January, 2016

Rationale for reduction of OHP Prior Authorization Obstacles to HCV Treatment

Since the introduction of the first direct acting antivirals (DAA's) to treat HCV about 2 years ago and adoption of the current OHP policies for HCV treatment, several developments highlight the rationale for expanding access to treatment for all HCV Patients in Oregon, with particular emphasis on Medicaid population.

1. A recent survey by the Public Health Division of the Oregon Health Authority, highlights that among the estimated 95,000 Oregonians infected with hepatitis C, 400 deaths per year from HCV in the state are twice the national average, twice as prevalent among minorities (African Americans and Native Americans), and 4-fold grater than HIV-related deaths in Oregon.[1]
2. Several large databases of HCV patients treated with new direct acting antiviral in real-world settings and the community experience in Oregon, recapitulate the HCV cure rates of >90% with few side-effects described in earlier clinical trials.[2]
3. Cure of HCV, which occurs in over 90% of persons after treatment, results in an 80% to 90% reduction in liver failure, liver cancer and liver transplantation. This treatment is highly cost-effective relative to accepted medical treatments. [3]
4. Initial cost-benefit analysis by the California Technology Assessment Forum (CTAF), January 2015, showed LDV/SOF was cost-effective from a societal perspective, but not affordable to treat all HCV patients due to high cost. The study stated prioritization of patients for HCV treatment would be necessary and that treatment would need to be less than $42,000 to be affordable.[4]
5. In response to high initial wholesale acquisition cost of the new HCV drugs, Medicaid and private payers in Oregon developed restrictive prior authorization criteria, based on patients' extent of liver fibrosis, their history of alcohol and drug use, and on the specialty of the prescribing provider, which are among the most restrictive in the country. The recent Center for Medicare and Medicaid Services (CMS) Guidance to the states concerning HCV Treatment indicates that there is no medical justification for such barriers to HCV treatment, suggests that such prior authorization

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[1] Viral Hepatitis in Oregon, The Oregon Health Authority, Public Health Division, May 2015.

[2] AASLD 2015; Abstracts #93, #94 and # 1108.

[3] Chhatwal. Ann Intern Med 2015; 162:407-419, Gastroenterology 2015; 148(4), Supplement 1:S1074.

[4] Institute for Clinical and Economic Review. 2015#

criteria for HCV treatment are inconsistent with SSA and ACA administrative rules and that they should be suspended.[5]

6. Such PA obstacles to HCV care in Oregon persist despite recent substantial reductions in HCV drug costs of an estimated 46% (and are expected to drop further with introduction of new drugs the next few months) and adoption of 1/3 shorter treatment courses for ~ 60% of HCV patients. These developments have caused several states (California, New York, Pennsylvania, Maryland and Massachusetts) to reduce or drop such barriers.[6]
7. In the setting of such obstacles to HCV treatment, it is estimated that ~300 OHP patients per year are currently treated for HCV, nearly all of whom have advanced liver damage or cirrhosis. At this rate, it is estimated that it would take > 25 years to treat only the OHP patients with advanced fibrosis (F3/F4= ~ 8,400 of an estimated 24,000 OHP patients with HCV, ~½ of whom are diagnosed).

The members of the Hepatitis C Advisory Board concur with the recommendations to the ASSLD/ISDA Guidance that recommends treatment of all patients with progressive fibrosis.[7] The Oregon Health Plan and private insurance companies in Oregon should now support treatment of all persons with HCV with progressive scarring (Stage II-IV). Treatment should be without barriers to care based on prior drug and alcohol abstinence, proven compliance with medical care or restriction of care providers who are otherwise knowledgeable concerning HCV treatment.

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[5] CMS HCV Guidance, Nov 5, 2015.
[6] Chhatwal. Clinical Gastroenterology and Hepatology 2015; 13:1711-1713.
[7] AASLD/ISDA Hepatitis C Guidance.

Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

OVERVIEW OF COST, REIMBURSEMENT, AND COST-EFFECTIVENESS CONSIDERATIONS FOR HEPATITIS C TREATMENT REGIMENS

The Hepatitis C Guidance describes how to diagnose, link to care, and treat most groups of patients with HCV. (AASLD/IDSA/IAS-USA, 2015 [1]) However, a common challenge is reduced access to treatment caused by restrictions on drug reimbursement. This section summarizes the US payer system, explains the concepts of cost, price, cost-effectiveness, value, and affordability, and reviews current evidence of the cost-effectiveness of strategies to improve access to treatment. Although these may sound similar and are often confused, the following discussion will seek to clarify these terms with regard to HCV therapy. To be clear, this section is informational. As explained below, actual costs are rarely known. Accordingly, the HCV Guidance does not utilize cost-effectiveness analysis to guide recommendations at this time.

Table. Abbreviations Specific to Overview of Cost, Reimbursement, and Cost-Effectiveness Considerations for Hepatitis C Treatment Regimens

Abbreviation	Expanded Name
ACA	Affordable Care Act
AMP	Average manufacturer price
AWP	Average wholesale price[a]
CEA	Cost-effectiveness analysis
Cn	Cost of new therapy
Co	Cost of old therapy

ICER	Incremental cost-effectiveness ratio
PBM	Pharmacy benefit manager
QALY	Quality-adjusted life-year
QALYn	Quality-adjusted life-year of new therapy
QALYo	Quality-adjusted life-year of old therapy
WAC	Wholesale acquisition cost[b]

[a] "List price" for wholesale pharmacies to purchase drugs.

[b] Typically, approximately 17% off of AWP.

Drug Cost and Reimbursement

There are many organizations involved with the distribution of hepatitis C drugs and each can impact costs, as well as the decision of which regimens are reimbursed. (US Government Accountability Office, 2015 [2]) (Congress of the United States Congressional Budget Office, 2015 [3]) The roles these organizations have in determining the actual price paid for drugs and who has access to treatment include the following:

- Pharmaceutical companies determine the wholesale acquisition cost (WAC) of a drug (like a “sticker price”). The company negotiates contracts with other organizations within the pharmaceutical supply chain that allow for rebates or discounts that decrease the actual price paid.
- Pharmacy benefit managers (PBMs) often negotiate contracts with pharmaceutical companies on behalf of health insurance companies. Such contracts may include restrictions on who can be reimbursed for treatment and may offer exclusivity (restrictions on which medications can be prescribed) in exchange for lower prices, often provided in the form of WAC discounts.
- Private insurance companies often have separate pharmacy and medical budgets and use PBMs or negotiate drug pricing directly with pharmaceutical companies. Insurance companies determine formulary placement, which impacts choice of regimens and out-of-pocket expenses for patients. An insurance company can cover private, managed care Medicaid, and Medicare plans and can have different formularies for each line of business.
- Medicaid is a heterogeneous compilation of insurance plans that includes fee-for-service and managed care options. Most plans negotiate rebates with pharmaceutical manufacturers (through PBMs or individually). Differences in negotiated contracts between plans have led to Medicaid patients in different states having widely varied access to HCV therapy. Disparities may even exist between patients enrolled in different Medicaid plans within the same state. (Barua, 2015 [4]) State Medicaid programs have benefited from the Patient Protection and Affordable Care Act (ACA), although such benefits are mitigated in states that have opted out of expanding Medicaid coverage under the ACA. In general, for single-source drugs such as the currently available hepatitis C treatments, Medicaid plans receive the lowest price offered to any other payer (outside certain government agencies), and the minimum Medicaid drug rebate is 23.1% of the average manufacturer price (AMP; another payment benchmark).
- Medicare covers HCV drugs through Part D benefits and is prohibited by law from directly negotiating drug prices. These drug plans are offered through PBMs or commercial health plans, which may

negotiate discounts or rebates with pharmaceutical companies.

