Level B

Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.

1. *Risk behaviors*
   - Injection drug use (current or ever, including those who injected once)
   - Intranasal illicit drug use
2. *Risk exposures*
   - Long-term hemodialysis (ever)
   - Getting a tattoo in an unregulated setting
   - Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-infected blood
   - Children born to HCV-infected women
   - Prior recipients of transfusions or organ transplants, including persons who:
     - were notified that they received blood from a donor who later tested positive for HCV infection
     - received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
     - received clotting factor concentrates produced before 1987
     - were ever Incarcerated
3. *Other medical conditions*
   - HIV infection
   - Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels

Rating: Class I, Level B

Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV.

Rating: Class IIA, Level C

An anti-HCV test is recommended for HCV testing, and if the result is positive, current infection should be confirmed by a sensitive RNA test.

Rating: Class I, Level A

Among persons with a negative anti-HCV test who are suspected of having liver disease, testing for HCV RNA or follow-up testing for HCV antibody is recommended if exposure to HCV occurred within the past 6 months; testing for HCV RNA can also be considered in persons who are immunocompromised.

Rating: Class I, Level C

Among persons suspected of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV-RNA testing is recommended because an anti-HCV test is expected to be positive.

Rating: Class I, Level C

Quantitative HCV RNA testing is recommended prior to the initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load).

Rating: Class I, Level A

Testing for HCV genotype is recommended to guide selection of the most appropriate antiviral regimen.

Rating: Class I, Level A

If found to have positive results for anti-HCV test and negative results for HCV RNA by PCR, persons should be informed that they do not have evidence of current (active) HCV infection.

Rating: Class I, Level A

Persons with current (active) HCV infection should receive education and interventions aimed at reducing progression of liver disease and preventing transmission of HCV.

Rating: Class IIa, Level B

1. *Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection.*

   Rating: Class IIa, level B

2. *Evaluation for other conditions that may accelerate liver fibrosis, including HBV and HIV infections, is recommended for all persons with HCV infection.*

   Rating: Class IIb, level B

3. *Evaluation for advanced fibrosis is recommended using liver biopsy, imaging, or non-invasive markers in all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional screening measures (eg, hepatocellular carcinoma [HCC] screening).*

   Rating: Class I, Level B

4. *Vaccination against hepatitis A and hepatitis B is recommended for all persons with HCV infection who are susceptible to these types of viral hepatitis.*

   Rating: Class IIa, Level C

5. *All persons with HCV infection should be provided education on how to avoid HCV transmission to others.*

   Rating: Class I, level C

Evaluation by a practitioner who is prepared to provide comprehensive management, including consideration of antiviral therapy, is recommended for all persons with current (active) HCV infection.

Rating: Class IIa, level C

Testing and Linkage to Care Table 1. FDA-approved, Commercially Available Anti-HCV Screening Assays

Assay	Manufacturer	Format
Abbott HCV EIA 2.0	Abbott	EIA (Manual)
Advia Centaur HCV	Siemens	CIA (Automated)
ARCHITECT Anti-HCV	Abbott	CMIA (Automated)
AxSYM Anti-HCV	Abbott	MEIA (Automated)
OraQuick HCV Rapid Antibody Test	OraSure	Immunochromatographic (Manual)
Ortho HCV Version 3.0 EIA	Ortho	EIA (Manual)
VITROS Anti-HCV	Ortho	CIA (Automated)

Anti-HCV = HCV antibody; EIA = enzyme immunoassay; CIA = chemiluminescent immunoassay; MEIA = microparticle enzyme immunoassay; CMIA = chemiluminescent microparticle immunoassay

Table prepared by Saleem Kamili, PhD, Centers for Disease Control and Prevention.

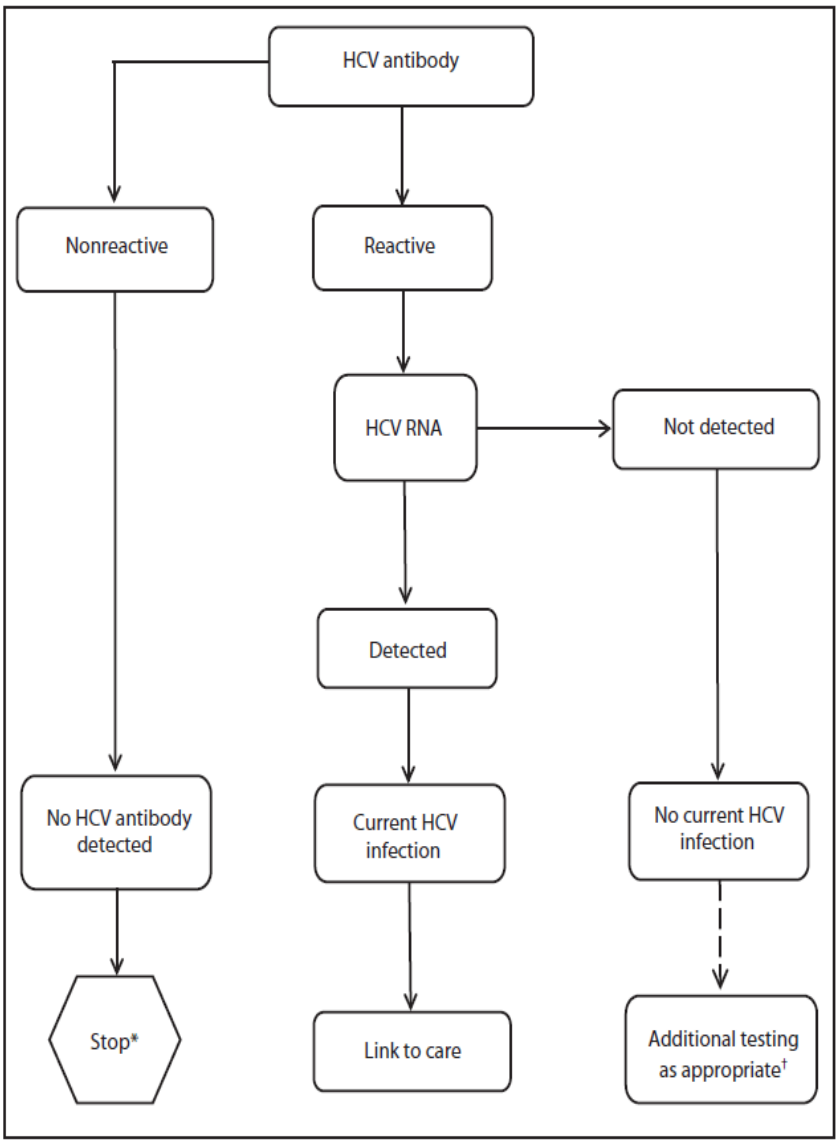
Testing and Linkage to Care Table 2. Measures Transmission of HCV

- Persons with HCV infection should be counseled to avoid sharing toothbrushes and dental or shaving equipment, and be cautioned to cover any bleeding wound to prevent the possibility of others coming into contact with their blood.
- Persons should be counseled to stop using illicit drugs and enter substance abuse treatment. Those who continue to inject drugs should be counseled to avoid reusing or sharing syringes, needles, water, cotton, and other drug preparation equipment; use new sterile syringes and filters and disinfected cookers; clean the injection site with a new alcohol swab; and dispose of syringes and needles after one use in a safe, puncture-proof container.
- Persons with HCV infection should be advised not to donate blood and to discuss HCV serostatus prior to donation of body organs, other tissue, or semen.
- MSM with HIV infection and those with multiple sexual partners or sexually transmitted infections should be encouraged to use barrier precautions to prevent sexual transmission. Other persons with HCV infection should be counseled that the risk of sexual transmission is low and may not warrant barrier protection.
- Household surfaces and implements contaminated with visible blood from an HCV-infected person should be cleaned using a dilution of 1 part household bleach to 9 parts water. Gloves should be worn when cleaning up blood spills.

Testing and Linkage to Care Table 3: Common Barriers to HCV Treatment and Potential Strategies

Barrier	Strategy
Contraindications to treatment (eg, comorbidities, substance abuse, and psychiatric disorders)	▪ Counseling and education ▪ Referral to services (eg, psychiatry and opioid substitution therapy) ▪ Optimize treatment with simpler and less toxic regimens
Competing priority and loss to follow-up	▪ Conduct counseling and education ▪ Engage case managers and patient navigators (HIV model) ▪ Co-localize services (eg, primary care, medical homes, and drug treatment)
Long treatment duration and adverse effects	▪ Optimize treatment with simpler and better tolerated regimens ▪ Education and monitoring ▪ Directly observed therapy (tuberculosis model)
Lack of access to treatment (high cost, lack of insurance, geographic distance, and lack of availability of specialists)	▪ Leverage expansion of coverage through the Patient Protection and Affordable Care Act ▪ Participate in models of care involving close collaboration between primary care practitioners and specialists ▪ Pharmaceutical patient assistance programs ▪ Co-localize services (primary care, medical homes, drug treatment)
Lack of practitioner expertise	▪ Collaboration with specialists (eg, via Project ECHO-like models and telemedicine) ▪ Develop accessible and clear HCV treatment guidelines ▪ Develop electronic health record performance measures and clinical decision support tools (eg, pop-up reminders and standing orders)

Testing and Linkage to Care Figure 1. CDC Recommended Testing Sequence for Identifying Current HCV Infection



* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody should be performed. For persons who are immunocompromised, testing for HCV RNA should be performed.

† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Adapted from Centers for Disease Control and Prevention (CDC), 2013. (Centers for Disease Control and Prevention [CDC], 2013)

INITIAL TREATMENT OF HCV INFECTION IN PATIENTS STARTING TREATMENT

A summary of recommendations for initial treatment is found in the box.

This section provides guidance on the recommended initial treatments for persons with chronic HCV infection who are naive to HCV treatment or who have achieved an undetectable level of virus during a prior treatment course of PEG/RBV and relapsed (relapsers). Although PEG/RBV relapsers are being retreated, their treatment recommendations are presently the same as for persons being treated for the first time as described below. This section assumes that ***a decision to treat has been made*** and provides guidance regarding optimal treatment. In many instances, however, it may be advisable to delay treatment for some patients with documented early fibrosis stage (F 0-2), because waiting for future highly effective, pangenotypic, DAA combinations in IFN-free regimens may be prudent. Potential advantages of waiting to begin treatment will be provided in a future update to this guidance.

The level of evidence available to inform the best treatment decisions for each patient varies, as does the strength of the recommendation, and is graded accordingly (see Methods Table 2). In addition, when treatment differs for a particular group, such as those infected with specific HCV genotypes, specific recommendations are given. A regimen is classified as either "Recommended" when it is favored for most patients or "Alternative" when optimal in a particular subset of patients in that category. When a treatment is clearly inferior or is deemed harmful, it is classified as "Not Recommended." Unless otherwise indicated, such regimens should not be administered to patients with HCV infection. Specific considerations of persons with HIV/HCV coinfection, compensated and decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C), post-liver transplant HCV, and those with severe renal impairment or ESRD are addressed in other sections of the document.

As always, patients receiving antiviral therapy require careful pretreatment assessment for comborbidities that may influence treatment response. All patients should have careful monitoring during treatment, particularly for anemia if ribavirin is included in the regimen.

I. Genotype 1

Recommended regimen for treatment-naive patients with HCV genotype 1 who are eligible to receive IFN.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.

Rating: Class I, Level A

Sofosbuvir is a prodrug of a nucleotide analogue inhibitor of the HCV NS5B RNA-dependent RNA polymerase. The phase 3 NEUTRINO trial evaluated sofosbuvir (400 mg daily) in combination with PEG (2a) (180 µg by subcutaneous injection weekly) and weight-based RBV (1000 mg to 1200 mg daily) for 12 weeks in 291 treatment-naive patients with chronic HCV genotype 1 infection. (Lawitz, 2013b) The SVR12 for patients with genotype 1 infection was 89%. SVR12 did not differ substantially by baseline characteristic but was lower in patients with cirrhosis (80%) than in those without cirrhosis (92%). (Lawitz, 2013b)

Recommended regimen for treatment-naive patients with HCV genotype 1 who are not eligible to receive IFN.

Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg) for 12 weeks is recommended for IFN-ineligible patients with HCV genotype 1 infection, regardless of subtype.

Rating: Class I, Level B

COSMOS is an ongoing phase 2 clinical trial of sofosbuvir (400 mg daily) plus simeprevir (150 mg daily), a specific inhibitor of the HCV NS3/4A serine protease, with or without RBV for 12 or 24 weeks. (Jacobson, 2013b) The study enrolled 2 cohorts: cohort 1 included patients with a prior null response to PEG/RBV with Metavir fibrosis stage of 0 or 2 (n=80); Cohort 2 included patients who were either treatment-naive or had a prior null response with Metavir fibrosis stage of 3 or 4 (n=87). In cohort 1, the 12-week treatment groups, SVR12 was 96% and 93% in patients treated with or without RBV, respectively. The 24-week treatment groups had SVR12 of 79.3% and 93% in patients treated with or without RBV, respectively. No viral breakthrough was observed in cohort 1 during treatment, and 3

patients experienced viral relapse after stopping therapy. All 3 patients with viral relapse were infected with HCV genotype 1a and had the Q80K polymorphism.

Preliminary SVR4 results are available for cohort 2. The 12-week treatment duration group had 100% SVR in treatment-naive patients treated with or without RBV, and 100% and 93.3% in prior null responder patients treated with or without RBV, respectively. No viral breakthrough was observed during treatment; 1 patient infected with HCV genotype 1a/Q80K experienced viral relapse after stopping therapy. No SVR data are yet available from cohort 2, which received 24 weeks of treatment.

Among patients who had viral relapse, simeprevir (protease) resistance-associated variants have been observed; sofosbuvir (polymerase) resistance-associated variants have not been detected. Safety data have been presented for all 167 patients treated. The combination was well tolerated, with only 2.4% of patients prematurely discontinuing therapy due to adverse events. Data on the use of simeprevir in patients with hepatic impairment are not available at this time.

For patients infected with genotype 1a HCV, baseline resistance testing for the Q80K polymorphism may be considered. However, in contrast to using simeprevir to treat a genotype 1a HCV patient with PEG/RBV when the mutation markedly alters the probability of an SVR, the finding of the Q80K polymorphism does not preclude treatment with simeprevir and sofosbuvir, because the SVR rate was high in patients with genotype 1a/Q80K infection (SVR12 rate for cohort 1 was 86% [24 of 28 patients]; SVR4 rate for cohort 2 was 90% [10 of 11 patients]). To date, virologic failure has not been observed in patients in either cohort infected with HCV genotype 1b and with HCV genotype 1a in the absence of the Q80K polymorphism. Thus Q80K testing can be considered but is not strongly recommended.

This regimen should be considered only in those patients who require immediate treatment, because it is anticipated that safer and more effective IFN-free regimens will be available by 2015.

Alternative regimens for treatment-naive patients with HCV genotype 1 who are eligible to receive IFN.

Daily simeprevir (150 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 24 weeks is an acceptable regimen for IFN-eligible persons with either

1. *HCV genotype 1b or*
2. *HCV genotype 1a infection in whom the Q80K polymorphism is not detected prior to treatment.*

Rating: Class IIa, Level A

Two randomized, placebo-controlled phase 3 trials evaluated the efficacy and safety of simeprevir (150 mg once daily) for 12 weeks plus PEG and weight-based RBV for a total of 24 weeks (RGT design found no advantage to extending PEG/RBV to 48 weeks). (Jacobson, 2013a); (Poordad, 2013)

In both studies, SVR24 rates were significantly higher among the simeprevir-containing arms (80% to 81%) than in the non-simeprevir-containing arms (50%). If the HCV RNA at week 4 of treatment is less than 25 IU/mL, therapy should be continued to week 24. If the HCV RNA is greater than 25 IU/mL at treatment week 4 or any treatment week thereafter, the regimen should be discontinued. In patients with HCV genotype 1a infection, the presence of a naturally occurring NS3-4A protease polymorphism (Q80K) prior to treatment was associated with a substantial reduction in SVR among patients treated with simeprevir. A statistically significant difference in SVR12 rates exists between simeprevir-treated persons who are infected with HCV genotype 1a but do not have the Q80K polymorphism and placebo-treated patients who likewise have no such polymorphism. This difference was noted in both the pooled treatment-naive studies and the relapser study (SVR rates of 84% versus 43%, respectively [treatment-naive study] and 78% versus 24%, respectively [relapse study]). The overall SVR in the subgroup of patients with baseline Q80K polymorphism was no better than that in the placebo group. In the United States, persons with genotype 1a HCV infection have a high prevalence of Q80K polymorphism. Because these persons may require alternative therapy, baseline testing for Q80K is recommended for all patients before treatment with the simeprevir plus PEG/RBV regimen is initiated.

For the simeprevir plus PEG/RBV treatment regimen, if the HCV RNA at week 4 of treatment is less than 25 IU/mL, therapy should be continued to week 24. If the HCV RNA is greater than 25 IU/mL at treatment week 4 or any treatment week thereafter, the regimen should be discontinued.

Alternative regimens for treatment-naive patients with HCV genotype 1 who are not eligible to receive IFN.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is an acceptable regimen for IFN-ineligible persons with HCV genotype 1 infection, regardless of subtype; however, preliminary data suggest that this regimen may be less effective than daily sofosbuvir (400 mg) plus simeprevir (150 mg), particularly among patients with cirrhosis.