- The Veterans Health Administration receives mandated rebates through the Federal Supply Schedule, which sets drug prices for a number of government agencies, including the Department of Veterans Affairs, federal prisons, and the Department of Defense, and typically receives substantial discounts over average wholesale price (AWP).
- State prisons and jails are usually excluded from Medicaid-related rebates and often do not have the negotiating leverage of larger organizations and may end up paying higher prices than most other organizations.
- Specialty pharmacies receive dispensing fees and may receive additional payments from contracted insurance companies, PBMs, or pharmaceutical companies to provide services such as adherence support, management of adverse effects, and outcomes measurements such as early discontinuation rates and sustained virologic response rates.
- Patients incur costs (eg, copayment or coinsurance) determined by their pharmacy plan. Patient assistance programs through pharmaceutical companies or foundations can cover many of these out-of-pocket expenses or provide drugs at no cost to qualified patients who are unable to pay.

With the exception of mandated rebates, negotiations of drug prices are considered confidential business contracts and, therefore, there is almost no transparency regarding the actual prices paid for hepatitis C drugs. (Saag, 2015 [5]) However, the average negotiated discount is reported to be 46% off the WAC in 2015, implying that most payers are paying well below the WAC price for HCV regimens. (The New York Times, 2015 [6])

Cost-effectiveness

Cost-effectiveness analysis (CEA) compares the relative costs and outcomes of 2 or more interventions. CEA explicitly recognizes budget limitations for health-care spending and seeks to maximize public health benefits within those budget constraints. CEA is typically expressed as an incremental cost-effectiveness ratio (ICER), the ratio of change in costs between 2 or more interventions to the change in effects. In short, CEA provides a framework for comparing the health-care costs and societal benefits of different technologies or therapies.

To make such comparisons, 3 questions first need to be answered:

1. How much more will we spend on a new intervention? This is not as simple as determining the cost of a new medication but also the cost of the intervention over the course of a person's lifetime and the cost savings from the prevention or attenuation of disease complications. Further, the cost of current standard therapy and the cost of the disease should be considered, so incremental cost-effectiveness requires understanding the incremental cost of new versus old. Given the lack of transparency in health-care costs in the United States, this is at best an inexact estimate.
2. How much more benefit accrues from a new intervention? To compare health interventions using a single metric across diseases and interventions and to integrate both duration and quality of life gained, benefit is measured in terms of quality-adjusted life-years (QALYs). CEA asks: "If a new therapy is implemented, how many more QALYs will likely be gained from the new medications?"
3. How much is society willing to pay to gain 1 additional QALY? This willingness-to-pay threshold typically varies by country and acknowledges opportunity costs. Spending more money on one disease may mean spending less money on other diseases. Similarly, spending more on health care means less spending for education, defense, or environment. Although it may seem inappropriate to set a monetary value on human life, willingness-to-pay thresholds only acknowledge that budgets are finite

and provide a measure of societal value. They are not intended to be a moral valuation.

Once these questions are answered, CEA provides a simple rubric for making normative determinations about whether a new technology provides good value for its cost. First, the ICER of the new therapy is calculated as: (Cn - Co) ÷ (QALYn – QALYo), where Cn is the cost of the new therapy, Co is the cost of the old (comparison) therapy, and QALY is quality-adjusted life-year, shown as new (n) or old (o).

Once the ICER is determined, it is compared with the societal willingness-to-pay threshold (typically considered to be $50,000 to $100,000/QALY gained in the United States). ICERs that are less than the willingness-to-pay threshold represent a good value, and such interventions can be considered cost-effective. Interventions with ICERs exceeding the willingness-to-pay threshold would be less efficient uses of limited budget resources.

Affordability

An intervention that is cost-effective is not necessarily affordable. Affordability refers to whether a payer has sufficient resources in its annual budget to pay for a new therapy for all who might need or want it within that year. Several characteristics of CEA limit its ability to speak to the budget impact of interventions being implemented in the real world:

1. **Perspective on cost:** CEA seeks to inform decisions about how society should prioritize health-care spending. As such, it typically assumes a societal perspective on costs and includes all costs from all payers, including out-of-pocket expenses for the patient. When making coverage decisions for therapy, however, an insurer considers only its own revenues and expenses.
2. **Time horizon:** CEA uses a lifetime time horizon, meaning that it considers lifetime costs and benefits, including those that occur in the distant future. Business budget planning, however, typically assumes a 1-year to 5-year perspective. Savings that may accrue 30 years from now have very little impact on spending decisions today, because they have little bearing on the solvency of the budget today.
3. **Weak association between willingness to pay and the real-world bottom line:** Societal willingness-to-pay thresholds in CEAs are not based on actual budget calculations and have little connection to a payer’s bottom line. Given the rapid development of new technologies, funding all of them, even if they all fell below the societal willingness-to-pay threshold, would likely lead to uncontrolled growth in demand and would likely exceed the limited health-care budget.

There is no mathematic formula that provides a good means of integrating the concerns of value and affordability. When new therapies for HCV are deemed cost-effective, it indicates that such therapies provide excellent benefits for the resources invested in their use and that providing more therapy is a good investment in the long term. Determining the total resources that can be spent on HCV treatment, however, depends on political and economic factors that are not captured by cost-effectiveness determinations.

Cost-effectiveness of Current All-Oral Regimens for Hepatitis C Treatment

Recently published studies compared all-oral, direct-acting antiviral (DAA) regimens to previous standard-of-care regimens (usually IFN based) to calculate ICERs. In general, treating patients with more advanced fibrosis or cirrhosis provided better value (lower ICERs) than treating those with milder disease. Indeed, the ICERs of therapy for treatment-naive patients who do not have cirrhosis are generally within the range of other widely used medical therapies. Although it is possible to make some general comments about cost-effectiveness for these new HCV drug regimens, it is important to recognize that

this task is difficult, owing to the rapid changes in available drugs, the variability in cost (see above), and individual patient characteristics such as fibrosis stage, comorbidities, estimated life expectancy, and HCV genotype.

HCV Genotype 1

There are several cost-effectiveness studies of IFN-free, DAA therapy for HCV genotype 1 infection across various models and using independently derived assumptions about disease progression, costs, and quality of life. Most have shown ICERs within the range of other accepted medical practices. Published ICERs of all-oral regimens for treatment-naive patients with HCV genotype 1 infection in the United States range from cost saving (less than $0) to $31,452 per QALY gained, depending on the presence or absence of cirrhosis. (Chatwal, 2015 [7]); (Najafzadeh, 2015 [8]); (Linas, 2015 [9]); (Younossi, 2015a [10]) However, ICERs as high as $84,744 to $178,295 per QALY gained have been reported among the more recalcitrant IFN-experienced patients with fibrosis who are being retreated using an IFN-free regimen. (Chatwal, 2015)

HCV Genotype 2

ICERs of all-oral regimens in HCV genotype 2–infected persons ranged from $35,500 to $238,000 per QALY gained, depending on the presence or absence of cirrhosis. (Chatwal, 2015 [7]); (Najafzadeh, 2015 [8]); (Linas, 2015 [9]) In analyses among treatment-naive patients without cirrhosis, the AWP of sofosbuvir led to ICERs being higher than US willingness-to-pay thresholds, but with the lower costs negotiated by some payers, the ICERs for all patient groups would fall within accepted pay thresholds for other accepted medical interventions in the United States. (Najafzadeh, 2015 [8]); (Linas, 2015 [9])

HCV Genotype 3

The ICERs of IFN-free therapy for HCV genotype 3 infection reflect the clinical reality that IFN-free regimens are less effective for treating patients with this genotype than any other genotype. As a result, ICERs of all-oral regimens ranged from being inferior (costing more with lower effectiveness) to $410,548 per QALY gained, depending on the presence or absence of cirrhosis. (Chatwal, 2015 [7]); (Linas, 2015 [9]) In one analysis, the preferred therapy for HCV genotype 3 infection from a purely cost-effectiveness–based perspective was PEG-IFN, RBV, and sofosbuvir. (Linas, 2015 [9])

HCV Genotype 4

For HCV genotype 4 infection, ICERs of all-oral regimens ranged from $34,349 to $80,793 per QALY gained, depending on the presence or absence of cirrhosis. (Chatwal, 2015 [7]) However, these findings are based on treatment efficacy from small studies and must be confirmed once better data on treatment response are available.

Limitations

These published CEAs considered a variety of all-oral and nonoral regimens, often for different treatment durations, and patient populations and were not always consistent with current treatment recommendations and guidelines. Some regimens recommended in the HCV Guidance have not yet been subjected to economic analyses. Other analyses that are not described here include, for example, the impact of immediate versus delayed treatment. No CEAs have addressed the potential benefit in reduction of HCV transmission (cure as prevention). Analyses used published WAC prices, which are

higher than the actual prices paid by most payers and reflect an upper threshold of ICER, but most also considered the impact of negotiated price discounts on cost-effectiveness conclusions. One sensitivity analysis found that it would be cost-effective to treat all patients (Metavir fibrosis stages F0-F4) with chronic HCV genotype 1 infection compared with waiting until patients' fibrosis had progressed to at least stage F1 if a total all-oral regimen were to cost less than $22,000. (Rein, 2015 [11])

Conclusions

Although the wholesale acquisition costs of HCV drugs often result in ICERs that make treatment appear unaffordable, the reality is that insurers, PBMs, and government agencies negotiate pricing and few actually pay the much-publicized WAC (retail). However, the negotiated pricing and cost structure for pharmaceutical products in the United States are not transparent, and it is therefore difficult to estimate the true cost and cost-effectiveness of HCV drugs. Whatever the actual current cost of HCV DAAs, competition and negotiated pricing have not improved access to care for many persons with HCV infection and continue to limit the public health impact of these new therapies. Insurers, government, and pharmaceutical companies should work together to bring medication prices to the point where all of those in need of treatment are able to afford and readily access it.

This section was added on August 20, 2015.

Links
[1] http://www.hcvguidelines.org/full-report/references#aasld-idsa-iasusa
[2] http://www.hcvguidelines.org/full-report/references#usgov2015
[3] http://www.hcvguidelines.org/full-report/references#congress2015
[4] http://www.hcvguidelines.org/full-report/references#barua
[5] http://www.hcvguidelines.org/full-report/references#saag2015
[6] http://www.hcvguidelines.org/full-report/references#nytimes2015
[7] http://www.hcvguidelines.org/full-report/references#chatwal2015
[8] http://www.hcvguidelines.org/full-report/references#najafzadeh
[9] http://www.hcvguidelines.org/full-report/references#linas2015
[10] http://www.hcvguidelines.org/full-report/references#younossi2015
[11] http://www.hcvguidelines.org/full-report/references#rein2015

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HCV TESTING AND LINKAGE TO CARE

Expansions and notes for abbreviations used in this section can be found in Methods Table 3. [1]

A summary of recommendations for Testing and Linkage to Care is found in the BOX [2].

One-time HCV testing is recommended for persons born between 1945 and 1965,* without prior ascertainment of risk.

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 needlesticks, 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
   - Persons who were ever incarcerated

3. *Other*
   - HIV infection
   - Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels
   - Solid organ donors (deceased and living)

Rating: Class I, Level B

*Regardless of country of birth

Of the estimated 2.2 to 3.2 million persons (2003 to 2010 National Health and Nutrition Examination Survey of the US noninstitutionalized civilian population) (Denniston, 2014 [3]) chronically infected with HCV in the United States, approximately 50 % are unaware that they are infected. (Denniston, 2012 [4]) Identification of those with active infection is the first step toward improving health outcomes among persons with HCV infection and preventing transmission. (Smith, 2012 [5]); (US Preventive Services Task Force, 2013 [6]); (Centers for Disease Control and Prevention, 1998 [7])

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 [5]); (US Preventive Services Task Force, 2013 [6]); (Centers for Disease Control and Prevention, 1998 [7])

HCV is primarily transmitted through percutaneous exposure to blood. Other modes of transmission include mother-to-infant and contaminated devices shared for noninjection 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 [8]) 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, needlestick 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 [6]); (Centers for Disease Control and Prevention, 1998 [7]). An estimated 29% of incarcerated persons in North America are anti-HCV positive, supporting the recommendation to test this population for HCV. (Larney, 2013 [9]) 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 [10]); (van de Laar, 2010 [11]) Recent data also support testing in all deceased and living solid-organ donors because of the risk of HCV infection posed to the recipient. (Seem, 2013 [12]); (Lai, 2013 [13]) Although Centers for Disease Control and Prevention (CDC) and US Preventive Services Task Force hepatitis C testing guidelines do not specifically recommend testing immigrants from countries with a high prevalence (eg, Egypt or Pakistan) of hepatitis C virus infection, such persons should be tested if they were born from 1945 through 1965 or if they have risk factors (listed in **Summary Box**) for infection.

In 2012, CDC expanded its guidelines originally issued in 1998 (Centers for Disease Control and Prevention, 1998 [7]) for risk-based HCV testing with a recommendation to offer a 1-time (see **Summary Box**) HCV test to all persons born from 1945 through 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, compared with 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 [14]) The cost-effectiveness of 1-time birth cohort testing is comparable to that of current risk-based screening strategies. (Smith, 2012 [5])

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 [15]); (Linas, 2012 [16]); (Wandeler, 2012 [17]); (Witt, 2013 [18]); (Bravo, 2012 [19]); (Williams, 2011 [20]), at least annual HCV testing is recommended in these subgroups.

Implementation of clinical decision support tools or prompts for HCV testing in electronic health records could facilitate reminding clinicians of HCV testing when indicated. (Hsu, 2013 [21]); (Litwin, 2012 [22]); (http://nvhr.org/EMR [23])

An anti-HCV test is recommended for HCV testing, and if the result is positive, current infection should be confirmed by a sensitive HCV 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 at risk 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 polymerase chain reaction (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 [24]); (Alter, 2003 [25]) 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 [26]) 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 [27]) 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 [28]) or who might have been exposed to HCV within the last 6 months because these persons may be anti-HCV negative. An HCV RNA test is also needed to detect reinfection in anti-HCV–positive persons after previous spontaneous or treatment-related viral clearance.

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** [29] lists FDA-approved, commercially available anti-HCV screening assays. **Testing and Linkage to Care Figure 1** [30] shows the CDC-recommended testing algorithm.

Persons who have positive results for an anti-HCV test and negative results for HCV RNA by polymerase chain reaction (PCR) should be informed that they do not have laboratory evidence of current (active) HCV infection. Additional HCV testing is typically unnecessary. The HCV RNA test can be repeated when there is a high index of suspicion for recent infection or in patients with ongoing risk factors for HCV infection.