Rating: Class IIb, Level B

Sofosbuvir plus RBV was evaluated in 60 treatment-naive patients with HCV genotype 1 with unfavorable treatment characteristics (eg, African American race and advanced fibrosis). (Osinusi, 2013) In part 1 of the study, 10 participants with early to moderate liver fibrosis were treated with sofosbuvir (400 mg daily) plus weight-based RBV for 24 weeks. Nine participants (90%) achieved SVR24. In part 2, 50 participants with any stage of liver fibrosis were randomized 1:1 to receive 400 mg sofosbuvir with RBV either weight-based or low-dose (600 mg daily) for 24 weeks; SVR24 was 68% (17/25) in the weight-based group and 48% (12/25) in the low-dose group. The regimens used in part 2 of this study were well tolerated, with no discontinuations due to adverse events. Seven of the 13 participants (54%) with advanced liver fibrosis treated in this study relapsed, including all 4 with cirrhosis.

Several additional studies have evaluated the effectiveness of sofosbuvir in persons with HCV genotype 1. In the QUANTUM trial, 38 treatment-naive patients with HCV genotype 1 who did not have cirrhosis were assigned either 12 (n=19) or 24 (n=19) weeks of sofosbuvir (400 mg daily) and weight-based RBV. (Lalezari, 2013) Ten of 19 (53%) in the 12-week arm and 9 of 19 (47%) subjects in the 24-week arm achieved SVR12 (overall 50%). In the ELECTRON trial, 25 treatment-naive subjects with HCV genotype 1 who did not have cirrhosis received sofosbuvir plus RBV for 12 weeks. Twenty-one (84%) achieved SVR12. (Gane, 2013b) In the PHOTON-1 trial, 86 of 113 (76%) treatment-naive subjects with genotype 1 HCV/HIV coinfection achieved SVR12 with sofosbuvir plus RBV for 24 weeks. (Sulkowski, 2013c) Taken together, in a total of 211 subjects, the range of SVR for regimens incorporating sofosbuvir plus daily weight-based RBV (1000 mg to 1200 mg) for up to 24 weeks in treatment-naive persons with HCV genotype 1 was 50% to 84%, with an overall SVR of 72%. Sofosbuvir resistance-associated amino acid variants have not been detected among those patients treated with this combination who did not achieve SVR.

This regimen should be considered only in those patients who require immediate treatment. It is estimated that the FDA will approve safer and more effective IFN-free regimens by 2015.

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 1.

- **PEG/RBV with or without telaprevir or boceprevir for 24 to 48 weeks**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

Although regimens of PEG/RBV plus telaprevir or boceprevir for 24 to 48 weeks using RGT are also FDA approved, they are markedly inferior to the preferred and alternative regimens. These regimens are associated with their higher rates of serious adverse events (eg, anemia and rash), longer treatment duration, high pill burden, numerous drug-drug interactions, frequency of dosing, intensity of monitoring for continuation and stopping of therapy, and the requirement to be taken with food or with high-fat meals.

PEG/RBV for 48 weeks for treatment-naive subjects with HCV genotype 1 has been superseded by treatments incorporating DAAs and should not be used.

II. Genotype 2

Recommended regimen for treatment-naive patients with HCV genotype 2, regardless of eligibility for IFN therapy:

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for treatment-naive patients with HCV genotype 2 infection.

Rating: Class I, Level A

Sofosbuvir (400 mg daily) was combined with weight-based RBV (1000 mg to 1200 mg) to treat HCV genotype 2 treatment-naive patients across 3 clinical trials: FISSION, POSITRON, and VALENCE. (Lawitz, 2013b); (Jacobson, 2013c); (Zeuzem, 2013b) The FISSION study randomized patients to daily PEG/RBV (800 mg) for 24 weeks or sofosbuvir plus daily weight-based RBV (1000 mg to 1200 mg). (Lawitz, 2013b) The SVR was higher (94%) in patients who received sofosbuvir plus RBV compared with those who received PEG/RBV (78%) (52/67). Across all 3 trials, 201 of 214 (94%) patients with HCV genotype 2 achieved SVR with sofosbuvir plus RBV. Among patients who did not achieve SVR, sofosbuvir resistance-associated amino acid variants were not detected. (US FDA, 2013a)

Alternative Regimens for treatment-naive patients with genotype 2:

None

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 2.

- **PEG/RBV for 24 weeks**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

- **Telaprevir-, boceprevir-, or simeprevir-based regimens**

  Rating: Class III, Level A

PEG (2a) (180 µg weekly) or PEG (2b) (1.5 µg/kg weekly) plus RBV (800 mg daily) for 24 weeks was directly compared with sofosbuvir (400 mg daily) plus weight-based RBV (1000 mg to 1200 mg daily) in the FISSION trial. (Lawitz, 2013b) The SVR12 achieved with PEG/RBV was lower than that achieved with sofosbuvir/RBV overall (78% and 95%, respectively) and in the subgroups of patients with or without cirrhosis. Safety and tolerability of PEG/RBV was inferior to the profile observed with sofosbuvir and RBV, with greater frequency of reported adverse events and laboratory abnormalities as well as a higher rate of treatment due to adverse events. Further, the duration of therapy with PEG/RBV is 12 weeks longer than that of sofosbuvir plus RBV.

Due to their poor in vitro and in vivo activity, boceprevir and simeprevir should not be used as therapy for patients with HCV genotype 2 infection. Although telaprevir combined with PEG/RBV has antiviral activity against HCV genotype 2, (Foster, 2011) the additional side effects and longer duration of therapy do not support use of this regimen.

III. Genotype 3

Recommended regimen for treatment-naive patients with HCV genotype 3, regardless of eligibility for IFN therapy:

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for treatment-naive patients with HCV genotype 3 infection.

Rating: Class I, Level B

The VALENCE study assessed the efficacy and safety of sofosbuvir (400 mg daily) plus RBV for 24 weeks in 250 treatment-naive (42%) and treatment-experienced (58%) subjects with HCV genotype 3 infection. The overall SVR12 was 84% and was higher among treatment-naive than treatment-experienced patients (93% versus 77%, respectively). These results suggest higher response rates can be achieved with a 24-week duration of sofosbuvir plus RBV than those reported for the 12- or 16-week durations studied in the FISSION (Lawitz, 2013b) (12 weeks, SVR12: 63%), POSITRON, (Jacobson, 2013c) (12 weeks, SVR 12: 61%) and FUSION (12 weeks, SVR12: 30%, 16 weeks, SVR12: 62%) trials. The primary reason for the higher SVR with extended therapy among treatment-naive patients was a reduction in the relapse rate from 40% to 5%. In sub-analysis, response rates were similarly high among those with (n=45) and without (n=100) cirrhosis (92% and 93%, respectively).

Alternative regimens for treatment-naive patients with genotype 3 who are eligible to receive IFN.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is an acceptable regimen for IFN-eligible persons with HCV genotype 3.

Rating: Class IIa, Level A

The combination of sofosbuvir plus PEG/RBV has been evaluated in patients with genotype 3 infection. In 2 phase 2 clinical trials, PROTON and ELECTRON, 38 of 39 (97%) treatment-naive patients with genotype 3 infection achieved SVR with sofosbuvir plus PEG (4 to 12 weeks of therapy)/RBV. (Gane, 2013b) For many patients with genotype 3, the adverse effects and increased monitoring requirements of PEG make this less acceptable than the recommended regimen of sofosbuvir plus weight-based RBV.

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 3.

- **PEG/RBV for 24 to 48 weeks**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

- **Telaprevir-, boceprevir-, or simeprevir-based regimens should not be used for patients with genotype 3 HCV infection.**

  Rating: Class III, Level A

Although the combination of PEG/RBV is an FDA-approved regimen for HCV genotype 3, its less acceptable adverse effect profile, requirement for more intensive monitoring, and overall lower efficacy make it less desirable than the recommended regimen.

Because of their limited in vitro and in vivo activity against genotype 3, boceprevir, telaprevir, and simeprevir should not be used as therapy for patients with HCV genotype 3 infection.

IV. Genotype 4

Few data are available to help guide decision-making in patients infected with HCV genotype 4. Nonetheless, for those patients for whom immediate treatment is required, the following recommendations have been drawn from available data.

Recommended regimen for treatment-naive patients with HCV genotype 4 who are eligible to receive IFN.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 4 infection.

Rating: Class IIa, Level B

In the Phase 3 NEUTRINO trial, (Lawitz, 2013b) 28 treatment-naive patients with HCV genotype 4 infection were treated with sofosbuvir (400 mg daily) plus PEG (2a) (180 µg weekly) and weight-based RBV (1000 mg 1200 mg once daily) for 12 weeks. Of the 28 patients with genotype 4, 27 (96%) achieved SVR12. The one patient who did not achieve SVR had cirrhosis and relapsed after therapy. The adverse event profile was similar to that seen with PEG/RBV therapy.

Recommended regimen for treatment-naive patients with genotype 4 who are not eligible to receive IFN.

Daily sofosbuvir (400 mg) plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for IFN-ineligible patients with HCV genotype 4 infection.

Rating: Class IIb, Level B

In a small study of Egyptian patients in the United States treated with sofosbuvir plus weight-based RBV (1000 mg to 1200 mg), SVR12 was achieved in 11 of 14 (79%) treatment-naive patients treated for 12 weeks; SVR24 was achieved in 100% of the 14 treatment-naive patients treated for 24 weeks. (Ruane, 2013)

Alternative regimens for treatment-naive patients with HCV genotype 4 who are eligible to receive IFN.

Daily simeprevir (150 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 24 to 48 weeks is an alternative regimen for IFN-eligible persons with HCV genotype 4 infection.

Rating: Class IIb, Level B

A Phase 3 trial in patients with HCV genotype 4 is currently under way. This trial compares PEG and weight-based RBV (1000 mg to 1200 mg) for 48 weeks with a 12-week regimen of simeprevir 150 mg once daily plus PEG and weight-based RBV (1000 mg to 1200 mg) followed by an additional 12 or 36 weeks of PEG/RBV alone. (Moreno, 2013) In another study, the RESTORE trial, an RGT approach is used in place of the simeprevir arm. Patients who have HCV RNA below 25 IU/mL at week 4 and undetectable HCV RNA by week 12 continue PEG/RBV for an additional 12 weeks, and those who do not achieve this response continue PEG/RBV for an additional 36 weeks (total 48 weeks of therapy). The study has enrolled 107 patients, of whom 35 are treatment-naive, including 2 with cirrhosis. To date, 10 of 11 patients (91%) who met criteria for shortened therapy have achieved SVR4, and 3 of 3 have achieved SVR12. To date, therapy has failed in 4 patients: 3 had detectable virus at the end of treatment and 1 experienced virologic relapse. Anemia was reported in 8.4% and hyperbilirubinemia in 1.9% of all study participants (n=107) (including treatment-experienced patients). Four serious adverse events were attributed to simeprevir. No episodes of rash were reported. (Moreno, 2013)

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 4.

- **PEG/RBV for 48 weeks**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

- **Telaprevir- or boceprevir-based regimens**

  Rating: Class III, Level A

PEG/RBV for 48 weeks was the previously recommended regimen for patients with HCV genotype 4. The addition of sofosbuvir (400 mg daily) to PEG/RBV increases response rates and markedly shortens therapy with no apparent additional adverse effects. The addition of simeprevir to PEG/RBV increases response rates with a minimal increase in adverse events and can shorten therapy to 24 weeks.

Because of their limited in vitro and in vivo activity against genotype 4, boceprevir or telaprevir should not be used as therapy for patients with HCV genotype 4 infection.

V. Genotype 5 or 6

Few data are available to help guide decision-making in patients infected with HCV genotype 5 or 6. Nonetheless, for those patients for whom immediate treatment is required, the following recommendations have been drawn from available data. No data are available to support the use of a non-PEG containing regimen for patients with HCV genotype 5 or 6 infection.

Recommended regimen for treatment-naive patients with HCV genotype 5 or 6.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 5 or 6 infection.

Rating: Class IIa, Level B

In the Phase 3 NEUTRINO trial (Lawitz, 2013b), treatment-naive patients with genotypes 1 (n=291), 4 (n=28), 5 (n=1), and 6 (n=6) were treated with sofosbuvir (400 mg daily) plus PEG (2a) (180 µg per week) and weight-based RBV (1000 mg 1200 mg once daily) for 12 weeks. All 6 patients with HCV genotype 6 and the 1 patient with genotype 5 achieved SVR12. The adverse event profile in these patients and in the larger study population was similar to that seen with PEG/RBV therapy.

Alternative regimens for treatment-naive patients with HCV genotype 5 or 6.

Daily weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 48 weeks is an acceptable regimen for persons infected with HCV genotype 5 or 6.

Rating: Class IIb, Level A

PEG/RBV for 48 weeks was the previously recommended regimen for patients infected with HCV genotype 5 or 6. Sofosbuvir has activity against genotypes 5 and 6, and when combined with PEG/RBV for 12 weeks led to SVR in the 6 patients in whom it was studied. (Lawitz, 2013b) The addition of sofosbuvir (400 mg daily) to PEG/RBV shortens duration of therapy with no apparent additional adverse effects and likely substantially increases response rates.

The following regimens are NOT recommended for treatment-naive patients with genotype 5 or 6 HCV.

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

- **Telaprevir- or boceprevir-based regimens**

  Rating: Class III, Level A

Because of their limited activity in vitro and in vivo against genotypes 5 and 6, boceprevir or telaprevir should not be used as therapy for patients with genotype 5 or 6 HCV infection.

Initial Treatment Box. Summary of Recommendations for Patients Who are Initiating Therapy for HCV Infection or Who Experienced Relapse after Prior PEG/RBV Therapy, by HCV Genotype

Genotype	Recommended	Alternative	NOT Recommended
1	**IFN eligible:** SOF + PEG/RBV x 12 weeks **IFN ineligible:** SOF + SMV ± RBV x 12 weeks	**IFN eligible:** SMV x 12 weeks + PEG/RBV x 24 weeks* **IFN ineligible:** SOF + RBV x 24 weeks	TVR + PEG/RBV x 24 or 48 weeks (RGT) BOC + PEG/RBV x 28 or 48 weeks (RGT) PEG/RBV x 48 weeks Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG or SMV
2	SOF + RBV x 12 weeks	None	PEG/RBV x 24 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV
3	SOF + RBV x 24 weeks	SOF + PEG/RBV x 12 weeks	PEG/RBV x 24-48 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV
4	**IFN eligible:** SOF + PEG/RBV x 12 weeks **IFN ineligible:** SOF + RBV x 24 weeks	SMV x 12 weeks + PEG/RBV x 24-48 weeks	PEG/RBV x 48 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR or BOC
5 or 6	SOF + PEG/RBV x 12 weeks	PEG/RBV x 48 weeks	Monotherapy with PEG, RBV, or a DAA Any regimen with TVR or BOC

For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present.

RETREATMENT OF PERSONS IN WHOM PRIOR THERAPY HAS FAILED

A summary of recommendations for retreatment is found in the box.

This section provides guidance on the retreatment of a person with chronic HCV infection in whom prior therapy has failed. In general, treatment responses of patients achieving an undetectable level of virus during a prior treatment course who relapse following cessation of therapy (**relapser**) are similar to those of treatment-naive persons (see Initial Treatment). Treatment responses are generally lower in prior **non-responders**, which includes null responders (those in whom serum HCV RNA levels declined less than 2 $\log_{10}$ IU/mL by week 12 during a prior treatment course) and partial responders (those with a ≥ 2 $\log_{10}$ IU/mL response whose virus remained detectable up to 24 weeks or the end of treatment). This section assumes that ***a decision to treat has been made*** and advises on the optimal treatment. In many instances, however, it may be advisable to delay treatment for some patients with documented early fibrosis stage (F 0-2), because waiting for future highly effective, pangenotypic, combinations in IFN-free regimens may be prudent. Potential advantages of waiting to begin to treatment will be provided in a future update to this guidance.

The level of the evidence supporting the best treatment for each patient and the corresponding confidence in the recommendation varies as does the strength of the recommendation, and is graded in the same manner as the section on initial treatment of treatment-naive patients (Methods Table 2). In addition, when treatment differs for a particular group (eg, those infected with various genotypes) specific recommendations are given. Regimens are classified as "Recommended" when it is favored for most patients or "Alternative" when it might be optimal in a particular subset of patients in that category. When a treatment is clearly inferior or should not be used, it is classified as "Not Recommended."

As always, patients receiving antiviral therapy require careful pretreatment assessment for comorbidities that may influence treatment response. All patients should have careful monitoring during treatment, particularly for anemia if ribavirin is included in the regimen.

I. Genotype 1

Recommended regimen for HCV genotype 1 PEG/RBV (without an HCV protease inhibitor) nonresponder patients:

Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for retreatment of HCV genotype 1 infection, regardless of subtype or IFN eligibility

Rating: Class IIa, Level B

COSMOS is a phase 2a randomized trial in which participants received sofosbuvir (400 mg once daily) plus simeprevir (150 mg once daily) with or without weight-based RBV (1000 mg to 1200 mg daily) for 12 or 24 weeks (Jacobson, 2013b). Of the 80 null responders with a Metavir fibrosis stage of 2 or less included in this trial, 79% to 96% achieved SVR (79%-96% in RBV-containing arms and 93% in both RBV-free arms). Among those null responders with a Metavir fibrosis stage of 3 or 4 (n=47) who received 12 weeks of sofosbuvir and simeprevir, SVR4 was observed in 14 (93%) of 15 patients in the ribavirin-containing arm and 100% (all 7 participants) in the RBV-free arm. Although benefit from RBV is not apparent from these preliminary results, it cannot be excluded before availability of SVR12 data. Post-treatment results are not yet available for the 24-week arms. Excluding nonvirologic failures, patients with HCV genotype 1a with Q80K mutations had slightly lower numeric response rates (fibrosis stage 0-2: SVR12=89% [n=27]; fibrosis stage 3 or 4: SVR4=91% [n=11]) than genotype 1a patients without Q80K and genotype 1b (fibrosis stage 2: SVR12 100%, n=47; fibrosis stage 3 or 4: SVR4=100% [n=29]). However, because the study was not powered to assess this comparison, insufficient evidence exists on the role of testing for the Q80K mutation at this time. These regimens were well tolerated, although adverse events (eg, anemia and hyperbilirubinemia) were seen more often in patients on RBV-containing regimens. (Jacobson, 2013b)

The safety and efficacy of simeprevir have not been studied in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). The uncertain impact of cholestasis and the occasional association of SMV with elevated transaminases create potential for drug accumulation or impaired hepatic function during SMV use. Clinical trials with SMV have been limited to patients with compensated disease who have CTP class A, total bilirubin of 1.5 x ULN or lower, and transaminases 10 x ULN or lower. For these reasons, simeprevir use should be limited to patients with compensated liver disease. Use of simeprevir is not recommended in patients with moderate to severe hepatic impairment. The combination of PEG/RBV is contraindicated in patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C).

Alternative regimen for PEG/RBV (with or without an HCV protease inhibitor) nonresponder patients with HCV genotype 1 who are eligible to receive IFN.

Daily sofosbuvir (400 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 to 24 weeks is an alternative for retreatment of IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.

Rating: Class IIb, Level C

NEUTRINO is an open-label, single-arm trial that evaluated 12 weeks of sofosbuvir plus PEG/RBV in treatment-naive subjects with HCV genotypes 1, 4, 5, or 6; 89% had HCV genotype 1, and 17% had cirrhosis. The SVR was 89% (261 of 292) and was somewhat lower in patients with genotype 1b than 1a (82% and 92%, respectively) and those with cirrhosis versus those without (80% versus 92%, respectively). (Lawitz, 2013a) Although treatment-experienced subjects were not included in this study, FDA estimates that the response rate in such patients would approximate the observed response rate in those NEUTRINO subjects with baseline factors traditionally associated with a lower response to IFN-based treatment. (US FDA, 2013a) In the NEUTRINO trial, SVR rate was 71% among participants with HCV genotype 1 with IL28B non-C/C alleles, high HCV RNA levels, and METAVIR 1 fibrosis stage F3 or F4 (37 of 52 patients). (Gilead Sciences, 2013; Solvadi package insert)

Alternative regimen for PEG/RBV (without an HCV protease inhibitor) nonresponder patients with HCV genotype 1 who are eligible to receive IFN.

Daily simeprevir (150 mg) for 12 weeks plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) and weekly PEG for 48 weeks is an alternative for IFN-eligible persons with HCV genotype 1 infection. (All patients with cirrhosis who are receiving simeprevir should have well compensated liver disease.)

Rating: Class IIa, Level A

Simeprevir was combined with PEG/RBV in patients who had previously failed to respond to PEG/RBV dual therapy in the Phase 2b ASPIRE trial. (Zeuzem, 2013a); (Janssen Therapeutics, 2013) (www.fda.gov; package insert). SVR24 after 48 weeks of triple therapy in the simeprevir 150 mg/day arm was 65% in patients with a previous partial response (n=23) and 53% in patients with a prior null response (n=17). Patients with HCV genotype 1a infection had inferior response rates compared with those with genotype 1b (SVR24: 47% vs 77% in patients with a partial response and 41% vs 47% in patients with a null response, respectively). Despite lower SVR in patients with HCV genotype 1a infection, SVR rates were similar with and without the presence of the Q80K mutations at baseline. SVR rates in patients with advanced fibrosis (METAVIR stage F3 or F4) treated with simeprevir (150 mg daily) plus PEG/RBV for 48 weeks were 59% in patients with a partial response (n=33) and 35% in patients with a null response (n=34). Safety in patients exposed to simeprevir was similar to that of persons in the placebo arms; however, there was a higher incidence of hyperbilirubinemia (8%) and photosensitivity/rash (5%). (Zeuzem, 2013a)

The safety and efficacy of simeprevir have not been studied in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). The uncertain impact of cholestasis and the occasional association of simeprevir with elevated transaminases pose potential for impaired hepatic function during simeprevir use. Clinical trials with simeprevir have been limited to patients with compensated disease who have CTP class A, total bilirubin level of 1.5 x ULN or lower, and transaminase level of 10 x ULN or lower. For these reasons, simeprevir use should be limited to patients with compensated liver disease. Use of simeprevir is not recommended in patients with moderate to severe hepatic impairment. Use of the drug in this population is not recommended at this time. The combination of PEG/RBV is contraindicated in patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C).

The following regimens are NOT recommended for PEG/RBV (with or without an HCV protease inhibitor) nonresponder patients with HCV genotype 1:

- **PEG/RBV with or without telaprevir or boceprevir**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

For nonresponder patients with genotype 1 and a history of decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C), treatment is not indicated because of the risks of PEG and boceprevir and telaprevir in this population.

Triple therapy with boceprevir plus PEG/RBV for 48 weeks may result in SVR for up to 52% of PEG/RBV partial responders (RESPOND 2; (Bacon, 2011)) and 38% of null responders (PROVIDE; (Di Bisceglie, 2013)). Similarly, telaprevir plus PEG/RBV resulted in SVR24 of 54% to 59% among partial responders and an SVR24 of 29% to 33% among null responders (REALIZE; (Zeuzem, 2011)). Due to the relatively poor efficacy, prolonged duration of therapy (48 weeks), and poor tolerability, these regimens are no longer recommended.

Monotherapy with PEG, RBV, or any of the available DAAs is ineffective; further, DAA monotherapy leads to rapid selection of resistant variants.

Patients with advanced liver disease are at increased risk for sepsis, worsening decompensation, and death when treated with dual or triple IFN-based therapy. (Crippin, 2002); (Coilly, 2014) Simeprevir is primarily metabolized by the liver and should not be used in patients with advanced cirrhosis (CTP B or C), as the AUC is increased 2.4- to 5.2-fold. (Janssen Therapeutics, 2013) (Olysio package insert, Janssen).

II. Genotype 2

Recommended regimen for genotype 2 PEG/RBV nonresponders.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for retreatment of HCV genotype 2 infection. (Patients with cirrhosis may benefit by extension of treatment to 16 weeks.)

Rating: Class I, Level A

High SVR12 rates have been demonstrated in non-cirrhotic genotype 2 treatment-experienced patients who received 12 weeks of sofosbuvir plus RBV. Limited data are available in cirrhotic genotype 2 treatment experienced patients; however, in the FUSION study, numerically higher SVR12 rates were seen with extension of therapy from 12 weeks (60%) to 16 weeks (78%). (Jacobson, 2013b) In contrast, the VALENCE trial found high SVR12 rates among HCV genotype 2-infected persons with cirrhosis after only 12 weeks of sofosbuvir plus RBV (88%). (Zeuzem, 2013b) Thus, at this time definitive recommendations on the appropriate duration of sofosbuvir and RBV for treatment-experienced, HCV genotype 2-infected persons with cirrhosis cannot be made. The decision to extend therapy to 16 weeks should be made on a case-by-case basis.

Alternative regimen for PEG/RBV nonresponder patients with HCV genotype 2 infection who are eligible to receive IFN.

Retreatment with daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is an alternative for IFN-eligible persons with HCV genotype 2 infection.

Rating: Class IIa Level B

Recognizing the potential limitations of sofosbuvir plus RBV in harder-to-treat genotype 2 nonresponders, particularly those with cirrhosis, combination therapy with PEG has been studied. The LONESTAR-2 trial (an open-label, single site, single-arm phase 2 trial) evaluated PEG (180 µg weekly), sofosbuvir (400 mg daily), and weight-based RBV (1000 mg to 1200 mg daily in 2 divided doses for 12 weeks) in treatment-experienced patients with HCV genotype 2 or 3. Cirrhosis was present at baseline in 61% of patients. SVR12 was achieved in 22 (96%) of 23 persons with genotype 2 HCV infection. For patients with and without cirrhosis, SVR occurred in 13 (93%) of 14 and 9 (100%) of 9, respectively. Despite the limitations of this small study (and accounting for the potential challenges inherent with IFN therapy), combination PEG plus sofosbuvir and RBV is an alternative 12-week regimen for genotype 2-infected patients with cirrhosis.

The following regimens are NOT recommended for nonresponder patients with HCV genotype 2.

- **PEG/RBV with or without telaprevir, boceprevir or simeprevir**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

No HCV protease inhibitors have been approved or are indicated for the treatment of genotype 2 infection. Although PEG/RBV has been the mainstay of treatment of genotype 2, it requires a longer duration of therapy, is less efficacious, and has more adverse effects than the regimen recommended above.

III. Genotype 3

Recommended regimen for HCV genotype 3 PEG/RBV nonresponders.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for retreatment of HCV genotype 3 infection.

Rating: Class IIa, Level A

The phase 3 FUSION trial compared 12 weeks (n=103) with 16 weeks (n=98) of daily sofosbuvir (400 mg) and weight-based RBV (1000 mg to 1200 mg) in genotype 2 or 3 HCV-infected patients in whom previous PEG/RBV therapy had failed. Of patients, 63% had genotype 3; 34% of all patients had cirrhosis. Because persons who had experienced prior relapses to IFN-based therapy accounted for 75% of patients, the number of patients with a prior nonresponse in the study was limited. The SVR rate for genotype 3 patients in the 12-week arm was 30% (19% among patients with cirrhosis and 37% among those without cirrhosis). Extending therapy to 16 weeks increased the SVR rate among genotype 3 patients to 62% (61% among patients with and 63% in those without cirrhosis).

Based on results from FUSION, the phase 3 multicenter, randomized placebo-controlled VALENCE trial was amended to evaluate the effect of extending sofosbuvir plus RBV therapy to 24 weeks in all patients with HCV genotype 3. As with the FUSION study, most (65%) treatment-experienced patients had relapsed. The SVR12 rates after 24 weeks of therapy for treatment-experienced patients with genotype 3 was 79% (60% among patients with and 87% in those without cirrhosis). The increased efficacy with 24 weeks of sofosbuvir plus RBV therapy across all fibrosis stages combined with a favorable safety and tolerability profile supports the recommendation to use 24 weeks of sofosbuvir plus RBV in all genotype 3 patients despite the minimal number of patients studied to date. The response rate for HCV genotype 3-infected patients with cirrhosis treated for 24 weeks in the VALENCE trial (60%) was similar to that observed after 16 weeks of treatment in the FUSION trial (61%). Although longer treatment duration with a well-tolerated regimen may potentially be more successful in these more difficult-to-treat patients, data remain limited. Either duration of treatment is considered acceptable at this time (see below).

Alternate regimen for HCV genotype 3 PEG/RBV nonresponder patients who are eligible to receive IFN.

Retreatment with daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is an alternative for IFN-eligible persons with HCV genotype 3 infection.

Rating: Class IIa Level B

Choice of specific regimen may be influenced by previous or anticipated tolerance to PEG or the presence of advanced fibrosis or cirrhosis. For most patients, the ease of administration and tolerability of sofosbuvir plus RBV will outweigh any potential benefit associated with the addition of PEG. However, for HCV genotype 3-infected patients who have cirrhosis, responses to sofosbuvir and RBV alone for 24 weeks were suboptimal.

In the LONESTAR-2 study, adding 12 weeks of PEG to the sofosbuvir and RBV regimen resulted in numerically higher response rates among persons with HCV genotype 3 than those obtained with sofosbuvir and RBV for 24 weeks. Of HCV genotype 3-infected patients with and without cirrhosis, 10 (83%) of 12 achieved SVR. Given the limited number of patients in this demographic in both the VALENCE and LONESTAR-2 studies, these differences in response rates should be interpreted with caution.

The following regimens are NOT recommended for nonresponder patients with HCV genotype 3 infection.

- **PEG/RBV with or without telaprevir, boceprevir or simeprevir**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

No HCV protease inhibitors have been approved or are indicated for the treatment of genotype 3 HCV infection. Although PEG/RBV has been the mainstay of treatment of genotype 3 HCV, it is less efficacious and has more adverse effects than the recommended regimens.

IV. Genotypes 4, 5 and 6

Recommended regimen for HCV genotype 4, PEG/RBV nonresponder patients.

Daily sofosbuvir (400 mg) for 12 weeks and daily weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for retreatment of IFN-eligible persons with HCV genotype 4 infection.

Rating: Class IIa, Level C

Alternate regimen for HCV genotype 4, PEG/RBV nonresponder patients.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for retreatment of HCV genotype 4 infection.

Rating: Class IIa, Level B

The following regimens are NOT recommended for nonresponder patients with genotype 4 HCV infection.

- **PEG/RBV with or without telaprevir or boceprevir**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

Recommended regimen for HCV genotype 5 or 6, PEG/RBV nonresponder patients.

Daily sofosbuvir (400 mg) for 12 weeks and daily weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for retreatment of IFN-eligible persons with HCV genotype 5 or 6 infection.

Rating: Class IIa, Level C

Alternate regimen for PEG/RBV nonresponder patients with HCV genotype 5 or 6.

None

The following regimens are NOT recommended for nonresponder patients with HCV genotype 5 or 6.

- **PEG/RBV with or without telaprevir or boceprevir**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

In the NEUTRINO trial, high SVR rates were seen in small numbers of treatment-naive patients with HCV genotypes 4, 5, and 6 treated with sofosbuvir plus PEG/RBV for 12 weeks (genotype 4: n=28, SVR=96%; genotype 5: n=1, SVR=100%; and genotype 6: n=6, SVR=100%). (Lawitz, 2013a) In a pilot study of treatment-experienced HCV genotype 4 patients of Egyptian ancestry, SVR12 was 59% in patients treated with sofosbuvir plus RBV for 12 weeks; SVR4 was 93% in patients treated for 24 weeks. In this cohort, 24% to 27% of patients had cirrhosis. (Ruane, 2013) The only available data with simeprevir for treatment-experienced patients with genotype 4 come from the ongoing RESTORE trial, in which patients (n=50) are receiving treatment with daily simeprevir 150 mg for 12 weeks plus PEG/RBV for a total of 48 weeks (10 prior partial responders, 40 prior null responders). Interim analysis revealed a 40% to 49% RVR rate using this regimen. Final SVR results are pending. (Moreno, 2013) Given the relative paucity of data, expert consultation is needed to determine optimal duration of therapy in patients with genotype 4, 5, or 6 treated with sofosbuvir.

Retreatment Box. Recommendations for Patients in Whom Previous PEG/RBV Treatment Has Failed†

Genotype	Recommended	Alternative	NOT Recommended
Patients in whom previous PEG/RBV has failed*			
1	SOF + SMV ± RBV x 12 weeks	SOF x 12 weeks + PEG/RBV 12 weeks SMV x 12 weeks + PEG/RBV x 24 weeks**	PEG/RBV ± telaprevir or boceprevir Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG or SMV
2	SOF + RBV x 12 weeks	SOF + PEG/RBV x 12 weeks	PEG/RBV ± telaprevir or boceprevir Monotherapy with PEG, RBV, or a direct-acting antiviral agent Do not treat decompensated cirrhosis with PEG
3	SOF + RBV x 24 weeks	SOF + PEG/RBV x 12 weeks	PEG/RBV ± any current protease inhibitor Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG
4	SOF x 12 weeks + PEG/RBV 12 weeks SOF + RBV x 24 weeks	SMV x 12 weeks + PEG/RBV x 24-48 weeks	PEG/RBV ± any current HCV protease inhibitor Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG
5 or 6	SOF x 12 weeks + PEG/RBV 12 weeks	SOF + RBV x 24 weeks	PEG/RBV ± any current HCV protease inhibitor Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG
Patients in whom previous treatment with PEG/RBV plus either telaprevir or boceprevir has failed †† †††***			
1a	SOF x 12 weeks + PEG/RBV x 24 weeks	SOF + RBV x 24 weeks	PEG/RBV ± telaprevir or boceprevir or SMV
1b	SOF x 12 weeks + PEG/RBV x 12-24 weeks	SOF + RBV x 24 weeks	Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG or SMV

*Non-responder is defined as partial or null response to treatment with PEG/RBV. Relapse to prior therapy should be treated the same as treatment-naive (see Initial Treatment section)

**For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present

*** Non-responder is defined as partial or null response to treatment with PEG/RBV plus telaprevir or boceprevir. Relapse to prior therapy should be treated the same as treatment naive (see Initial Treatment section)

† Consideration should be given to postponing treatment, pending release of new drugs for patients with limited (F 0-2) hepatic fibrosis

†† A recommendation for simeprevir use for patients with previous telaprevir or boceprevir exposure not provided due to potential risk of preexistant resistance to protease inhibitor treatment.