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 [25]) 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 [31]); (Centers for Disease Control and Prevention [CDC]), 2013 [24]) Prior to the initiation of HCV therapy, quantitative HCV RNA testing may be used to determine the baseline level of viremia (ie, viral load) in order to define the duration of treatment for certain regimens. The degree of viral load decline after initiation of treatment is less predictive of sustained virologic response in the era of direct-acting antiviral therapy (**see section on Pretreatment and On-Treatment Monitoring [32]**). Testing for HCV genotype helps to guide selection of the most appropriate treatment regimen.

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 noninvasive markers is recommended for all persons with HCV infection, to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening).***Rating:** Class I, Level B
4. *Vaccination against hepatitis A and hepatitis B is recommended for all susceptible persons with HCV infection.***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 the development of hepatocellular carcinoma. (Poynard, 1997 [33]); (Harris, 2001 [34]); (Wiley, 1998 [35]); (Corrao, 1998 [36]); (Bellentani, 1999 [37]); (Noda, 1996 [38]); (Safdar, 2004 [39])

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 has a deleterious effect on the liver; however, these data are controversial. (Westin, 2002 [40]) Excess alcohol intake may also cause steatohepatitis. 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 [41]) 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 [42]); (Dieperink, 2010 [43]); (Proeschold-Bell, 2012 [44]) 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, 2008a [45]); (Zarski, 1998 [46]) Owing 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 hepatitis B surface antigen (HBsAg) using standard assays for screening (Moyer, 2013 [47]); (Centers for Disease Control and Prevention, 2008 [48]) (http://www.aafp.org/afp/2008/0315/p819.html [49] and http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm [50]) and counseled on 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 [51]); (Ortiz, 2002 [52]) 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 [53]); (Shaw, 2006 [54]) 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 [55]) 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 may have a lower response to HCV therapy, they are also most likely to derive the greatest survival benefit. (Ghany, 2011 [56]) A liver biopsy can provide objective, semiquantitative information regarding the amount and pattern of collagen or scar tissue in the liver that can assist with treatment and monitoring plans. The Metavir fibrosis score (F0-F4) 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 [57]) 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 [58]) Noninvasive methods frequently used to estimate liver disease severity include a liver-directed physical exam (normal in most patients), routine blood tests (eg, serum alanine aminotransferase [ALT] and aspartate aminotransferase [AST], albumin, bilirubin, international normalized ratio levels, and complete blood cell counts with platelets), serum fibrosis marker panels, liver imaging (eg, ultrasound, computed tomography scan), and transient elastography. Simple blood tests (eg, serum AST-to-platelet ratio index [APRI]) (Wai, 2003 [59]) (http://www.hepatitisc.uw.edu/page/clinical-calculators/apri [60]) 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 [61]); (Rockey, 2006 [62]) Liver elastography can provide instant information regarding liver stiffness at the point of care and can reliably distinguish patients with a high versus low likelihood of cirrhosis. (Castera, 2012 [63]); (Bonder, 2014 [64]) Because 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 should also avoid hepatotoxic drugs (eg, excessive acetaminophen [ie, ≥2 g/d] or certain herbal supplements) or nephrotoxic drugs (eg, nonsteroidal antiinflammatory drugs) and receive ongoing imaging surveillance for liver cancer and gastroesophageal varices. (Sangiovanni, 2006 [65]); (Fontana, 2010 [66])

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 [67]); (Urbanus, 2009 [68]); (Fierer, 2008 [69]) **Testing and Linkage to Care Table 2** [70] 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 and consultation are required for persons with HCV infection who have advanced fibrosis or cirrhosis (stage F3 or above on Metavir scale), including possible referral for consideration of liver transplantation. In the United States, only an estimated 13% to 18% of HCV-infected persons receive treatment.

(Holmberg, 2013 [71]) 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 [72]); (Arora, 2011 [73]); (Clark, 2012 [74]) 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 [75]); (Reilley, 2013 [76]); (McGowan, 2013 [77]) Data are lacking to support exclusion of HCV-infected persons from considerations for hepatitis C therapy based on the amount of alcohol intake or the use of illicit drugs. Based on data from IFN-based treatment, SVR rates among people who inject drugs are comparable to those among people who do not inject drugs. (Aspinall, 2013 [78]). Some possible strategies to address these barriers are listed in **Testing and Linkage to Care Table 3** [79]. One strategy that addresses several barriers is colocalization or integrated care of HCV screening, evaluation, and treatment with other medical or social services. Colocalization 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 [80]); (Stein, 2012 [81]); (Bruggmann, 2013 [82]) Integrated care, consisting of multidisciplinary care coordination and patient case management, increased the proportion of patients with HCV infection and psychiatric illness or substance use who begin antiviral therapy and achieve an SVR, without serious adverse events. (Ho, 2015 [83]).

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 [73]); (Rossaro, 2013 [84]); (Miller, 2012 [85]) Such collaborations have used telemedicine and knowledge networks to overcome geographic distances to specialists. (Arora, 2011 [73]); (Rossaro, 2013 [84]) For example, Project ECHO (Extension for Community Healthcare Outcomes [http://www.echohcvexperts.com [86]]) uses videoconferencing to enhance primary care practitioner capacity in rendering HCV care and treatment to New Mexico's large rural and underserved population. (Arora, 2011 [73]) 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. The short duration of therapy and few serious adverse events related to the new hepatitis C medications present an opportunity to expand the number of mid-level practitioners and primary care physicians in the management and treatment of HCV infection.

Additional strategies for enhancing linkage to and retention in care could be adapted from other fields, such as tuberculosis and HIV. For example, use of directly observed therapy has enhanced adherence to tuberculosis treatment, and use of case managers and patient navigators has reduced loss of follow-up in HIV care. (Govindasamy, 2012 [87]) Recent hepatitis C test and care programs have identified the use of patient navigators or care coordinators to be an important intervention in overcoming challenges to linkage to and retention in care (Trooskin, 2015 [88]); (Coyle C, 2015 [89]) Ongoing assessment of efficacy and comparative effectiveness of this and additional 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.

Changes made on June 28, 2015.