††† Given the lack of prior approval PI therapy for genotypes 2, 3, 4, 5, 6, and the lack of sufficient data, no recommendations are given for these genotype at this time

UNIQUE PATIENT POPULATIONS

1. Patients with HIV/HCV Coinfection

The summary of recommendations for HIV-coinfected patients is in the Unique Patient Populations: HIV/HCV Coinfection Box.

Recommended regimen(s) for treatment-naive and prior relapser HIV/HCV-coinfected patients with genotype 1 infection who are eligible to receive IFN:

- **Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.**

  Rating: Class I, Level B

Recommended regimen(s) for treatment-naive and prior relapser HIV/HCV-coinfected patients with genotype 1 who are ineligible or unwilling to receive IFN.

- **Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 24 weeks is recommended for treatment-naive HIV/HCV-coinfected patients with HCV genotype 1 infection.**

  Rating: Class I, Level B

- **Sofosbuvir (400 mg once daily) plus simeprevir (150 mg once daily), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 12 weeks is recommended for treatment-naive and prior PEG/RBV relapser HIV/HCV-coinfected patients with genotype 1 infection. Simeprevir should only be used with antiretroviral drugs with which it does not have significant interactions: raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, and abacavir.**

  Rating: Class IIa Level C

Recommended regimen(s) for treatment-experienced patients with HCV genotype 1 with a history of PEG/RBV nonresponse, regardless of IFN eligibility

- **Sofosbuvir (400 mg once daily) plus simeprevir (150 mg once daily) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 12 weeks is recommended for prior PEG/RBV nonresponder, HIV/HCV-coinfected patients with genotype 1 infection. Simeprevir should only be used with antiretroviral drugs with which it does not have significant interactions: raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, and abacavir.**

  Rating: Class IIa, Level C

Recommended regimen(s) for treatment-experienced patients with HCV genotype 1 with a history of PEG/RBV plus telaprevir or boceprevir nonresponse

- **Treat as recommended for HCV-monoinfected individuals.**

Recommended regimen(s) for treatment-naive and treatment-experienced HIV/HCV-coinfected patients with genotype 2 and 3 infection

- **Use the same regimens as is recommended for persons with HCV monoinfection; specifically:**
  - *For patients with genotype 2 infection: sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 12 weeks is recommended for treatment-naive and treatment-experienced HIV/HCV-coinfected patients. Patients who are prior nonresponders and have cirrhosis may benefit by extension of treatment to 16 weeks.*

    Rating: Class I, Level B
  - *For patients with genotype 3 infection: sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 24 weeks is recommended for treatment-naive and treatment-experienced HIV/HCV-coinfected patients.*

    Rating: Class I, Level B

Recommended regimen(s) for treatment-naive and treatment-experienced HIV/HCV-coinfected patients with genotype 4, 5, or 6 HCV:

- **Treat as recommended for persons with HCV monoinfection.**

HIV/HCV coinfection results in increased liver-related morbidity and mortality, non-hepatic organ dysfunction, and overall mortality. Even in the potent antiretroviral era, HIV infection remains independently associated with advanced liver fibrosis and cirrhosis in patients with HCV coinfection. (Thein, 2008); (de Ledinghen, 2008); (Fierer, 2013) Similar to HCV-monoinfected patients, HIV/HCV-coinfected patients cured with PEG/RBV have lower rates of hepatic decompensation, hepatocellular carcinoma, and liver related mortality. (Berenguer, 2009); (Limketkai, 2012); (Mira, 2013) Uptake of HCV therapy is limited in the HIV/HCV-coinfected population due to historically lower response rates, patient comorbidities, patient and practitioner perception, and the adverse events associated with IFN-based therapy. (Mehta, 2006); (Thomas, 2008) Due to the special population designation, the first 2 approved DAAs, telaprevir and boceprevir, remain off label for use in HIV/HCV-coinfected patients, further limiting access to treatment in this population. With the availability of the DAAs sofosbuvir and simeprevir, a milestone has been reached in HIV/HCV coinfected patients. Treatment of HIV/HCV-coinfected patients requires awareness and attention to the complex drug interactions that can occur between DAA and HIV antiretroviral medications.

Pharmacokinetics and Drug Interactions

Sofosbuvir is not metabolized by the hepatic P450 enzyme complex and is a substrate (but not an inhibitor) of drug transporters, p-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). It is not a substrate of OATP. Drug interaction studies with antiretroviral drugs (ie, efavirenz, tenofovir, emtricitabine, rilpivirine, darunavir/ritonavir, and raltegravir) in non-infected persons identified no clinically significant interactions (Kirby, 2013) making sofosbuvir an ideal therapy for patients with HIV/HCV coinfection. Sofosbuvir is not recommended for use with tipranavir because of the potential of this antiretroviral drug to induce P-gp (see package insert).

Simeprevir is metabolized primarily by cytochrome P450 3A4 (CYP3A4) and therefore is susceptible to drug interactions with inhibitors and inducers of the enzyme. Simeprevir is also an inhibitor of the OATP and P-gp transporters leading to additional drug interaction concerns. Drug interaction studies with antiretroviral drugs in non-infected volunteers suggested no substantial interactions with tenofovir, rilpivirine, or raltegravir; however, simeprevir concentrations were substantially decreased when dosed with efavirenz and substantially increased when dosed with darunavir/ritonavir, resulting in their exclusion from the Phase III C212 clinical trial investigating simeprevir in combination with PEG/RBV in patients with HIV/HCV coinfection. (Ouwerkerk-Mahadevan, 2012)

Ribavirin has the potential for dangerous drug interactions with didanosine resulting in mitochondrial toxicity with hepatomegaly/steatosis, pancreatitis, and lactic acidosis; thus the concomitant administration of these 2 drugs is contraindicated. (Fleischer, 2004) The combined use of RBV and zidovudine has been reported to increase the rates of anemia and the need for RBV dose reduction, and thus zidovudine is not recommended for use with RBV. (Alvarez, 2006)

Sofosbuvir (400 mg once daily) as part of a triple-therapy regimen with PEG (180 µg weekly) and weight-based RBV (1000 mg to 1200 mg daily given in divided doses) is safe and efficacious in patients with HCV monoinfection, with an overall SVR12 of 89% in HCV genotype 1 patients. The P7977-1910 study was a single-center, single-arm trial (N=23) investigating this same 12-week triple therapy regimen in HIV-infected patients coinfected with HCV genotypes 1, 2 3, or 4. (Rodriguez-Torres, 2013) Allowable antiretrovirals included either efavirenz, atazanavir/ritonavir, darunavir/ritonavir, raltegravir, or rilpivirine in combination with tenofovir/emtricitabine. Of patients with HCV genotype 1 (N=19), 89% achieved SVR12; 2 patients discontinued the study early due to adverse events (ie, anemia and altered mood). This regimen is therefore recommended for persons with HIV/HCV genotype 1 coinfection who are eligible to receive IFN and are either treatment-naive or have had prior PEG/RBV relapse.

The Phase III PHOTON-1 study enrolled 182 treatment-naive patients with HIV/HCV coinfection (n=114 with genotype 1; n=26 with genotype 2; n=42 with genotype 3) in a single-arm clinical trial investigating sofosbuvir (400 mg once daily) plus weight-based RBV (1000 mg to 1200 mg daily given in divided doses) for 24 (genotype 1) or 12 (genotypes 2 and 3) weeks. (Sulkowski, 2013c) The population had well-controlled HIV with mean CD4 counts of 559 to 636 cells/µL. The same ARVs were allowed as those in the P7977-1910 study. Of participants, 90% completed treatment and 3% discontinued treatment due to adverse events. SVR12 was achieved in 76%, 88%, and 67% of participants with HCV genotypes 1, 2, and 3, respectively. For the combination of sofosbuvir plus RBV, genotype 1b subtype was a predictor of poorer response. Cirrhosis and African American race also exhibited trends toward lower SVR12. Based on the potential for lower response in HIV/HCV-coinfected patients with cirrhosis, the use of sofosbuvir plus PEG/RBV should be considered over sofosbuvir plus RBV. This regimen is otherwise recommended for HIV/HCV genotype 1-coinfected patients who are treatment naive or have relapsed after receipt of PEG/RBV and are ineligible for IFN.

The combination of simeprevir plus sofosbuvir with or without RBV has been studied in the phase II COSMOS trial in patients with HCV monoinfection. (Jacobson, 2013b) This study is the basis for the recommendation supporting the use of this all-oral combination as an alternative regimen for patients with HCV monoinfection who cannot tolerate the recommended regimens. Although sofosbuvir plus simeprevir has been used anecdotally in patients with HIV/HCV coinfection, this drug combination has never been studied in this population. Despite the absence of data, this regimen may be considered for the treatment of HCV genotype 1 infection in patients with HIV infection who are not eligible for IFN and who are receiving antiretroviral therapy that may be coadministered with simeprevir (ie, raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, and abacavir).

Similarly, no data exist for the combination of sofosbuvir plus simeprevir for the (re)treatment of HCV infection in HIV-infected patients. However, preliminary results obtained in HCV-monoinfected patients, including those with prior treatment failure and advanced fibrosis, support the expectation that this regimen will be highly effective in coinfected patients receiving compatible antiretroviral therapy as

described above (see Retreatment of HCV Monoinfected Patients). (Jacobson, 2013b) Given the lack of clinical data in this population, it may be prudent to reserve this regimen for the treatment of persons with advanced fibrosis in whom a delay of therapy may lead to adverse clinical outcomes.

No data with sofosbuvir currently exist to guide retreatment recommendations for coinfected patients with HCV genotype 2 or 3 HCV infection. The ongoing PHOTON-1 study enrolled 41 treatment-experienced patients coinfected with HCV genotype 2 or 3, receiving sofosbuvir (400 mg once daily) plus weight-based RBV (1000 mg to 1200 mg daily given in divided doses) for 24 weeks. (Sulkowski, 2013b) Results are expected in early 2014. In the absence of data, current recommendations for the retreatment of HIV patients coinfected with HCV genotype 2 or 3 are the same as those for HCV-monoinfected patients. Data also are lacking regarding use of sofosbuvir among patients coinfected with HCV genotype 4, 5, or 6 and HIV. Similarly, with no current data on the use of sofosbuvir in patients with genotype 4, 5, or 6 HCV and HIV coinfection, but given evidence of safety and efficacy of sofosbuvir-based regimens in this population, the recommended regimens for treatment in treatment-naive and treatment-experienced patients with HIV/HCV coinfection are the same as those for HCV-monoinfected patients.

Alternative regimen(s) for treatment-naive or treatment-experienced (prior PEG/RBV relapse) HIV/HCV- coinfected patients with genotype 1 who are eligible to receive IFN

- **Simeprevir (150 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 24 weeks (for treatment-naive and treatment-experienced with prior relapse to PEG/RBV) is an acceptable regimen for IFN-eligible HIV/HCV-coinfected persons with either (1) HCV genotype 1b or (2) HCV genotype 1a infection in whom the Q80K polymorphism is not detected prior to treatment. Simeprevir can only be used with the following antiretroviral drugs: raltegravir, rilpivirine, maraviroc, enfuvirtide tenofovir, emtricitabine, lamivudine, and abacavir.**

  Rating: Class IIa, Level B

Alternative regimen(s) for treatment-experienced (PEG/RBV nonresponders) HIV/HCV-coinfected patients with genotype 1 who are eligible for IFN

- **Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 12 weeks is an acceptable regimen for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.**

  Rating: Class IIb, Level C

Alternative regimen(s) for treatment-naive and PEG/RBV relapser HIV/HCV-coinfected patients with genotype 1 who are ineligible or unwilling to receive IFN.

- **None**

Alternative regimen(s) for treatment-experienced (PEG/RBV nonresponder) HIV/HCV-coinfected patients with genotype 1 who are ineligible to receive IFN.

- **Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 24 weeks is an acceptable regimen for treatment-experienced (nonresponder) HIV/HCV-coinfected patients with HCV genotype 1 infection.**

  Rating: Class IIb, Level C

Alternative regimen(s) for treatment-naive and PEG/RBV relapser, HIV/HCV-coinfected patients with genotype 2 or 3 infection.

- **None**

Alternative regimen(s) for treatment-experienced (PEG/RBV nonresponder) HIV/HCV-coinfected patients with genotype 2 or 3 infection who are eligible to receive IFN.

- **Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 12 weeks is an acceptable regimen for treatment-experienced IFN-eligible persons with HCV genotype 2 or 3 infection.**

  Rating: Class IIa, Level C

Alternative regimen(s) for treatment-naive and treatment-experienced HIV/HCV-coinfected patients with HCV genotype 4, 5, or 6 infection.

- **None**

The TMC435-C212 is a Phase III, open-label, single-arm study investigating simeprevir plus PEG/RBV (fixed-dose ribavirin) in treatment-naive and treatment-experienced patients coinfected with HCV genotype-1 and HIV. (Dieterich, 2013) The study used an RGT design for treatment-naive and prior PEG/RBV relapsers; prior partial and null responders and all patients with cirrhosis (regardless of treatment history) received 48 weeks of therapy (SMV x 12 weeks plus PEG/RBV x 48 weeks). The primary analysis reported an overall SVR12 of 74% (treatment naive: 79%; prior relapsers, 87%: prior partial responders: 70%; prior null responders: 57%). Most (89%) eligible patients met criteria for RGT and were able to shorten therapy to 24 weeks, after which time 78% achieved SVR12. Lower SVR12 was reported in several clinically relevant subgroups: genotype 1a (71% vs 89% in genotype 1b); genotype 1a with the Q80K mutation at baseline (67%); advanced fibrosis or cirrhosis (64%); IL28B unfavorable genetic polymorphisms (68% and 61% for the CT and TT variants vs 96% for the favorable CC variant); high baseline HCV RNA (70% for >800,000 IU/mL or 93% for <800,000 IU/mL); and patients not receiving antiretroviral therapy (62% vs 75% in subjects on antiretroviral drugs). As with patients with HCV monoinfection, baseline resistance testing for the Q80K polymorphism should be performed in all patients harboring the genotype 1a subtype and a different regimen considered if the polymorphism is present. Virologic failures occurred; most failures (79%) were associated with the emergence of resistant-associated mutations.

The adverse event profile was similar to that of patients with HCV monoinfection, with a higher frequency of pruritus, rash, photosensitivity, and increased bilirubin than is observed in patients receiving PEG/RBV alone. Due to the complexity of antiretroviral drug-associated drug interactions with simeprevir, the longer course of PEG/RBV, the adverse effect profile, and the risk of resistance emergence with treatment failure, simeprevir plus PEG/RBV is considered an alternative regimen for treatment-naive and prior PEG/RBV relapse patients with HIV coinfection with genotype HCV who cannot tolerate the recommended regimens. This regimen is not recommended in prior nonresponders or patients with cirrhosis because of observed lower response rates seen and the poor tolerability of 48 weeks of PEG/RBV. Due to diminished activity in vitro (for genotype 2 and 3) and insufficient data (for genotype 4) this regimen cannot be recommended for these genotypes.

Sofosbuvir plus PEG/RBV has not been studied in patients with HIV/HCV genotype 1 coinfection in whom previous IFN-based HCV therapy has failed. However, in a study of a limited number of patients (n=19), the efficacy of this regimen in treatment-naive subjects with HIV/HCV genotype 1 coinfection was equivalent to that in patients with HCV monoinfection. (Rodriguez-Torres, 2013) An exploratory FDA analysis estimated the SVR rate of this regimen to be 78% among a treatment-experienced population with HCV monoinfection, including 71% in those with multiple poor pretreatment response predictors. (US FDA, 2013b) These data, along with the absence of antiretroviral drug limitations, support inclusion of this regimen as a recommended option for treatment-experienced patients with HIV/HCV coinfection.

Sofosbuvir plus RBV has not been studied in prior HCV treatment-experienced patients with HIV/HCV genotype 1 coinfection. This regimen yielded an SVR12 rate of 76% among treatment-naive HIV/HCV genotype 1-coinfected patients. (Sulkowski, 2013b) However, responses to this regimen are expected to be lower in treatment-experienced coinfected subjects based on limited data in treatment-experienced HCV-monoinfected patients treated for 12 weeks with sofosbuvir (400 mg once daily) plus weight-based RBV (1000 mg to 1200 mg daily in divided doses). (Gane, 2013a) Further, response rates are expected to be lower than those associated with the recommended and alternative regimens. This regimen should be reserved for coinfected patients who cannot tolerate IFN and do not have antiretroviral regimen options compatible with simeprevir. These patients require expert consultation with careful consideration of fibrosis stage; in some cases, deferral of therapy may be a more appropriate action.

Sofosbuvir plus PEG/RBV has not been studied in patients with HIV/HCV genotype 2 or 3 coinfection in whom previous IFN-based HCV therapy has failed. However, recognizing the potential limitations of sofosbuvir plus RBV in more difficult to treat genotype 2 and 3 patients, particularly those with prior nonresponse and cirrhosis, the addition of IFN to the regimen can be considered for those patients who are eligible. The LONESTAR-2 (open-label, single-site, single-arm phase 2 trial) evaluated PEG (180 µg weekly), sofosbuvir (400 mg once daily), and weight-based RBV (1000 mg to 1200 mg daily in divided doses) for 12 weeks in HCV-monoinfected treatment-experienced patients with genotype 2 or 3 infection. Cirrhosis was present at baseline in 55% of patients. Overall, SVR12 was achieved in 96% (22 of 23) of those with genotype 2 infection. SVR occurred in 93% (13/14) and 100% (9 of 9) of patients with and without cirrhosis, respectively. Because sofosbuvir is safe and effective when used to treat HIV/HCV-coinfected patients, the combination of sofosbuvir plus PEG/RBV for 12 weeks can be considered for appropriate genotype 2 and 3 HIV/HCV-coinfected patients.

The following regimens are NOT recommended for treatment-naive or treatment-experienced HIV/HCV-coinfected patients

- **PEG/RBV with or without telaprevir or boceprevir for 24 to 48 weeks**

  Rating: Class IIb, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

Due to its prolonged treatment course, adverse effects, and poor response rates, PEG/RBV is no longer recommended for the treatment of patients with HCV genotypes 1, 2, 3, or 4 who are coinfected with HIV. Neither telaprevir nor boceprevir is approved for use in patients with HIV/HCV coinfection. However, when combined with PEG/RBV and used for 48 weeks, these drugs have reported efficacy and safety in patients with HIV/HCV genotype 1 coinfection similar to that in patients with HCV genotype 1 monoinfection. (Sulkowski, 2013d); (Sulkowski, 2013a) Ongoing Phase III trials will investigate the use of RGT for select patient groups. Telaprevir and boceprevir are each substrates and inhibitors of CYP3A4 and thus have substantial drug interactions with antiretroviral drugs. (van Heeswijk, 2011a); (van Heeswijk, 2011b); (Kakuda, 2012); (Johnson, 2013); (Kasserra, 2011); (Hulskotte, 2013); (Garraffo, 2013); (de Kanter, 2012); (Hammond, 2013); (Vourvahis, 2013) Due to the adverse effect profile, prolonged required course of PEG/RBV, and substantial drug interactions, these agents are no longer recommended for HIV/HCV-coinfected patients.

Because of their limited activity in vitro and in vivo against HCV genotypes 2 and 3, boceprevir, telaprevir, and simeprevir should not be used as therapy for HIV/HCV-coinfected patients with HCV genotype 2 or 3 infection. Boceprevir and telaprevir also have limited activity against HCV genotype 4 and should not be used as therapy for HIV/HCV coinfected patients with HCV genotype 4 infection. There are currently not enough data to support a recommendation for the use of simeprevir for genotype 4 infection in HIV/HCV-coinfected patients.

2. Patients with Cirrhosis

The summary of recommendations for patients with cirrhosis is in the box.

Compensated Cirrhosis

Treatment-naive patients with compensated cirrhosis, including those with hepatocellular carcinoma, should receive the same treatment as recommended for patients without cirrhosis.

Rating: Class I, Level A

This statement is supported by a number of studies (described above) that included patients with compensated cirrhosis who were evaluated in sub-group analyses.

Decompensated Cirrhosis

Patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).

Rating: Class I, Level C

If the decision to treat has been made, the recommended regimen for patients with any HCV genotype who have decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. This regimen should be used only by highly experienced HCV providers

Daily sofosbuvir (400 mg) plus weight-based RBV (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks

Rating: Class IIb, Level B

In one study, 61 patients with HCV infection and hepatocellular carcinoma meeting MILAN criteria for liver transplant were treated with sofosbuvir plus RBV for up to 48 weeks. (Curry MP, 2013) At the time of treatment initiation, the median MELD score was 8 (range: 6-14), and 17 patients had CTP scores of 7 or 8 (CTP Class B). To date, 44 patients have undergone liver transplantation, of whom 41 (93%) had HCV RNA below the lower limit of quantification. At 12 weeks post-transplant, 23 of 37 (62%) had no detected HCV RNA consistent with prevention of recurrent HCV infection. In the post-transplant period, 10 patients experienced recurrent HCV infection. Among the 10 patients who experienced recurrent graft infection, 9 had HCV RNA not detected for less than 30 days pretransplant. The most common adverse effects were fatigue, anemia, and headache; adverse effects led to treatment discontinuation for 2 patients (3%).

In a sofosbuvir compassionate-use program for patients with severe recurrent HCV infection following liver transplantation who were predicted to have a less than 6-month survival, (Forns, 2013b) 44 patients were treated with sofosbuvir plus RBV 32 patients were also given PEG. At treatment initiation, the median MELD score was 16 (range: 6-43), and fibrosing cholestatic hepatitis was documented in 20 patients. After week 12 of treatment, 91% of patients treated with sofosbuvir plus RBV and 75% of those treated with the addition of PEG achieved HCV RNA less than the lower limit of quantification. Of 27 patients evaluated at 12 weeks post-treatment, 15 patients (56%) achieved SVR. Overall, 75% had improved or stable clinical liver disease including improvement in hyperbilirubinemia and coagulopathy as well as decrease in MELD score. In this very sick population, 8 patients died, most from liver disease progression.

The following regimens are NOT recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C):

- **Any IFN-based therapy**

  Rating: Class III, Level A

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

- **Telaprevir-, boceprevir-, or simeprevir-based regimens**

  Rating: Class III, Level A

IFN should not be given to patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) because of the potential for worsening hepatic decompensation. Neither telaprevir nor boceprevir should be used for this population because they must be coadministered with PEG/RBV. Very minimal data exist for the use of simeprevir in patients with decompensated cirrhosis. Until additional data become available, simeprevir should not be used in patients with decompensated cirrhosis.

3. Patients Who Develop Recurrent HCV Infection Post-Liver Transplantation

The summary of recommendations for patients who develop recurrent HCV infection post-liver transplantation is in the box.

Recommended regimen for treatment-naive patients with HCV genotype 1 in the allograft liver, including those with compensated cirrhosis

Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg), for 12 weeks to 24 weeks is recommended for patients with compensated allograft HCV genotype 1 infection.

Rating: Class IIb, Level C

Recommended regimen for treatment-naive patients with HCV genotype 2 or 3 in the allograft liver, including those with compensated cirrhosis

Daily sofosbuvir (400 mg) and RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg) with consideration of the patient's CrCl value and hemoglobin level for 24 weeks is recommended for patients with compensated allograft HCV genotype 2 or 3 infection.

Rating: Class IIb, Level C

Alternate regimen for treatment-naive patients with genotype 1 HCV in the allograft liver, including those with compensated cirrhosis.

Daily sofosbuvir (400 mg) and RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg) with consideration of the patient's CrCl value and hemoglobin level, with or without PEG (in the absence of contraindication to its use), for 24 weeks is recommended for patients with compensated allograft HCV genotype 1 infection.

Rating: Class IIb, Level C

Simeprevir has not been studied with sofosbuvir in the post-transplant setting; however, drug interaction studies in non-infected participants indicate that simeprevir can be dosed safely in conjunction with calcineurin inhibitors. Based on these data, clinicians may consider the use of sofosbuvir plus simeprevir as described for non-transplant patients, particularly in those expected to have difficulty tolerating RBV (eg, patients with impaired renal function and anemia). Consideration should be given to pretreatment resistance testing for the Q80K polymorphism in genotype 1a-infected patients.

In addition to the sofosbuvir compassionate-use program, (Forns, 2013a) 40 patients with recurrent HCV infection following liver transplantation were treated for 24 weeks with sofosbuvir (400 mg daily) plus RBV (starting at 600 mg daily followed by dose escalation as tolerated). (Charlton, 2013) At study entry, patients were required to be at least 6 months post-transplant, to have a CTP score of 7 or lower, and to have a MELD score of 17 or lower. Bridging fibrosis or cirrhosis was documented in 25 patients (63%). At the end of treatment, all patients had HCV RNA levels below the lower limit of quantification and, at 4 weeks after treatment discontinuation, 27 of 35 patients (77%) had undetectable levels of HCV RNA. The most common adverse events were fatigue, headache, and arthralgia. Anemia was reported in 20% of patients. Two patients discontinued therapy due to adverse events. No deaths, graft loss, or episodes of rejection were reported.

The addition of PEG to sofosbuvir plus RBV may also be considered in the absence of contraindications.

The following regimens are NOT recommended for treatment-naive patients with compensated allograft hepatitis C virus infection.

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

- **Telaprevir- or boceprevir- based regimens should not be used for patients with compensated allograft hepatitis C virus infection.**

  Rating: Class III, Level A

Telaprevir or boceprevir should not be used in the post-liver transplant population because of surrounding toxicity and drug interactions with calcineurin inhibitors.

Decompensated Cirrhosis

Treatment-naive patients with decompensated allograft HCV infection should receive the same treatment as recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C).

Rating: Class I, Level C

4. Patients with Renal Impairment, Including Severe Renal Impairment (CrCl <30 mL/min) or ESRD Requiring Hemodialysis or Peritoneal Dialysis

Summary of Recommendations for Patients with Renal Impairment Including, Severe Renal Impairment (CrCl <30 mL/min) or ESRD Requiring Hemodialysis or Peritoneal Dialysis is found in the Unique Patient Populations: Renal Impairment Box.

When using sofosbuvir to treat or retreat HCV infection in patients with appropriate genotypes, no dosage adjustment is required for patients with mild to moderate renal impairment (CrCl ≥30 mL/min). Sofosbuvir is not recommended in patients with severe renal impairment/ESRD (CrCl <30 mL/min) or those who require hemodialysis, because no dosing data are currently available for this patient population.

Rating: Class IIa, level B

Sofosbuvir enters the hepatocyte, where it is metabolized to its active form, GS-461203. The downstream inactive nucleoside metabolite GS-331007 is almost exclusively eliminated from the body renally, mediated through a combination of glomerular filtration and active tubular secretion. Results of phase 2 and 3 sofosbuvir clinical trials have excluded patients with serum Cr level above 2.5 and/or CrCl level below <60 mL/min. The pharmacokinetics of a single dose of sofosbuvir 400 mg was assessed in persons not infected with HCV (study P7977-0915) with mild (estimated glomerular filtration rate [eGFR] ≥50 and <80 mL/min/1.73m^2), moderate (eGFR ≥30 and <50 mL/min/1.73m^2), severe renal impairment (eGFR <30 mL/min/1.73m^2) and persons with ESRD requiring hemodialysis. Relative to persons with normal renal function (eGFR >80 mL/min/1.73m^2), the sofosbuvir AUC (0-inf) was 61%, 107%, and 171% higher in subjects with mild, moderate, and severe renal impairment, respectively. The GS-331007 AUC (0-inf) was 55%, 88%, and 451% higher, respectively. No safety signals have been seen under similar conditions. In subjects with ESRD (relative to subjects with normal renal function), sofosbuvir and GS-331007 AUC (0-inf) was 28% and 1280% higher, respectively, when sofosbuvir was dosed 1 hour before hemodialysis, compared with 60% and 2070% higher, respectively, when sofosbuvir was dosed 1 hour after hemodialysis. No dose adjustment is required for patients with mild or moderate renal impairment. The safety of sofosbuvir has not been established in patients with severe renal impairment or ESRD. Therefore, a dose recommendation cannot be provided for these populations at this time, although a dedicated study to evaluate optimal dosing of sofosbuvir in HCV-infected patients with severe renal impairment or ESRD on hemodialysis is currently underway.

When using simeprevir in treatment/retreatment of HCV-infected patients, no dosage adjustment is required for patients with mild to moderate to severe renal impairment. Simeprevir has not been studied in patients with ESRD, including those requiring hemodialysis.

Rating: Class IIa, level B

Simeprevir is primarily metabolized by liver CYP3A4, and renal clearance plays an insignificant role (<1%) in the elimination of simeprevir and its metabolites.

Simeprevir 150 mg daily for 7 days has been studied in non-HCV infected patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) and healthy volunteers (eGFR > mL/min/1.73 m^2). For persons with severe renal impairment, simeprevir C_{min}, C_{max}, and AUC (24 hour) were 71%, 34%, and 62% higher, respectively, compared with matched healthy controls. Simeprevir exposure was higher in patients with severe renal impairment (steady-state by day 7), but no significant difference was observed in simeprevir plasma protein binding. Simeprevir was generally safe and well tolerated in subjects with severe renal impairment. Therefore, no dose adjustment of simeprevir is required in these patients. No clinically significant differences in pharmacokinetics were observed in HCV-uninfected participants with mild, moderate, or severe renal impairment. CrCl level was not identified as a significant covariate of simeprevir population pharmacokinetics in HCV-infected patients. Simeprevir has not been evaluated in patients receiving hemodialysis.

In patients with renal impairment/ESRD/HD, dosing of PEG and RBV should follow updated FDA recommendations or package insert recommendations based on calculated GFR. Caution should be used in administering RBV to these patients, and close monitoring of hemoglobin is required.

Rating: Class IIa, level B

HCV infection is a major health problem in patients with ESRD. The incidence of acute HCV infection during maintenance dialysis is much higher than that in the general population because of the risk for nosocomial transmission. The kidney is important for the catabolism and filtration of both IFN and RBV, and therefore, reduced doses of both PEG and RBV are warranted in patients with ESRD.

Impaired excretion of RBV occurs in patients with chronic kidney disease, as RBV is mostly eliminated by the kidney. Very little RBV is removed via dialysis. Thus, the drug can accumulate, exacerbating hemolysis in the dialysis population already at substantial risk for anemia. If a decision is made to use RBV in patients on maintenance hemodialysis, it should be used only after the implementation of several safety precautions, including (1) administering very low doses of RBV (200 mg daily), (2) monitoring hemoglobin levels on a weekly basis, (3) titrating epoetin alfa to treat anemia, and (4) providing intravenous iron supplementation to boost erythropoietin activity.

Dose adjustments needed for patients with renal impairment are summarized in the Renal Impairment Table.

Unique Patient Populations: HIV/HCV Coinfection Box. Recommendations for HIV/HCV Coinfected Patients Who are Being Treated for HCV, by Genotype

Genotype	Recommended	Alternative	NOT Recommended	Allowable Antiretroviral Therapy
1	**Treatment-naive and prior PEG/RBV relapsers** **IFN eligible:** SOF + PEG/RBV x 12 weeks **IFN ineligible:** SOF + RBV x 24 weeks SOF + SMV ± RBV x 12 weeks **Treatment experienced (prior PEG/RBV nonresponders) regardless of IFN eligibility:** SOF + SMV ± RBV x 12 weeks	**Treatment-naive and prior PEG/RBV relapsers** **IFN eligible:** SMV x 12 weeks + PEG/RBV x 24 weeks* **IFN ineligible:** None **Treatment experienced (prior PEG/RBV nonresponders)** **IFN eligible:** SOF + PEG/RBV x 12 Weeks **IFN ineligible:** SOF + RBV x 24 Weeks	TVR + PEG/RBV x 24 or 48 weeks (RGT) BOC + PEG/RBV x 28 or 48 weeks (RGT) PEG/RBV x 48 weeks SMV x 12 weeks + PEG/RBV x 48 wks	**For SOF use:** ALL except didanosine, zidovudine **For SMV use:** LIMITED to raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir
2	SOF + RBV x 12 weeks regardless of treatment history	**Treatment naive and prior PEG/RBV relapsers: None** **Treatment experienced (prior PEG/RBV nonresponders)** **IFN eligible:** SOF + PEG/RBV X 12 Weeks **IFN ineligible:** None	PEG/RBV x 24-48 weeks Any regimen with TVR, BOC, or SMV	ALL except didanosine, zidovudine
3	SOF + RBV x 24 weeks regardless of treatment history	**Treatment naive and PEG/RBV relapsers: None** **Treatment experienced (prior PEG/RBV nonresponders)** **IFN eligible:** SOF + PEG/RBV X 12 Weeks **IFN ineligible:** None	PEG/RBV x 24 - 48 weeks Any regimen with TVR, BOC, or SMV	ALL except didanosine, zidovudine
4	**Regardless of treatment history:** **IFN eligible:** SOF + PEG/RBV x 12 weeks **IFN ineligible:** SOF + RBV x 24 weeks	None	PEG/RBV x 48 weeks Any regimen with TVR or BOC	ALL except didanosine, zidovudine
5 or 6	**Regardless of treatment history:** SOF + PEG/RBV x 12 weeks	None	PEG/RBV x 48 weeks Any regimen with TVR, BOC, or SMV	ALL except didanosine, zidovudine

*For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if present

Unique Patient Populations: Cirrhosis Box. Summary of Recommendations for Patients with Cirrhosis

Treatment-naive patients with compensated cirrhosis, including those with hepatocellular carcinoma, should receive the same treatment as recommended for patients without cirrhosis.

Rating: Class I, Level A

Patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).

Rating: Class I, Level C

The recommended regimen for patients with any HCV genotype who have decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. This regimen should be used only by highly experienced HCV providers

Daily sofosbuvir (400 mg) plus weight-based RBV (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks

Rating: Class IIb, Level B

The following regimens are NOT recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C):

- **Any IFN-based therapy**

  Rating: Class III, Level A
- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A
- **Telaprevir-, boceprevir-, or simeprevir-based regimens**

  Rating: Class III, Level A

Unique Patient Population: Post-Liver Transplantation Box. The summary of recommendations for patients who develop recurrent HCV infection post-liver transplantation

Recommended regimen for treatment-naive patients with HCV genotype 1 in the allograft liver, including those with compensated cirrhosis

Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg), for 12 weeks to 24 weeks is recommended for patients with compensated allograft HCV genotype 1 infection.