Links
[1] http://www.hcvguidelines.org/node/11
[2] http://www.hcvguidelines.org/node/69
[3] http://www.hcvguidelines.org/full-report/references#denniston2014
[4] http://www.hcvguidelines.org/full-report/references#denniston2012
[5] http://www.hcvguidelines.org/full-report/references#smith2012
[6] http://www.hcvguidelines.org/full-report/references#uspstf2013
[7] http://www.hcvguidelines.org/full-report/references#cdc1998
[8] http://www.hcvguidelines.org/full-report/references#schmidt2014
[9] http://www.hcvguidelines.org/full-report/references#larney2013
[10] http://www.hcvguidelines.org/full-report/references#hosein2013
[11] http://www.hcvguidelines.org/full-report/references#vandelaar2010
[12] http://www.hcvguidelines.org/full-report/references#seem2013
[13] http://www.hcvguidelines.org/full-report/references#lai2013
[14] http://www.hcvguidelines.org/full-report/references#mahajan2013
[15] http://www.hcvguidelines.org/full-report/references#aberg2013
[16] http://www.hcvguidelines.org/full-report/references#linas2012
[17] http://www.hcvguidelines.org/full-report/references#wandeler2012
[18] http://www.hcvguidelines.org/full-report/references#witt2013
[19] http://www.hcvguidelines.org/full-report/references#bravo2012
[20] http://www.hcvguidelines.org/full-report/references#williams2011
[21] http://www.hcvguidelines.org/full-report/references#hsu2013
[22] http://www.hcvguidelines.org/full-report/references#litwin2012
[23] http://nvhr.org/EMR
[24] http://www.hcvguidelines.org/full-report/references#cdc2013
[25] http://www.hcvguidelines.org/full-report/references#alter2003
[26] http://www.hcvguidelines.org/full-report/references#lee2011
[27] http://www.hcvguidelines.org/full-report/references#pawlotsky2002
[28] http://www.hcvguidelines.org/full-report/references#kdigo2008
[29] http://www.hcvguidelines.org/node/30
[30] http://www.hcvguidelines.org/node/70
[31] http://www.hcvguidelines.org/full-report/references#vermeersch2008
[32] http://www.hcvguidelines.org/node/92#pretreatment
[33] http://www.hcvguidelines.org/full-report/references#poynard1997
[34] http://www.hcvguidelines.org/full-report/references#harris2001
[35] http://www.hcvguidelines.org/full-report/references#wiley1998
[36] http://www.hcvguidelines.org/full-report/references#corrao1998
[37] http://www.hcvguidelines.org/full-report/references#bellentani1999
[38] http://www.hcvguidelines.org/full-report/references#noda1996
[39] http://www.hcvguidelines.org/full-report/references#safdar2004
[40] http://www.hcvguidelines.org/full-report/references#westin2002
[41] http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm
[42] http://www.hcvguidelines.org/full-report/references#whitlock2004
[43] http://www.hcvguidelines.org/full-report/references#dieperink2010

[44] http://www.hcvguidelines.org/full-report/references#proeschold2012
[45] http://www.hcvguidelines.org/full-report/references#thein2008a
[46] http://www.hcvguidelines.org/full-report/references#zarski1998
[47] http://www.hcvguidelines.org/full-report/references#moyer2013
[48] http://www.hcvguidelines.org/full-report/references#cdc2008
[49] http://www.aafp.org/afp/2008/0315/p819.html
[50] http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm
[51] http://www.hcvguidelines.org/full-report/references#hourigan1999
[52] http://www.hcvguidelines.org/full-report/references#ortiz2002
[53] http://www.hcvguidelines.org/full-report/references#musso2010
[54] http://www.hcvguidelines.org/full-report/references#shaw2006
[55] http://www.hcvguidelines.org/full-report/references#lewis2007
[56] http://www.hcvguidelines.org/full-report/references#ghany2011
[57] http://www.hcvguidelines.org/full-report/references#kleiner2005
[58] http://www.hcvguidelines.org/full-report/references#regev2002
[59] http://www.hcvguidelines.org/full-report/references#wai2003
[60] http://www.hepatitisc.uw.edu/page/clinical-calculators/apri
[61] http://www.hcvguidelines.org/full-report/references#chou2013
[62] http://www.hcvguidelines.org/full-report/references#rockey2006
[63] http://www.hcvguidelines.org/full-report/references#castera2012
[64] http://www.hcvguidelines.org/full-report/references#bonder2014
[65] http://www.hcvguidelines.org/full-report/references#sangiovanni2006
[66] http://www.hcvguidelines.org/full-report/references#fontana2010
[67] http://www.hcvguidelines.org/full-report/references#vandelaar2009
[68] http://www.hcvguidelines.org/full-report/references#urbanus2009
[69] http://www.hcvguidelines.org/full-report/references#fierer2008
[70] http://www.hcvguidelines.org/node/58
[71] http://www.hcvguidelines.org/full-report/references#holmberg2013
[72] http://www.hcvguidelines.org/full-report/references#khokhar2007
[73] http://www.hcvguidelines.org/full-report/references#arora2011
[74] http://www.hcvguidelines.org/full-report/references#clark2012
[75] http://www.hcvguidelines.org/full-report/references#morrill2005
[76] http://www.hcvguidelines.org/full-report/references#reilley2013
[77] http://www.hcvguidelines.org/full-report/references#mcgowan2013
[78] http://www.hcvguidelines.org/full-report/references#aspinall2013
[79] http://www.hcvguidelines.org/node/64
[80] http://www.hcvguidelines.org/full-report/references#islam2012
[81] http://www.hcvguidelines.org/full-report/references#stein2012
[82] http://www.hcvguidelines.org/full-report/references#bruggmann2013
[83] http://www.hcvguidelines.org/full-report/references#ho2015
[84] http://www.hcvguidelines.org/full-report/references#rossaro2013
[85] http://www.hcvguidelines.org/full-report/references#miller2012
[86] http://www.echohcvexperts.com
[87] http://www.hcvguidelines.org/full-report/references#govindasamy2012
[88] http://www.hcvguidelines.org/full-report/references#trooskin2015
[89] http://www.hcvguidelines.org/full-report/references#coyle2015

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WHEN AND IN WHOM TO INITIATE HCV THERAPY

Successful hepatitis C treatment results in sustained virologic response (SVR), which is tantamount to virologic cure, and as such, is expected to benefit nearly all chronically infected persons. When the US Food and Drug Administration (FDA) approved the first IFN-sparing treatment for HCV infection, many patients who had previously been "warehoused" sought treatment, and the infrastructure (experienced practitioners, budgeted health-care dollars, etc) did not yet exist to treat all patients immediately. Thus, the panel offered guidance for prioritizing treatment first to those with the greatest need. Since that time, there have been opportunities to treat many of the highest-risk patients and to accumulate real-world experience of the tolerability and safety of newer HCV medications. More importantly, from a medical standpoint, data continue to accumulate that demonstrate the many benefits, within the liver and extrahepatic, that accompany HCV eradication. Therefore, the panel continues to recommend treatment for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Accordingly, prioritization tables are now less useful and have been removed from this section.

Despite the strong recommendation for treatment for nearly all HCV-infected patients, pretreatment assessment of a patient's understanding of treatment goals and provision of education on adherence and follow-up are essential. A well-established therapeutic relationship between practitioner and patient remains crucial for optimal outcomes with new direct-acting antiviral (DAA) therapies. Additionally, in certain settings there remain factors that impact access to medications and the ability to deliver them to patients. In these settings, practitioners may still need to decide which patients should be treated first. The descriptions below of unique populations may help physicians make more informed treatment decisions for these groups. (See sections on **HIV/HCV coinfection** [1], **cirrhosis** [2], **liver transplantation** [3], and **renal impairment** [4]).

Expansions and notes for abbreviations used in this section can be found in Methods Table 3 [5].

A summary of recommendations for When and in Whom to Initiate HCV Therapy is found in the BOX [6].

Goal of treatment

The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response.

Rating: Class I, Level A

Recommendations for when and in whom to initiate treatment

Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.

Rating: Class I, Level A

Clinical Benefit of Cure

The proximate goal of HCV therapy is SVR (virologic cure), defined as the continued absence of detectable HCV RNA at least 12 weeks after completion of therapy. SVR is a marker for cure of HCV infection and has been shown to be durable, in large prospective studies, in more than 99% of patients followed up for 5 years or more. (Swain, 2010 [7]); (Manns, 2013 [8]) Patients in whom an SVR is achieved have HCV antibodies but no longer have detectable HCV RNA in serum, liver tissue, or mononuclear cells, and achieve substantial improvement in liver histology. (Marcellin, 1997 [9]); (Coppola, 2013 [10]); (Garcia-Bengoechea, 1999 [11]) Assessment of viral response, including documentation of SVR, requires use of an FDA-approved quantitative or qualitative nucleic acid test (NAT) with a detection level of 25 IU/mL or lower.