Rating: Class IIb, Level C

Recommended regimen for treatment-naive patients with HCV genotype 2 or 3 in the allograft liver, including those with compensated cirrhosis

Daily sofosbuvir (400 mg) and RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg) with consideration of the patient's CrCl value and hemoglobin level for 24 weeks is recommended for patients with compensated allograft HCV genotype 2 or 3 infection.

Rating: Class IIb, Level C

Alternate regimen for treatment-naive patients with genotype 1 HCV in the allograft liver, including those with compensated cirrhosis.

Daily sofosbuvir (400 mg) and RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg) with consideration of the patient's CrCl value and hemoglobin level, with or without PEG (in the absence of contraindication to its use), for 24 weeks is recommended for patients with compensated allograft HCV genotype 1 infection.

Rating: Class IIb, Level C

The following regimens are NOT recommended for treatment-naive patients with compensated allograft hepatitis C infection

- **Monotherapy with PEG, RBV, or a DAA**

  Rating: Class III, Level A

- **Telaprevir- or boceprevir- based regimens should not be used for patients with compensated allograft hepatitis C infection.**

  Rating: Class III, Level A

Treatment-naive patients with decompensated allograft HCV infection should receive the same treatment as recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C).

Rating: Class I, Level C

Renal Impairment Box. Summary of recommendations for Patients with Renal Impairment, Including Severe Renal Impairment (CrCl <30 ML/min) or ESRD Requiring Hemodialysis or Peritoneal Dialysis

When using sofosbuvir to treat or retreat HCV infection in patients with appropriate genotypes, no dosage adjustment is required for patients with mild to moderate renal impairment (CrCl ≥30 mL/min). Sofosbuvir is not recommended in patients with severe renal impairment/ESRD (CrCl <30 mL/min) or those who require hemodialysis, because no dosing data are currently available for this patient population.

Rating: Class IIa, level B

When using simeprevir in treatment/retreatment of HCV-infected patients, no dosage adjustment is required for patients with mild to moderate to severe renal impairment. Simeprevir has not been studied in patients with ESRD, including those requiring hemodialysis.

Rating: Class IIa, level B

In patients with renal impairment/ESRD/HD, dosing of PEG and RBV should follow updated FDA recommendations or package insert recommendations based on calculated GFR. Caution should be used in administering RBV to these patients, and close monitoring of hemoglobin is required.

Rating: Class IIa, level B

Unique Patient Populations: Renal Impairment Table. Dose Adjustments Needed for Patients with Renal Impairment

Renal Impairment	eGFR/CrCl level (mL/min/ 1.73 m^2)	Interferon	Ribavirin	Sofosbuvir	Simeprevir
Mild	50-80	180 µg PEG (2a); PEG (2b) 1.5 µg/kg	Standard	Standard	Standard
Moderate	30-50	180 µg PEG (2a); PEG alfa-2b1 µg/kg or 25% reduction	Alternating doses 200 and 400 mg every other day	Standard	Standard
Severe	<30	135 µg PEG (2a); PEG (2b)1 µg/kg or 50% reduction	200 mg/d	Data not available	Standard
ESRD/HD		PEG (2a) 135 µg/wk or PEG (2b) 1 µg/kg/wk or standard IFN 3 mU 3x/wk	200 mg/d	Data not available	Data not available

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The following guidelines were created by a Hepatitis C Clinical Advisory Group composed of the following clinicians specializing in hepatology in the metro area around Portland: Atif Zaman and Ken Ingram (OHSU); Ken Flora, Ken Benner, Adrian Davies, Jeremy Holden (Oregon Clinic); Brian Willis, Jennifer Urquhart, Jason Snider (Kaiser Permanente).

Medicaid guidelines for use of Sovaldi.

These guidelines are based on agents and evidence available as of July 2014. They will be reviewed and updated when new agents and new evidence are available over the next 6-12 months.

HCV patients who need treatment with Sovaldi in next 6-12 months in order to avoid poorer outcomes if treatment is delayed include:

1. Patients with the extrahepaitic manifestations of hepatitis C infection listed below who have formal documentation from a relevant specialist that their condition is HCV related.
a. Vasculitis
b. Glomerulonephritis
c. Cryoglobulinemia
d. Lymphoma

2. HIV/HCV co-infected patients with cirrhosis (Stage 4 disease).

3. HCV infection in the transplant setting (approval needs to be cleared by the OHSU Liver Transplant Program)
a. Listed patients who it is essential to eradicate the virus in order to realistically prevent a transplant or it is critical to prevent recurrent HCV infection post-transplant
b. Post-transplant patients with Stage 4 fibrosis
c. Post-transplant patients with fibrosing cholestatic hepatitis due to HCV infection

4. Cirrhotic (Stage 4) patients without ongoing progressive decompensation
a. MELD between 8-11
b. MELD>11 patients if cleared for treatment by the HCV Advisory Panel

5. Other scenarios not included can be brought to the Advisory Group on a case by case basis.

6. In all cases, expected survival from non-HCV associated morbidity should be >5 years.

Sofosbuvir (Sovaldi®)

Goal(s) :

- Approve cost effective treatments of chronic hepatitis C which are supported by the medical literature when there is available evidence. When evidence is lacking, consult with local specialists and the community standard.

Length of Authorization

- Initial trial of 12 weeks
- Continuation of therapy up to 24-48 weeks of total therapy based on therapy regimen, genotype, and patient population

Requies PA:

- Sofosbuvir

Approval Criteria		
1. What diagnosis is being treated?	**Record ICD9 code**	
2. Is the request for treatment of Chronic Hepatitis C Virus?	**Yes:** Go to #4	**No:** Pass to RPh, Deny For Appropriateness
3. Is the request for continuation of therapy?	**Yes:** Go to "Continuation of Therapy"	**No:** Go to #4
4. Is the medication being prescribed by or in consultation with a hepatologist or gastroenterologist with experience in Hepatitis C?	**Yes:** Go to #5	**No:** Pass to RPh, Deny For Appropriateness Forward to DMAP for further review to determine appropriateness of prescriber
5. Does the patient have a biopsy or other non-invasive technology (Fibroscan), including serum tests (Fibrosure, Fibrotest) to indicate severe fibrosis (stage 4) OR radiologic, laboratory, or clinical evidence of cirrhosis without ongoing progressive decompensation (MELD score between 8 and 11), and expected survival from non-HCV associated morbidity should be greater than 5 years?	**Yes:** Go to #10	**No:** Go to #6 **Note**: Patients with a MELD score >11 may be eligible for therapy, but only after review by the DMAP medical director. Forward case to DMAP for Medical Director Review and notify requesting provider of pending review.

6. Does the patient have one of the following extrahepatic manifestations of hepatitis C and who have formal documentation from a relevant specialist that their condition is HCV related, and expected survival from non-HCV associated morbidity should be greater than 5 years? a. Vasculitis b. Glomerulonephritis c. Cryoglobulinemia d. Lymphoma	**Yes:** Go to #10	**No:** Go to #7
7. Does the patient have a HIV coinfection with cirrhosis (Stage 4 disease), and expected survival from non-HCV associated morbidity should be greater than 5 years?	**Yes:** Go to #8	**No:** Go to #9
8. Is the patient under the supervision of an HIV specialist?	**Yes:** Go to #10	**No:** Pass to RPh; Deny (medical appropriateness)
9. Does the patient have Hepatitis C Virus in the transplant setting, including the following scenarios: a. Patient is listed for a transplant and it is essential to prevent recurrent hepatitis C infection post-transplant b. Post-transplant patients with Stage 4 fibrosis c. Post-transplant patients with fibrosing cholestatic hepatitis due to HCV infection	**Yes:** Go to #10 Note: Patients in the transplant setting may be eligible for therapy, but only after review by the DMAP medical director. Forward case to DMAP for Medical Director Review and notify requesting provider of pending review.	**No:** Pass to RPh: Deny (medical appropriateness) Other Scenarios not included can be brought to the Medical Director on a case by case basis
10. If applicable, has the patient been abstinent from IV drug and marijuana use, AND alcohol abuse for ≥ 6 months?	**Yes**: Go to #11	**No:** Pass to RPh, Deny for appropriateness
11. Does the patient have significant renal impairment (CrCl < 30 ml/min) or end stage renal disease (ESRD)?	**Yes:** Pass to RPh; Deny for appropriateness	**No:** Go to #12
12. What Hepatitis C genotype is the patient? Record Genotype:	Record Genotype and go to #13	
13. Does the patient have genotype 1 or 4 chronic hepatitis C?	**Yes:** Go to # 14	**No:** Go to #17
14. Is the medication being used as triple therapy with both ribavirin and peginterferon alfa and meets criteria for pegylated interferon-alfa and ribavirin?	**Yes:** Approve for 12 weeks total therapy	**No:** Go to #15
15. Is the medication being used with ribavirin or simeprevir?	**Yes:** Go to #16	**No:** Pass To RPh; Deny for Appropriateness
16. Is the patient interferon ineligible defined by having one of the following conditions: • Previous adverse reaction or hypersensitivity to interferon • Decompensated liver disease • Severe or uncontrolled psychiatric disorder in consult with a psychiatrist • Autoimmune hepatitis or other autoimmune	**Yes:** Approve initial trial of 12 weeks for total therapy of 12 weeks for sofosbuvir + simeprevir combination **OR** a total of 24 weeks for sofosbuvir + ribavirin therapy	**No:** Pass To RPh; Deny for Appropriateness

disorders • Unstable cardiac disease • Severe cytopenias • Other comorbidities that would be exacerbated by interferon use Note: Patient's or prescribers not wanting to go through treatment with interferon does not meet the criteria for being "interferon ineligible"		
17. Does the patient have genotype 2 chronic hepatitis C?	**Yes:** Go to #18	**No:** Go to #19
18. Is the medication being used with ribavirin?	**Yes:** Approve for 12 weeks total therapy	**No:** Pass To RPh; Deny for Appropriateness
19. Does the patient have genotype 3 chronic hepatitis C?	**Yes:** Go to #20	**No:** Pass To RPh; Deny for Appropriateness
20. Is the medication being used with both ribavirin and peginterferon alfa and meets criteria for pegylated interferon-alfa and ribavirin?	**Yes:** Approve for 12 weeks total therapy	**No:** Go to #21
21. Is the medication being used with only ribavirin and the patient is interferon ineligible as defined by the conditions listed above in #18?	**Yes:** Approve for 12 weeks initial fill for a total 24 weeks of therapy	**No:** Pass To RPh; Deny for Appropriateness

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P&T Board Action: 1/30/13 (MH)
Revision(s): 3/27/13, 7/31/13 (MH)
Initiated:

Continuation of Therapy- Sofosbuvir		
Has the patient been adherent to and tolerated initial therapy?	**Yes**: Approve for additional 12 weeks in genotype 3 patients and genotype 1 patients who are interferon ineligible (refer to dosage and administration table below).	**No:** DENY (Medical Appropriateness)

Readiness to Refer Assessment

GOALS: Support patient readiness to engage effectively with hepatitis C treatment prescriber by assessing potential barriers to treatment readiness, supporting patients to address barriers through referral to appropriate services and programs, and educate patient about actions that he or she can take to protect liver and slow hepatitis C disease progression.

These actions can be initiated by primary care provider with patients infected with chronic hepatitis C, including those interested in or waiting for specialist appointments. These action steps support liver health and can help prepare patients interested in hepatitis C treatment to engage successfully with specialists. Currently in Oregon, Medicaid requires prior authorization for hepatitis C treatment medications and limits prescribers to specially trained providers.

ACTIONS: Assess patient alcohol and substance use, mental health status and life planning/stability needs and provide referrals to existing treatment programs, community services and social supports. Educate patients about protecting the liver and liver health for people with hepatitis C.

CHECKLIST AND NOTES

❑ Patient education about liver health, including the impact of alcohol use on hepatitis C progression
- o Discussion Date: _____Written information provided? ❑ Yes ❑No ❑Do not know
  - ▪ Health education referral: ❑ Yes ❑No
  - ▪ Date and action: _____

- o Discussion Date: _____Written information provided? ❑ Yes ❑No ❑Do not know
  - ▪ Health education referral: ❑ Yes ❑No
  - ▪ Date and Action: _____

❑ Patient interest in hepatitis C treatment
- o Discussed patient interest in hepatitis C treatment, including engagement in screenings and follow up action steps identified with the primary care provider while waiting for specialist appointment
  - o Discussion Date:_____
  - o Discussion Date:_____
  - o Discussion Date:_____
  - o Discussion Date:_____
- o Follow-up action steps
  - o Date and Action: _____
  - o Date and Action: _____
  - o Date and Action: _____

□ Alcohol and substance use assessment (See details below)
- o Completed the SBIRT within the last 6-12 months
  - o Assessment Date:_____
  - o Assessment Date:_____
- o Completed CAGE or AUDIT within the last 6-12 months
  - o Assessment Date:_____
  - o Assessment Date:_____
- o Follow-up action steps if needed, including referral and linkage to alcohol or substance abuse treatment and services.
  - o Date and Action: _____
  - o Date and Action:_____

□ Mental health Assessments (See details below)
- o Screened for uncontrolled depression, psychosis, or suicidality using validated screening tool such as the Beck Assessment within last year
  - o Assessment Date:_____
  - o Assessment Date:_____
- o Follow-up action steps if needed, including referral and linkage to behavioral or mental health treatment and services.
  - o Date and Action: _____

Date and Action: _____

□ Life planning, stability and major issues that could impact adherence (See details below)
- Discussed potential events or issues in the coming year
  - Discussion Date:_____
  - Discussion Date:_____
- Follow-up action steps if needed, including referral and linkage to community support programs and services.
  - Date and Action: _____
  - Date and Action: _____

Alcohol and Substance Use:

- Alcohol consumption, even what is usually considered moderate, can damage the liver of a person with chronic hepatitis C infection and contribute to faster liver disease progression.
- All patients should be evaluated for current alcohol and other substance use, with validated screening instruments such as AUDIT C or CAGE. The presence of current heavy alcohol use (> 14 drinks per week for men or > 7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once a month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. Patients with active substance or alcohol-use disorders should be carefully considered for therapy in coordination with substance-use treatment specialists.
- SBIRT is a public health approach to the delivery of early intervention and treatment services for people with substance use disorders and those at risk of developing these disorders. Oregon specific screening forms and tools can be found at: http://www.sbirtoregon.org/screening.php

Behavioral and Mental Health Status

- Behavioral health issues are not absolute contraindications for hepatitis C treatment. However, patients with severe mental health conditions should be engaged in mental health treatment and managed in collaboration with behavioral and mental health providers to determine the risks, benefits and support needed with regard to hepatitis C treatment options.
- Use validated screening tools such as the Beck Depression Inventory to evaluate for depression and suicide ideation. Information and tips for the Beck Depression Inventory and other assessment tools (anxiety, suicide ideation) can be found here: http://www.beckinstitute.org/beck-inventory-and-scales/

Life Planning

- Work with the patient to address any psychosocial factors that could potentially interfere with treatment adherence. Once identified, refer patient to community mental health and social services and programs to address identified challenges. Confirm successful referral with patient and social service providers.
-
- These risk factors may include, but are not limited to:
  - Transportation challenges, homelessness, or limited phone access
  - Developmental mental delay/decreased cognition or other issues that may impact the patient's ability to understand or follow medication instructions
  - A likely or expected major life event in upcoming months (changing jobs, moving, health procedure)

This tool is meant to support patients and providers to work together to prepare for specialty care and treatment initiation. The information from the completed screenings should be included along with relevant medication information on the patient referral form.

Primary Care Provider Referral to a Specialist for Hepatitis C Treatment Evaluation

Directions: Primary care providers referring a patient to a specialist for HCV treatment evaluation should provide the following medical information to the specialist prior to the first appointment. Information may be placed on the form or provided via attachment or excerpt from the medical record.

Date of Referral: _____
Referring physician:
Office Address
Phone: Fax: Email:

Patient				**Date**	
Address					
Phone				Mobile	
Allergies				**DOB**	
Height		Weight		BMI	

CONCOMITANT MEDICAL DIAGNOSES	**CURRENT MEDICATIONS**

HEALTH SCREENING/MAINTENANCE		
1.	Smoking	
2.	Alcohol and Substance Use	SBIRT screening: ❑Y ❑N Date:_____ Other Screenings: ❑Y ❑N Name:_____ Date: _____ Name:_____ Date: _____
3.	Mental health assessment	Beck Depression Scale: ❑Y ❑N Date:_____ Other Screenings: ❑Y ❑N Name:_____ Date: _____ Name:_____ Date: _____
4.	Pregnancy/ Contraception	
5.	Hepatitis A and B	Hepatitis B screening ❑Y ❑N Date:_____ Hepatitis A and B vaccinations completed? ❑Y ❑N Dates:_____

RECOMMENDED LABRATORY TESTING PRIOR TO INITIAL APPOINTMENT WITH SPECIALIST					
HCV Genotype		ALT	Date:	Creatinine	
HCV RNA	Date:	AST	Date:	Platelet Count	
Albumin		Total bilirubin		Hemoglobin	

ASSESSMENT OF LIVER (COMPLETE IF AVAILABLE)		
Test performed	**Date**	**Findings/ Results**
Liver biopsy		
Ultrasound		
Transient Elastography		

OTHER RECOMMENDATIONS/REFERRALS
Patient education and written information
Other referrals provided

United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

July 11, 2014

Dr. John C. Martin,
Chairman and Chief Executive Officer
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Martin:

The Committee on Finance has jurisdiction of matters related to "health programs under the Social Security Act and health programs financed by a specific tax or trust fund," as provided by Rule XXV of the Standing Rules of the Senate. These federal health care programs include Medicare and Medicaid, which together provide health care to over 100 million Americans and represent nearly $900 billion in annual federal spending.

The Federal government is the health care industry's largest customer, and Congress has a responsibility to conduct oversight and ensure that taxpayer dollars are used wisely in a transparent market. Gilead received federal regulatory approval last year for Sovaldi, a drug developed to treat and cure the Hepatitis C virus (HCV). The drug has been hailed as a breakthrough treatment, and its commercial release is a welcome advance in medical research for the 3.2 million Americans infected with HCV and their families.[1]

Although Sovaldi has the potential to help people with HCV, at $1,000 per pill, its pricing has raised serious questions about the extent to which the market for this drug is operating efficiently and rationally. While a standard course of treatment for Sovaldi has been widely reported to cost $84,000 in the United States, Gilead will offer the drug in other countries for a fraction of the price. In Egypt, for example, Sovaldi could be offered for as low as $900 per course of treatment – a 99 percent discount of the price in the U.S.[2]

The total cost of a course of this therapy also remains in question. The U.S. Food and Drug Administration dosage approval shows the price could be higher than the $84,000 for a standard treatment. Some patients with HCV genotypes 1 and 3 will require 24 weeks of treatment.[3] The longer treatment regimen roughly doubles the cost-per-patient-per-treatment to

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[1] Centers for Disease Control and Prevention, *Hepatitis C FAQs for the Public*, http://www.cdc.gov/Hepatitis/C/cFAQ.htm#statistics, accessed July 10, 2014.
[2] Maggie Fick and Ben Hirschler, Gilead offers Egypt new hepatitis C drug at 99 percent discount, *Reuters*, March 21, 2014, http://www.reuters.com/article/2014/03/21/us-hepatitis-egypt-gilead-sciences-idUSBREA2K1VF20140321, accessed July 10, 2014.
[3] U.S. Food & Drug Administration, *Label for Sovaldi (NDA no. 204671)*, December 6, 2013, http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204671s000lbl.pdf, accessed July 10, 2014.

$168,000 for Sovaldi, not including the additional cost of peg-interferon alfa and ribavirin used in combination treatments.[4] HCV patients with liver cancer could require 48 weeks of treatment.[5]

The large patient population combined with the high price of each individual treatment creates a question as to whether payors of health care, including Medicare and Medicaid, can carry such a load. Health care experts recently estimated that Sovaldi alone could increase Medicare's spending on prescription drugs by $2 billion between 2014 and 2015 if just 25,000 patients enrolled in the program's prescription drug benefit, known as Part D, receive prescriptions.[6] That represents "roughly 10 percent of Part D enrollees with the hepatitis C virus and about one-fourth of enrollees who have been diagnosed." If 75,000 Part D enrollees took the drug during the same period, program costs would increase by $6.5 billion and premiums for all Part D enrollees could jump 8 percent, "a bigger increase than in any year since 2008."[7]

Sovaldi's cost also could dramatically increase the government's spending in other programs, including health care for prisoners with HCV. According to a recent survey, over 1.8 million people with hepatitis C are currently incarcerated.[8] This represents up to 32.8 percent of the total cases of HCV in the U.S.[9] The Federal Bureau of Prisons within the Department of Justice has already approved Sovaldi for use in treating prison populations, and it is reported that it receives a 44 percent discount.[10] Even with this discount, American taxpayers could end up paying billions of dollars buying Sovaldi to treat inmates infected with HCV.

Given the impact Sovaldi's cost will have on Medicare, Medicaid and other federal spending, we need a better understanding of how your company arrived at the price for this drug. In order for a marketplace to function properly, it must be competitive, fair, and transparent. It is unclear how Gilead set the price for Sovaldi. That price appears to be higher than expected given the costs of development, and production and the steep discounts offered in other countries. An efficient market needs informed consumers to keep costs down. Consequently, we have directed our staff to investigate issues related to Sovaldi and Gilead's pricing of the drug. As part of this investigation, we are seeking information and documents related to the merger of Gilead Sciences, Inc. and Pharmasset, Inc., the original developer of Sovaldi, that was announced November 21, 2011, and the subsequent pricing of Sovaldi.

The following document requests, questions and statements use "Gilead" to refer to Gilead Sciences, Inc., its board of directors, any subsidiaries and contracted third parties; "Pharmasset" is used to refer to Pharmasset, Inc., its board of directors, any subsidiaries and contracted third parties; "Morgan Stanley" refers to Morgan Stanley & Co., LLC, and all its subsidiaries.

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[4] Leof, A., et al., (2014). *Sofosbuvir for the treatment of hepatitis C and evaluation of the 2014 American Association for the Study of Liver Diseases treatment guidelines.* Portland, OR: Center for Evidence-Based Policy, Oregon Health & Science University, p. 7-8, http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/med/upload/Sofosbuvir_for_HepatitisC_FINAL_5_19_2014.pdf, accessed July 10, 2014.

[5] *Supra* at note 3.

[6] Tricia Neuman, et al., The Cost Of A Cure: Medicare's Role In Treating Hepatitis C, *Health Affairs*, June 5, 2014, http://healthaffairs.org/blog/2014/06/05/the-cost-of-a-cure-medicares-role-in-treating-hepatitis-c/, accessed July 10, 2014.

[7] *Ibid.*

[8] Varan, A.K., et al. "Hepatitis C Seroprevalence among Prison Inmates Since 2001: Still High But Declining." *Public Health Reports*, 129, no. 2 (March/April, 2014): 187-195. (http://www.ncbi.nlm.nih.gov/pubmed/24587554), accessed July 10, 2014.

[9] *Ibid.*

[10] Peter Loftus, New Hepatitis Drugs Vex Prisons, *Wall Street Journal,* April 24, 2014, http://online.wsj.com/news/articles/SB10001424052702304311204579510054146055222, accessed July 10, 2014.

"Barclays" refers to Barclays Bank PLC, and all its subsidiaries, including but not limited to Barclays Capital. "Bank of America Merrill Lynch" refers to Bank of America Corporation, and all its subsidiaries, including, but not limited to Merrill Lynch. Any reference to "Sovaldi", "PSI-7977" or "GS-7977" refers to sofosbuvir, a drug used in the treatment of hepatitis C virus, and any other names or codenames used to refer to said drug, its predecessor, and related formulas, compounds, research or development projects. "Supporting documents" refers to, but is not limited to, emails, faxes, notes, minutes, memoranda, reports, forecasts, transcripts, charts, spreadsheets and government forms.

Please answer the following questions and provide the following documents:

1. Please provide copies of all presentations, financial analyses, and supporting documents given to Pharmasset and/or to Gilead from 2010 to present from Morgan Stanley in its role as Pharmasset's financial advisor.[11]

2. Please provide a copy of the fairness opinion prepared by Morgan Stanley in conjunction with Gilead's final offering price,[12] and all supporting documents related to or referencing the fairness opinion, including but not limited to assumptions about the pricing and market for PSI-7977.

3. Please provide copies of the three prospective commercialization forecasts prepared by Pharmasset's management "in and prior to September 2011"[13] and all supporting documents.

4. Please provide copies of Pharmasset's revised forecasts (prepared before the American Association for the Study of Liver Diseases conference in November 2011)[14] and all supporting documents, including but not limited to assumptions about the pricing and market for PSI-7977.

5. Please provide copies of all communications between Pharmasset's board and its senior management regarding PSI-7977 and all supporting documents, including assumptions about the pricing and market for the drug.

6. In its final annual financial filing with the Securities and Exchange Commission (SEC), Pharmasset reported that its research and development costs totaled $176.7 million for the fiscal years ending 2009, 2010 and 2011, the period during which PSI-7977 was being developed.[15] Of that total, Pharmasset attributed $62.4 million directly to the development of PSI-7977.

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[11] Pharmasset Schedule 14D-9, December 6, 2011, p. 8.
[12] Ibid., p. 12-13.
[13] Ibid., p. 29-30.
[14] Ibid., p.31-32. Referred to as the "Updated Forecast", management assumed PSI-7977 would be launched in the United States no earlier than the third quarter of 2014; that a course of treatment using PSI-7977 would be priced at $36,000 in the United States, and that European Union pricing would be 60% to 70% of the U.S. price.
[15] Pharmasset, Inc., 10-K for the fiscal year ended September 30, 2011, November, 14, 2011, p. 60.

a. Please provide an itemized accounting of Pharmasset's total research and development costs prior to the completion of the merger with Gilead on January 17, 2012.
b. Please provide an itemized accounting of Pharmasset's research and development costs directly attributable to the development of PSI-7977 prior to the completion of the merger with Gilead on January 17, 2012.

7. Gilead retained Barclays and Bank of America Merrill Lynch as its financial advisors for the acquisition of Pharmasset.[16]
    a. Please provide copies of all communication between Barclays and Gilead relating to the valuation and acquisition of Pharmaset, including assumptions, projections, analyses, recommendations, and any related supporting documents about the pricing and market for PSI-7977.
    b. Please provide copies of all communication between Bank of America Merrill Lynch and Gilead, relating to the valuation and acquisition of Pharmasett, including assumptions, projections, analyses, recommendations, and any related supporting documents about the pricing and market for PSI-7977.

8. Please provide all analyses, recommendations, and supporting documents related to the proposed valuation and acquisition of Pharmasset, including assumptions and projections about the price and market for PSI-7977. Please include all documents related to the following:
    a. The September 2, 2011 meeting between Pharmasset and Gilead to discuss acquisition;
    b. The October 7, 2011 proposal from Gilead to purchase Pharmasset for $125 per share;
    c. The November 17, 2011 proposal from Gilead to purchase Pharmasset for $135 per share;
    d. The November 20, 2011 proposal from Gilead to purchase Pharmasset for $137 per share.

9. Please provide copies of all communications between Gilead and Pharmasset concerning the proposed valuation and acquisition of Pharmasset, including assumptions and projections about the price and market for PSI-7977. Please include all supporting documents related to the following:
    a. The September 2, 2011 meeting between Pharmasset and Gilead to discuss acquisition;
    b. The October 7, 2011 proposal from Gilead to purchase Pharmasset for $125 per share;
    c. The November 17, 2011 proposal from Gilead to purchase Pharmasset for $135 per share;
    d. The November 20, 2011 proposal from Gilead to purchase Pharmasset for $137 per share.

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[16] Gilead Sciences, Inc., and Pharmasset, Inc., *Gilead Sciences to Acquire Pharmasset, Inc., for $11 Billion*, November 21, 2011, http://gilead.com/news/press-releases/2011/11/gilead-sciences-to-acquire-pharmasset-inc-for-11-billion, accessed July 10, 2014.

10. Please provide copies of the analysis of the fair value of the In-Process Research and Development (IPR&D) related to GS-7977 cited in Gilead's 10-Q filed with the U.S. Securities and Exchange Commission (SEC) for the quarter ending March 31, 2012,[17] and all supporting documents related to the preparation of this valuation. Identify and describe the key assumptions in the IPR&D valuation.

11. Please provide copies of the analysis of the fair value of IPR&D related to sofosbuvir cited in Gilead's 10-K filed with the SEC for the fiscal year ending December 31, 2012,[18] and all supporting documents related to the preparation of this valuation. Identify and describe the key assumptions in the IPR&D valuation.

12. Please provide an itemized accounting of research and development costs[19] related directly to the development of sofosbuvir that was incurred by Gilead after the completion of the Pharmasset merger on January 17, 2012. This accounting should include separate line items for personnel costs, clinical studies, materials and supplies, licenses and fees, milestone payments under collaboration arrangements, overhead allocations, facilities costs and the value contracts with contract research organizations (CROs) related directly to the development of sofosbuvir.

13. Before Gilead could complete its acquisition of Pharmasset, both companies were required to file pre-merger notifications with the U.S. Federal Trade Commission (FTC).
    a. Please provide copies of Gilead's filing with the FTC, all documents provided to the FTC pursuant to 16 C.F.R. §803.1 and 16 C.F.R. §803.2, all communications with the FTC related to the filing, and all supporting documents related to the filing.
    b. Please provide copies of Pharmasset's filing with the FTC, all documents provided to the FTC pursuant to 16 C.F.R. §803.1 and 16 C.F.R. §803.2, all communications with the FTC related to the filing, and all supporting documents related to the filing.

14. Please provide copies of the marketing and pricing plans prepared for, and being used in, the launch of Sovaldi in the U.S. and internationally,[20] including all communications and supporting documents related to the preparation of these plans, materials, and prices.
    a. Looking forward, please describe how the commercial success of Sovaldi, as evidenced by first quarter sales, will affect marketing and pricing plans, including the cost of production, and future prices in the U.S. and internationally. If there will not be any effect, explain why.

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[17] Gilead Sciences, Inc. Form 10-Q for the quarterly period ended March 31, 2012, May 4, 2012, p. 16.
[18] Gilead Sciences, Inc., Form 10-K for the fiscal year ended December 31, 2012, February, 27, 2013, p. 105.
[19] Gilead Sciences, Inc., Form 10-K for the fiscal year ended December 31, 2013, February 25, 2014, p. 60.
[20] Gilead Sciences., Inc., Form 10-Q for the quarterly period ended March 31, 2014, May 5, 2014, p. 29. Gilead's Selling, General, and Administrative expenses (SG&A) for the quarter ending March 31, 2014, "increased by $173.8 million or 46%, compared to the same period in 2013, due primarily to a $113.6 million increase in headcount and other expenses to support the ongoing growth and expansion of our business, which includes ongoing launches of Sovaldi in the United States and internationally as well as the anticipated launch of idelalisib."

15. Sovaldi is currently prescribed in combination with other medications, which increases the total cost per patient per course of treatment.[21] Gilead has applied for approval to sell single-dose combinations of Sovaldi with other drugs.
    a. If approval is granted for a single-dose combination drug, how will it affect the future price of Sovaldi?
    b. Please provide copies of any pricing plans, marketing plans, or price estimates related to these pending combination drugs, and all supporting documents related to the plans and related forecasts.

16. Please provide copies of Gilead's estimates of the U.S. treatment cost-per-patient and U.S. cost-per-cure for each of the FDA's approved genotype-based treatment regimens for Sovaldi, including itemization of the cost of Sovaldi, the cost of combination drugs, and all supporting documents used in developing such estimates.

17. Looking forward, what are Gilead's expected changes in the treatment cost-per-patient and the cost-per-cure of Sovaldi-based treatment over the next five years for each of the FDA approval regimens for the U.S. HCV populations?

18. Oregon Health & Science University researchers reviewed treatment guidelines for Sovaldi jointly issued by several professional societies, concluding there is a "substantial risk of conflict of interest influencing the recommendations from both individual panel members and funding sources."[22] The organizations' website shows 18 of the 27 panel members involved in developing the guidance for the American Association for the Study of Liver Disease (AASLD) and the Infectious Diseases Society of America (IDSA) disclosed either a direct financial relationship with Gilead or received institutional funding from the company.[23] Both groups, and a third collaborating partner, the International Antiviral Society-USA (IAS-USA), have all received funding from Gilead.[24]
    a. Please provide an itemized accounting of all payments from 2009 to present between Gilead and/or Pharmasset and the following organizations:
        i. AASLD
        ii. IDSA
        iii. IAS-USA
    b. Please provide an itemized accounting of all payments from 2009 to present between Gilead and/or Pharmasset and the expert panel members that developed the AASLD/IDSA treatment guidelines for HCV.[25]
    c. For each organization or individual identified in (a) or (b), provide:
        i. Date of payment
        ii. Payment description

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[21] *Supra* at note 3.
[22] *Supra* at note 4, p. 21
[23] AASLD/IDSA, Recommendations for Testing, Managing, and Treating Hepatitis C, Disclosure Information, http://hcvguidelines.org/disclosure_information, accessed July 10, 2014.
[24] See AASLD 2012 Annual Report p. 29, http://www.aasld.org/aboutus/Documents/2012AnnualReport.pdf, accessed July 10, 2014; IDSA Industry relations, Grants and Contributions 2010 – 2014, http://www.idsociety.org/IDSA_Industry_Relations, accessed on July 10, 2014; IAS-USA Cases on the Web Grant Support, https://www.iasusa.org/cow-grant-support, accessed on July 10, 2014.
[25] AASLD/IDSA, Recommendations for Testing, Managing, and Treating Hepatitis C, Disclosure Information, http://hcvguidelines.org/disclosure_information, accessed on July 10, 2014.

iii. Amount of payment
iv. Year-end or year-to-date payment total and cumulative total payments for each organization or individual

d. Describe any communications between employees of Gilead and the organizations and individuals identified in (a) and (b) regarding the AASLD/IDSA treatment guidelines for HCV. Please provide all supporting documents related to those communications.