Patients who are cured of their HCV infection experience numerous health benefits, including a decrease in liver inflammation as reflected by improved aminotransferase (ie, alanine aminotransferase [ALT], aspartate aminotransferase [AST]) levels and a reduction in the rate of progression of liver fibrosis. (Poynard, 2002b [12]) Of 3010 treatment-naive HCV-infected patients with pretreatment and posttreatment biopsies from 4 randomized trials of 10 different IFN-based regimens (biopsies separated by a mean of 20 months), 39% to 73% of patients who achieved an SVR had improvement in liver fibrosis and necrosis (Poynard, 2002b [12]), and cirrhosis resolved in half of the cases. Portal hypertension, splenomegaly, and other clinical manifestations of advanced liver disease also improved. Among HCV-infected persons, SVR is associated with a more than 70% reduction in the risk of liver cancer (hepatocellular carcinoma [HCC]) and a 90% reduction in the risk of liver-related mortality and liver transplantation. (Morgan, 2013 [13]); (van der Meer, 2012 [14]); (Veldt, 2007 [15])

Cure of HCV infection also reduces symptoms and mortality from severe extrahepatic manifestations, including cryoglobulinemic vasculitis, a condition affecting 10% to 15% of HCV-infected patients. (Fabrizi, 2013 [16]); (Landau, 2010 [17]) HCV-infected persons with non-Hodgkin lymphoma and other

lymphoproliferative disorders achieve complete or partial remission in up to 75% of cases following successful therapy for HCV infection. (Gisbert, 2005 [18]); (Takahashi, 2012 [19]); (Svoboda, 2005 [20]); (Mazzaro, 2002 [21]); (Hermine, 2002 [22]) These reductions in disease severity contribute to dramatic reductions in all-cause mortality. (van der Meer, 2012 [14]); (Backus, 2011 [23]) Lastly, patients who achieve SVR have substantially improved qualities of life, which include physical, emotional, and social health. (Neary, 1999 [24]); (Younossi, 2013 [25]) Because of the many benefits associated with successful HCV treatment, clinicians should treat HCV-infected patients with antiviral therapy with the goal of achieving an SVR, preferably early in the course of chronic HCV infection before the development of severe liver disease and other complications.

Benefits of Treatment at Earlier Fibrosis Stages (Metavir Stage Below F2)

Initiating therapy in patients with lower-stage fibrosis augments the benefits of SVR. In a long-term follow-up study, 820 patients with Metavir stage F0 or F1 fibrosis confirmed by biopsy were followed up for up to 20 years. (Jezequel, 2015 [26]) The 15-year survival rate was statistically significantly better for those who experienced an SVR than for those whose treatment had failed or for those who remained untreated (93%, 82%, and 88%, respectively; P =.003). The study results argue for consideration of earlier initiation of treatment. Several modeling studies also suggest a greater mortality benefit if treatment is initiated at fibrosis stages prior to F3. (Øvrehus, 2015 [27]); (Zahnd, 2015 [28]); (McCombs, 2015 [29])

Treatment delay may decrease the benefit of SVR. In a report of long-term follow-up in France, 820 patients with biopsy-confirmed Metavir stage F0 or F1 fibrosis were followed up for as long as 20 years. (Jezequel, 2015 [26]) The authors noted rapid progression of fibrosis in 15% of patients during follow-up, and in patients treated successfully, long-term survival was better. Specifically, at 15 years, survival rate was 92% for those with an SVR versus 82% for treatment failures and 88% for those not treated. In a Danish regional registry study, investigators modeled treatment approaches with the aim of evaluating the benefit to the region in terms of reductions in morbidity and mortality and HCV prevalence. (Øvrehus, 2015 [27]) Although they note that in their situation of low HCV prevalence (0.4%), with approximately 50% undiagnosed, a policy that restricts treatment to those with Metavir fibrosis stage F3 or higher would decrease mortality from HCC and cirrhosis, the number needed to treat to halve the prevalence of the disease is lower if all eligible patients receive treatment at diagnosis. A modeling study based on the Swiss HIV Cohort Study also demonstrated that waiting to treat HCV infection at Metavir fibrosis stages F3 and F4 resulted in 2- and 5-times higher rates of liver-related mortality, respectively, compared with treating at Metavir stage F2. (Zahnd, 2015 [28])

A US Veterans Administration dataset analysis that used very limited end points of virologic response dating from the IFN-treatment era suggested that early (at a Fibrosis-4 [FIB-4] score of <3.25) initiation of therapy increased the benefit attained with respect to likelihood of treatment success and mortality reduction and ultimately decreased the number of patients needed to treat to preserve 1 life by almost 50%. (McCombs, 2015 [29])

Considerations in Specific Populations

Despite the recommendation for treatment of nearly all patients with HCV infection, it remains important for clinicians to understand patient- and disease-related factors that place individuals at risk for HCV-related complications (liver and extrahepatic) as well as for HCV transmission. Although these groups are no longer singled out for high prioritization for treatment, it is nonetheless important that practitioners

recognize the unique dimensions of HCV disease and its natural history in these populations. The discussions offered below may assist clinicians in making compelling cases for insurance coverage of treatment when necessary.

Persons With Advanced Liver Disease

For persons with advanced liver disease (Metavir stage F3 or F4), the risk of developing complications of liver disease such as hepatic decompensation (Child Turcotte Pugh [CTP] Class B or C [30] [**Methods Table 3** [5]]) or HCC is substantial and may occur in a relatively short timeframe. A large prospective study of patients with cirrhosis resulting from HCV infection examined the risk of decompensation, including HCC, ascites, jaundice, bleeding, and encephalopathy, and found that the overall annual incidence rate was 3.9%. (Sangiovanni, 2006 [31]) The National Institutes of Health (NIH)-sponsored HALT–C study included a group of 220 patients with cirrhosis resulting from HCV infection who were observed for approximately 8 years. A primary outcome of death, hepatic decompensation, HCC, or increase in CTP score of 2 or higher occurred at a rate of 7.5% per year. (Everson, 2006 [32]); (Di Bisceglie, 2008 [33]) Patients with a CTP score of 7 or higher experienced a death rate of 10% per year.

Numerous studies have demonstrated that hepatitis C therapy and the achievement of an SVR in this population results in dramatic decreases in hepatic decompensation events, HCC, and liver-related mortality. (Morgan, 2013 [13]); (van der Meer, 2012 [14]); (Backus, 2011 [23]); (Dienstag, 2011 [34]); (Berenguer, 2009 [35]); (Mira, 2013 [36]) In the HALT-C study, patients with advanced fibrosis secondary to HCV infection who achieved an SVR, compared with patients with similarly advanced liver fibrosis who did not achieve an SVR, had a decreased need for liver transplantation (hazard ratio [HR], 0.17; 95% confidence interval [CI], 0.06–0.46), decreased development of liver-related morbidity and mortality (HR, 0.15; 95% CI, 0.06–0.38) and decreased HCC (HR, 0.19; 95% CI, 0.04–0.80). (Dienstag, 2011 [34]) Importantly, persons with advanced liver disease also require long-term follow-up and HCC surveillance regardless of treatment outcome (see **Monitoring Section** [37]).

Given the clinical complexity and the need for close monitoring, patients with advanced liver disease that has already decompensated (CTP Class B or C [30] [**Methods Table 3** [5]]) should be treated by physicians with experience in treating HCV in conjunction with a liver transplantation center if possible.