19. Gilead's advertising and promotional expenses have increased from $116.6 million in 2011 to $216.2 million in 2013.[26]
    a. How much money does Gilead plan to spend on advertising and promotional expenses in 2014?
    b. How much money does the company plan to spend on advertising and promotion of Sovaldi in 2014?
    c. How much money did the company spend on advertising and promotion of Sovaldi prior to January 1, 2014?

20. Gilead has included Sovaldi in its patient assistance program, which includes coupons for reducing the cost of patient co-pays.[27] Gilead estimated that 30,000 patients were treated with Sovaldi during the first quarter of 2014:[28]
    a. How many patients have been treated in the United States with Sovaldi to date?
    b. How many patients in the United States have been assisted by Gilead's patient assistance program to date?
    c. What percentage of patients does Gilead expect to be covered under this program?
    d. What is the average outlay-per-patient in the patient assistance program?
    e. What percentage of the patient's cost for Sovaldi will the payment assistance program cover for each of the FDA-approved treatment regimens?
    f. What patients are eligible for this assistance? What patients are ineligible for this assistance?
    g. There are a number of HCV-infected populations, such as those exposed through intravenous drug use, contaminated blood and those born to someone infected with the virus. Describe the patient populations expected to be covered by the Sovaldi patient assistance program.
    h. How are the costs of this assistance accounted for within Gilead's financials, e.g. are they deducted as part of the company's Selling, General, and Administrative (SG&A) expenses?

21. Sovaldi is and will be sold in multiple countries, many of which are expected to receive significant discounts compared to the price in the U.S.

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[26] *Supra* at note 19, p. 96.
[27] Gilead, *Support Path for Sovaldi*, http://www.gilead.com/responsibility/us-patient-access/support%20path%20for%20sovaldi, accessed on July 10, 2014.
[28] *Supra* note at note 20, p. 27.

a. Please provide a list of all countries where Sovaldi is or will be sold, and the corresponding price or planned price for each country. Describe how the company reached the price for each country.
b. How are the revenue, costs and any discounts associated with international sales, such as Egypt, accounted for within Gilead's financials, e.g. are they deducted as part of the company's Selling, General, and Administrative (SG&A) expenses?

Thank you in advance for your assistance in this matter. Please begin producing documents and information on a rolling basis no later than 14 days —and complete production no later than 60 days— after the receipt of this letter. Please contact our staff as soon as possible to discuss prioritizing the order in which responsive documents and information should be produced.

Please direct any questions about this letter to David Berick, Chief Investigator, or Elizabeth Jurinka, Chief Health Policy Advisor for Chairman Wyden, and to Jason Foster, Chief Investigative Counsel, or Rodney Whitlock, Health Policy Director for Senator Grassley.

Sincerely,

Ron Wyden
Chairman

Charles E. Grassley
Member

To: **Catherine Livingston, MD**
Medical Director, Oregon Health Evidence Review Commission (HERC)

From: **Bill Guyer, PharmD**
Vice President, Medical Affairs
Gilead Sciences, Inc.

Date: **July 18, 2014**

Re: **Reply to Oregon Health Evidence Review Commission (HERC) "*Treatment of Hepatitis C with Newer Agents*" Draft Report (June 12, 2014)**

We read with interest and are providing responses to the Oregon Health Authority's **Health Evidence Review Commission's Value-based Benefits Subcommittee** (June 12, 2014) report entitled "*Treatment of Hepatitis C with Newer Agents*".

The U.S. Food and Drug Administration (FDA) held an independent Antiviral Drugs Advisory Committee on Oct. 25th, 2013, which voted unanimously (15-0) that the available data supported approval of sofosbuvir in combination with pegylated interferon and ribavirin for the treatment of chronic hepatitis C in treatment-naïve adult patients with genotype 1 and 4 infection. The Advisory Committee members also voted unanimously (15-0) that the data submitted for review supported approval of sofosbuvir in combination with ribavirin for the treatment of chronic hepatitis C in adult patients with genotype 2 and 3 infection.

In casting her vote in favor of approving sofosbuvir, Elizabeth Connick, MD, a professor of medicine at University of Colorado Denver, Division of Infectious Diseases, in Aurora, Colorado stated "This is a tremendous advance for patients, and I think both the sponsor and the FDA should be applauded for having gotten us here."

We wanted to take this opportunity to provide clarification regarding the clinical- and cost-effectiveness data that have been generated with SOVALDI (sofosbuvir).

Executive Summary

Sofosbuvir, the first FDA approved NS5B nucleotide polymerase inhibitor, provides an interferon-limiting or interferon-free regimen for patients infected with HCV genotypes (GT) 1 and 4, interferon-free for GT 2 and 3, and treatment options for interferon-ineligible and -intolerant patients.

- It is estimated that chronic HCV infection affects the lives of at least 3.2 million Americans, of whom 30% are estimated to have progressed to cirrhosis in 2015, and are at risk of disease progression to hepatocellular carcinoma, liver failure and potentially, liver transplant.[1,2]
- Physicians have long sought better treatments for HCV because the prior approaches with protease inhbitors + pegylated interferon + ribavirin (PI+PegIFN+RBV) required patients to take up to 12 pills a day for 24-48 weeks, combined with interferon injections that cause flu-like symptoms, severe rash, profound anemia, and depression. The cure rate for patients who complied with this regimen has been in the range of 60-75%, but studies have shown that up to half of patients discontinue treatment owing to the severity of side effects. From the patient's perspective, sofosbuvir-based regimens are both better tolerated and more effective than the PI+PegIFN+RBV treatments, with a far shorter duration (12-24 weeks). In consequence, a higher percentage of sofosbuvir-treated patients remain on treatment and are cured.
- Treating chronic HCV provides value by reducing the human and economic costs of cirrhosis, liver cancer, liver transplants and deaths from HCV. A 2011 Henry Ford Foundation study of patients with end-stage liver disease estimated their annual medical cost at $60,000, and liver transplantation costs exceed $145,000 in the

first year and are associated with substantial long-term medical expenses.[3] Based on studies by Bichoupan and colleagues and Sethi and colleagues evaluating cost per SVR, the low efficacy and high adverse events contributed substantially to cost of HCV treatment with PI+PegIFN+RBV. Based on lower real-world SVR rates than seen in phase 3 trials, the overall real-world cost per SVR was estimated to be $173,000 to $189,000 in these two single-center studies, and increased to $254,000 to $267,000 in patients with cirrhosis at baseline.[4,5,6]

- The Sofosbuvir development program was robust with 6 Phase 3 trials that were inclusive of real-world patients: 20% cirrhotics (F4), Black and Hispanic patients proportional to the US population, no upper limit of age or BMI, and patients receiving opiate replacement therapy, which is unique to these trials and differentiates the sofosbuvir clinical profile from all other agents approved for the treatment of HCV.
- Sofosbuvir-based regimens provide:
  - The highest efficacy rates, shortest treatment duration regimen (12 weeks) in combination with RBV + PegIFN for patients infected with GT 1 or 4
  - The highest efficacy rates, and the first all oral HCV regimen in combination with RBV for patients infected with GT 2 (12 weeks) and GT 3 (24 weeks)
  - Excellent safety and tolerability profile, with low discontinuation rates due to AEs from 0 to 2%
  - First all oral regimen for patients who have no treatment options who are interferon -ineligible or –intolerant
  - FDA approved for patients of all genotypes with HCC meeting Milan criteria (awaiting liver transplantation)
  - The only approved DAA available for patients with HCV/HIV-1 coinfection, with SVR rates and a safety/tolerability profile similar to those observed for HCV monoinfected patients
  - Lack of food effect, once daily administration, and very limited drug-drug interactions
- Sofosbuvir-based regimens allow clinicians, payers and policy makers to begin moving from a chronic disease state management model to a curative and preventive model

Sofosbuvir brings significant value to payers, providers, patients and society by providing the following:

- Gilead priced SOF comparable to other DAA regimens, especially when taking into account the total cost of an SVR. It is important to consider the overall value of Sofosbuvir regimens and total cost of cure

Regimen	Duration (weeks)	Total Regimen Cost
Sofosbuvir + Pegasys + RBV	**12**	**$94,078**
Sofosbuvir + RBV	**12**	**$84,823**
	24	**$169,646**
Telaprevir + Pegasys + RBV	**24**	**$86,312**
	48	**$106,468**
Simeprevir + Pegasys + RBV	**24**	**$86,516**
	48	**$106,673**
Boceprevir + PegIntron + RBV	**28**	**$64,825**
	36	**$85,257**
	48	**$95,845**

- Economic analyses shows that, compared with current treatment regimens, sofosbuvir-based regimens yield the most favorable future health outcomes and the fewest cases of liver disease complications and HCV-related deaths across patients infected with HCV genotypes 1, 2, 3, and 4, whether treatment-naïve or treatment experienced, fibrosis and cirrhosis stages, and in patients with or without HIV coinfection.

- In the one-year analysis, the cost per SVR for the Sofosbuvir-based regimen is lowest of all currently approved regimens due to higher efficacy rates, a high barrier to resistance, and improved tolerability. In the long-term, the Sofosbuvir-based regimens are the most cost-effective treatment options for patients infected with HCV genotype 1, because of fewer treatment failures, fewer adverse events, and averted liver-disease costs.
- Earlier initiation of the more effective Sofosbuvir-based treatment yields better health and economic outcomes compared with later initiation, reducing advanced liver disease complications and the downstream costs associated with advancing disease.
- IFN-free regimens and regimens of shorter duration with PegIFN+RBV are associated with better health status and substantial declines in fatique and depression during treatment. Patients achieving SVR showed improvement in their activity, work productivity and presenteeism scores compared to their baselines.

Specific responses to HERC comments

The HERC report acknowledged the substantial literature evidence from multiple studies which support the value of HCV-infected patients achieving the surrogate endpoint of sustained virologic response (SVR), as demonstrated by long-term reductions in all-cause mortality, liver-related mortality and hepatocellular carcinoma (HCC).

Historically, the measure of SVR was at 24 weeks (SVR24), however more recently, the assessment of SVR made at 12 weeks after completion of therapy (SVR12) has been adopted by the FDA, the European Medicines Agency and other health authorities worldwide, as the primary endpoint of clinical trials with direct-acting antivirals such as sofosbuvir and all other agents in development, with SVR 24 being accepted as a secondary endpoint.[7]

The HERC report raised the question of the concordance between SVR12 and SVR24 in the sofosbuvir trials. There was 99% concordance between SVR12 and SVR24 in the NEUTRINO, FISSION, FUSION and POSITRON studies. These data were provided to the FDA during the review process for sofosbuvir and have been presented at major international hepatology conferences in the past year.[8] In addition, the durability of SVR beyond 24 weeks from these trials is being followed for 3 years after study completion. As of April 2014, the durability of SVR24 in these trials has been 100%.[9]

Additional questions were raised in the HERC report with regard to study design employed in sofosbuvir registrational trials. Six phase 3 clinical trials of 1,851 patients comprised the dataset supporting the approval of sofosbuvir for HCV patients infected with genotypes 1, 2, 3 and 4, including in HIV/HCV co-infected and pre-transplant patients. All six were controlled trials, of varying designs corresponding to the characteristics of patients enrolled, and the appropriateness of the existing standard of care at the time that the studies were conducted.

NEUTRINO was designed as a single-arm study based on a number of clinical considerations.[10] Treatment with SOF+PegIFN+RBV for 12 weeks achieved a high SVR rate in the Phase 2 ATOMIC study, with ≥ 90% of subjects achieving SVR24. This response rate was substantially higher than previously observed with regimens including a protease inhibitor (PI), and was accomplished without the increased toxicities (severe rash, profound anemia, burning diarrhea, and others) associated with PI+PegIFN+RBV regimens. Since SOF had demonstrated pangenotypic activity, Gilead also included subjects with genotype 4, 5, or 6 infection in the NEUTRINO study. Inclusion of these subjects would not have been possible with a PI-based regimen since PIs lack antiviral activity against these genotypes. The single-arm study design also allowed broader inclusion of subjects than would be possible with a PI-based control arm, including no upper age limit and inclusion of subjects receiving stable opioid substitution therapy. Since there are few potential drug-drug interactions with SOF (as contrasted with multiple P450 drug interactions with PIs), the single-arm study design had fewer disallowed medications and thus expanded the range of subjects who could participate in this study, resulting in a study group which is more reflective of the real-world population of HCV-infected patients.

Blinding a study with a PI-comparator regimen would have been impossible due to the different treatment durations (12 weeks for SOF-treated patients vs. 24-48 weeks for PI-treated patients), the need for response guided therapy in the PI+PegIFN+RBV arm, and the increased toxicity profiles of the PIs compared to SOF. Based on investigator feedback, Gilead would have had significant challenges enrolling a PI-controlled study in 2012, given investigator's and subject's perceptions of increased toxicities with PI-based regimens and their lower perceived efficacy, which could have resulted in an increased number of premature treatment discontinuations in the PI+PegIFN+RBV arm.

The current FDA Guidance for Industry document regarding development of direct-acting antiviral drugs states "The risk-benefit profile of the investigational drug and the available approved treatment options for the indicated population are important factors to determine an appropriate trial design. Although randomized controlled comparative trials are preferable, in some situations, single-arm trials using a historical control may be appropriate".[7]

Regulatory discussions in the United States and the European Union acknowledged that the HCV field was rapidly evolving and that there was not a need for an active control in a Phase 3 study given that there was the potential to demonstrate the FDA requirement of "clear advantages of the experimental regimen being tested based upon strong Phase 2 data."[7]

The NEUTRINO study compared the SVR12 achieved with 12 weeks of sofosbuvir + pegylated interferon + ribavirin (SOF+PegIFN+RBV) to a pre-specified historical control SVR of 60%, based on modeled data from trials conducted with the previous standard of care (24-48 weeks of telaprevir or boceprevir + PegIFN+RBV). The sofosbuvir regimen was significantly more effective, with an overall SVR rate of 90% ($p < 0.001$; 95% CI of 87-93%).[10]

There is a very low likelihood that this difference was due to chance or the choice of the historical control rate, since there is overwhelming evidence of the reproducibility of control results in HCV clinical trials. The PegIFN+RBV control arms (no PI treatment included) of Janssen's QUEST-1 and QUEST-2 trials were conducted contemporaneously to NEUTRINO and enrolled 130 and 134 patients, respectively, and resulted in identical SVR12 rates of 50%, lower than the pre-specified historical control of 60% used in the NEUTRINO trial.[11,12]

The FISSION trial, the first phase 3 trial of an all-oral regimen of sofosbuvir + ribavirin (SOF+RBV) in HCV genotypes 2 or 3, was compared to a control arm of PegIFN+RBV. In GT2 patients, SVR for 12 weeks of SOF+RBV (95%) was superior to 24 weeks of PegIFN+RBV (78%). In GT3 patients, the SVR for SOF+RBV was non-inferior to PegIFN+RBV. There were statistically fewer adverse events with all-oral SOF+RBV therapy.[10]

The FUSION trial compared two different durations of all-oral SOF+RBV (12 vs. 16 weeks) in a double-blind design, and established that 12 weeks or 16 weeks of therapy in GT2 patients were comparable, however 16 weeks of SOF+RBV yielded improved SVR rates for GT3 (62% vs. 30%). The possibility that SVR rates could be increased with a longer duration of therapy in GT3 patients was subsequently studied with 24 weeks of SOF+RBV in the VALENCE trial, which demonstrated 93% SVR12 in treatment-naïve GT3 patients.[13,14]

The POSITRON study compared 12 weeks of SOF+RBV in 278 GT2 or 3 patients to placebo who were interferon-intolerant, -ineligible or –unwilling, and demonstrated superior SVR for both genotypes, with comparable safety.[13]

The PHOTON-1 study built upon the SOF+RBV regimens from previous trials and demonstrated that the SVRs observed in HIV/HCV co-infected patients were comparable to HCV mono-infected patients.[15]

It is relevant to recognize that the SVR endpoint is not subject to observer bias, and requires confirmation of undetectable HCV RNA in the blood at both the SVR12 and SVR24 timepoints. In addition, all trials employed a strict intent-to-treat analysis which further eliminated observer bias by counting patients who were lost-to-follow up or discontinued treatment as failures. The outcomes of both patients who achieved SVR and those who

relapsed following completion of treatment in the phase 3 sofosbuvir clinical trials are being followed for up to 3 years.

Finally, in addition to SVR, the 12 week regimen of SOF+PegIFN+RBV for GT 1 or 4, and 12-24 weeks of SOF+RBV for GT 2 or 3 has minimized the deleterious impact of adverse events associated with PegIFN+RBV-based regimens, and also shown improvements in Health-Related Quality of Life.[16]

In sum, these benefits have been recognized by treatment guidance documents from the AASLD/IDSA, the European Association for the Study of the Liver, the World Health Organization, the Veterans Administration, and the Federal Bureau of Prisons, which all recommend sofosbuvir-based regimens for treatment of chronic HCV. [17-21]

The HERC report also calls into question the value of treatment for all HCV infected patients, since not all patients will progress to cirrhosis and further disease progression such as liver failure, liver cancer or liver transplant, but despite substantial scientific effort over the past 15 years, there do not exist a set of predictive criteria for disease progression with which to select patients for treatment.

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