Persons Who Have Undergone Liver Transplantation

In HCV-infected individuals, HCV infection of the liver allograft occurs universally in those with viremia at the time of transplantation. Histologic features of hepatitis develop in about 75% of recipients in the first 6 months following liver transplantation. (Neumann, 2004 [38]) By the fifth postoperative year, up to 30% of untreated patients have progressed to cirrhosis. (Neumann, 2004 [38]); (Charlton, 1998 [39]) A small proportion of patients (4%-7%) develop an accelerated course of liver injury (cholestatic hepatitis C, associated with very high levels of viremia) with subsequent rapid allograft failure. Recurrence of HCV infection posttransplantation is associated with decreased graft survival for recipients with HCV infection compared to recipients who undergo liver transplantation for other indications. (Forman, 2002 [40])

Effective HCV therapy pretransplantation resulting in an SVR (virologic cure) prevents HCV recurrence posttransplantation. (Everson, 2003 [41]) In addition, complete HCV viral suppression prior to transplantation prevents recurrent HCV infection of the graft in the majority of cases. (Forns, 2004 [42]); (Everson, 2005 [43]) Preliminary data from a study of patients with complications of cirrhosis secondary to HCV infection, who were wait-listed for liver transplantation, that included patients with MELD scores up to 14 and CTP scores up to 8 found that treatment with sofosbuvir and weight-based RBV for up to 48

weeks was well tolerated and was associated with an overall posttransplant SVR rate of 70%. (Curry, 2015 [44]) Posttransplant SVR was nearly universal among patients who had undetectable HCV RNA for 28 days or longer prior to transplantation.

Treatment of established HCV infection posttransplantation also yields substantial improvements in patient and in graft survival. (Berenguer, 2008 [45]); (Picciotto, 2007 [46]) The availability of effective IFN-free HCV treatments has addressed the major hurdles to treating HCV recurrence posttransplantation: poor tolerability and efficacy. In a multicenter, open-label study that evaluated the ability of sofosbuvir plus RBV to induce virologic suppression in 40 patients post–liver transplant with compensated recurrence of HCV infection, daily sofosbuvir and RBV for 24 weeks achieved an SVR at 12 weeks (SVR12) in 70%. (Charlton, 2015 [47]) No deaths, graft losses, or episodes of rejection occurred. Six patients had serious adverse events, all of which were considered unrelated to study treatment. There were no drug interactions reported between sofosbuvir and any of the concomitant immunosuppressive agents. In contrast, treatment with sofosbuvir plus RBV with or without PEG-IFN in 64 patients with severe, decompensated cirrhosis resulting from recurrence of HCV infection following liver transplantation was associated with an overall SVR12 rate of 59% and a mortality rate of 13%. (Forns, 2015 [48]) On an intent-to-treat basis, treatment was associated with clinical improvement in 57% and stable disease in 22% of patients.

Persons at Greater Risk for Rapidly Progressive Fibrosis and Cirrhosis

Fibrosis progression is variable across different patient populations as well as within the same individual over time. Many of the components that determine fibrosis progression and development of cirrhosis in an individual are unknown. However, certain factors, such as coinfection with HIV or hepatitis B virus (HBV) and prevalent coexistent liver diseases (eg, nonalcoholic steatohepatitis [NASH]), are well-recognized contributors to accelerated fibrosis progression.

HIV coinfection. HIV coinfection accelerates fibrosis progression among HCV-infected persons, (Benhamou, 1999 [49]); (Macias, 2009 [50]); (Konerman, 2014 [51]) although control of HIV replication and restoration of CD4+ cell counts may mitigate this to some extent. (Benhamou, 2001 [52]); (Bräu, 2006 [53]) However, antiretroviral therapy is not a substitute for HCV treatment. In the largest paired-biopsy study, 282 HIV/HCV-coinfected patients with 435 paired biopsies were prospectively evaluated; (Konerman, 2014 [51]) one-third of patients showed fibrosis progression of at least one Metavir stage at a median of 2.5 years. Importantly, 45% of patients with no fibrosis on initial biopsy had progression. Finally, a more rapid progression to death following decompensation combined with a lack of widespread access to liver transplantation and poor outcomes following transplantation highlight the need for treatment in this population regardless of current fibrosis stage. (Pineda, 2005 [54]); (Merchante, 2006 [55]); (Terrault, 2012 [56])

HBV coinfection and other coexistent liver diseases. The prevalence of HBV/HCV coinfection is estimated at 1.4% in the United States and 5% to 10% globally. (Tyson, 2013 [57]); (Chu, 2008 [58]) Persons with HBV/HCV coinfection and detectable viremia of both viruses are at increased risk for disease progression, decompensated liver disease, and the development of HCC.

HBV/HCV coinfected individuals are susceptible to a process called viral interference wherein one virus may interfere with the replication of the other virus. Thus, when treating one or both viruses with antiviral drugs, periodic retesting of HBV DNA and HCV RNA levels during and after therapy is prudent, particularly if only one of the viruses is being treated at a time. Treatment of HCV infection in such cases

utilizes the same genotype-specific regimens as are recommended for HCV monoinfection **(see Treatment Section [59])**. HBV infections in such cases should be treated as recommended for HBV monoinfection. (Lok, 2009 [60])

Persons with other chronic liver diseases who have coincident chronic HCV infection should be considered for hepatitis C therapy, given the potential for rapid progression of liver disease. An IFN-free regimen is generally preferred for immune-mediated liver diseases such as autoimmune hepatitis, because of the potential for IFN-related exacerbation.

Persons With Extrahepatic Manifestations of Chronic HCV Infection

Severe renal impairment. Chronic hepatitis C is associated with a syndrome of cryoglobulinemia and an immune complex and lymphoproliferative disorder that produces arthralgias, fatigue, palpable purpura, renal disease (eg, membranoproliferative glomerulonephritis), neurologic disease (eg, peripheral neuropathy, central nervous system vasculitis), and reduced complement levels. (Agnello, 1992 [61]) Because patients with chronic hepatitis C frequently have laboratory evidence of cryoglobulins (more than 50% in some series), antiviral treatment is imperative for those with the syndrome of cryoglobulinemia and symptoms or objective evidence of end-organ manifestations. IFN-based regimens can produce clinical remission; however, the adverse effects of IFN may mimic manifestations of cryoglobulinemia. (Saadoun, 2014 [62]) Although clinical data are not yet available, the use of IFN-free DAA regimens is an attractive alternative for these patients. Organ-threatening disease (eg, severe neuropathy, renal failure, digital ischemia), in addition to antiviral HCV therapy, should be treated more acutely with immunosuppressive agents or plasmapheresis to clear immune complexes.

Glomerular disease results from deposition of HCV-related immune complexes in the glomeruli. (Johnson, 1993 [63]) Successful treatment of HCV using IFN-based regimens can reverse proteinuria and nephrotic syndrome but usually does not fully ameliorate azotemia. (Johnson, 1994 [64]) No clinical trial data are yet available on IFN-free regimens, but the high rates of SVR (virologic cure) with antiviral therapy support their use in management of hepatitis C–related renal disease and cryoglobulinemia.

Nonhepatic Manifestations of Chronic HCV Infection

The relationship between chronic hepatitis C and diabetes (most notably type 2 diabetes and insulin resistance) is complex and incompletely understood. The prevalence and incidence of diabetes is increased in the context of hepatitis C. (White, 2008 [65]) In the United States, type 2 diabetes occurs more frequently in HCV-infected patients, with a more than 3-fold greater risk in persons older than 40 years. (Mehta, 2000 [66]) The positive correlation between quantity of plasma HCV RNA and established markers of insulin resistance confirms this relationship. (Yoneda, 2007 [67]) Insulin resistance and type 2 diabetes are independent predictors of a more rapid progression of liver fibrosis and an impaired response to IFN-based therapy. (Petta, 2008 [68]) Patients with type 2 diabetes and insulin resistance are also at increased risk for HCC. (Hung, 2010 [69])

Successful antiviral treatment has been associated with improved markers of insulin resistance and greatly reduced incidence of new onset of type 2 diabetes and insulin resistance in HCV-infected patients. (Arase, 2009 [70]) Most recently, antiviral therapy for HCV infection has been shown to improve clinical outcomes related to diabetes. In a large prospective cohort from Taiwan, the incidence of end-stage renal disease, ischemic stroke, and acute coronary syndrome was greatly reduced in HCV-infected patients with diabetes who received antiviral therapy compared with untreated, matched controls. (Hsu, 2014 [71]) Therefore, antiviral therapy may prevent progression to diabetes in patients with prediabetes

who have hepatitis C and may reduce renal and cardiovascular complications in patients with established diabetes who have hepatitis C.

In patients with chronic hepatitis C, fatigue is the most frequently reported symptom and has a major effect on quality of life and activity level evidenced by numerous measures of impaired quality of life. (Foster, 1998 [72]) The presence and severity of fatigue appears to correlate poorly with disease activity, although it may be more common and severe in HCV-infected individuals with cirrhosis. (Poynard, 2002a [73]) Despite difficulties in separating fatigue symptoms associated with hepatitis C from those associated with other concurrent conditions (eg, anemia, depression), numerous studies have reported a reduction in fatigue after cure of HCV infection. (Bonkovsky, 2007 [74]) In the Virahep-C study, 401 patients with HCV infection were evaluated for fatigue prior to and after treatment, using validated scales to assess the presence and severity of fatigue. (Sarkar, 2012 [75]) At baseline, 52% of patients reported having fatigue, which was more frequent and severe in patients with cirrhosis than in those without cirrhosis. Achieving an SVR was associated with a substantial decrease in frequency and severity of fatigue. A recent analysis of 413 patients from the NEUTRINO and FUSION trials who were treated with a sofosbuvir-containing regimen and who achieved an SVR12 demonstrated improvement in patient fatigue (present in 12%) from the pretreatment level. (Younossi, 2014 [76]) After achieving an SVR12, participants had marked improvements in fatigue over their pretreatment scores measured by 3 separate validated questionnaires. Additional studies support and extend these findings beyond fatigue, with improvements in overall health-related quality of life and work productivity observed following successful HCV therapy.(Gerber, 2015 [77]); (Younossi, 2015b [78]); (Younossi, 2015c [79]); (Younossi, 2015d [80])

The reported prevalence of HCV infection in patients with porphyria cutanea tarda approximates 50% and occurs disproportionately in those with cirrhosis. (Gisbert, 2003 [81]) The treatment of choice for active porphyria cutanea tarda is iron reduction by phlebotomy and maintenance of a mildly iron-reduced state without anemia. However, although improvement of porphyria cutanea tarda during HCV treatment with IFN has frequently been described (Takikawa, 1995 [82]), there are currently insufficient data to determine whether treating HCV infection with DAAs and achievement of SVR improve porphyria cutanea tarda.

Lichen planus is characterized by pruritic papules involving mucous membranes, hair, and nails. Antibodies to HCV are present in 10% to 40% of patients with lichen planus, but a causal link with chronic infection is not established. Resolution of lichen planus has been reported with IFN-based regimens, but there have also been reports of exacerbation of lichen planus with these treatments. Although it is unknown whether DAAs will have more success against lichen planus, treatment with IFN-free regimens would appear to be a more advisable approach to addressing this disorder. (Gumber, 1995 [83])

Benefit of Treatment to Reduce Transmission

Persons who have successfully achieved an SVR (virologic cure) no longer transmit the virus to others. As such, successful treatment of HCV infection benefits public health. Several health models have shown that even modest increases in successful treatment of HCV infection among persons who inject drugs can decrease prevalence and incidence. (Martin, 2013a [84]); (Durier, 2012 [85]); (Martin, 2013b [86]); (Hellard, 2012 [87]) Models developed to estimate the impact of HCV testing and treatment on the burden of hepatitis C at a country level reveal that large decreases in HCV prevalence and incidence are possible as more persons are successfully treated. (Wedemeyer, 2014 [88]) There are also benefits to eradicating HCV infection between couples and among families, and thus eliminating the perception that an individual might be contagious. In addition, mother-to-child transmission of HCV does not occur if the woman is not

viremic, providing an additional benefit of curing a woman before she becomes pregnant. (Thomas, 1998 [89]) However, the safety and efficacy of treating women who are already pregnant to prevent transmission to the fetus have not yet been established, and thus treatment is not recommended for pregnant women.

The Society for Healthcare Epidemiology of America (SHEA) advises that health-care workers who have substantial HCV viral replication (≥104 genome equivalents/mL) be restricted from performing procedures that are prone to exposure (Henderson, 2010 [90]) and that all health-care workers with confirmed chronic HCV infection should be treated. For reasons already stated above, the achievement of an SVR in such individuals will not only eliminate the risk of HCV transmission to patients but also decrease circumstantial loss of experienced clinicians. Given concerns about underreporting of infection and transmission (Henderson, 2010 [90]), the availability of effective, all-oral regimens should lead to greater willingness on the part of exposure-prone clinicians to be tested and treated.

Successful treatment of HCV-infected persons at greatest risk for transmission represents a formidable tool to help stop HCV transmission in those who continue to engage in high-risk behaviors. To guide implementation of hepatitis C treatment as a prevention strategy, studies are needed to define the best candidates for treatment to stop transmission, the additional interventions needed to maximize the benefits of HCV treatment (eg, preventing reinfection), and the cost-effectiveness of the strategies when used in target populations.

Persons who inject drugs. Injection drug use (IDU) is the most common risk factor for HCV infection in the United States and Europe, with an HCV seroprevalence of 10% to 70%; (Amon, 2008 [91]); (Nelson, 2011 [92]) IDU also accounts for the majority of new HCV infections (approximately 70%) and is the key driving force in the perpetuation of the epidemic. Given these facts and the absence of an effective vaccine against HCV, testing and linkage to care combined with treatment of HCV infection with potent IFN-free regimens has the potential to dramatically decrease HCV incidence and prevalence. (Martin, 2013b [86]) However, treatment-based strategies to prevent HCV transmission have yet to be studied, including how to integrate hepatitis C treatment with other risk-reduction strategies (eg, opiate substitution therapy, needle and syringe exchange programs). (Martin, 2013a [84])

In studies of IFN-containing treatments in persons who inject drugs, adherence and efficacy rates are comparable to those of patients who do not use injection drugs. A recent meta-analysis of treatment with PEG-IFN with or without RBV in active or recent injection drug users showed SVR rates of 37% and 67% for HCV genotype 1 or 4 and 2 or 3, respectively. (Aspinall, 2013 [93]) As shorter, better-tolerated, and more efficacious IFN-free therapies are introduced, these SVR rates are expected to improve. Importantly, the rate of reinfection in this population is lower (2.4/100 person-years of observation) than that of incident infection in the general population of injection drug users (6.1-27.2/100 person-years), although reinfection increases with active or ongoing IDU (6.44/100 person-years) and available data on follow-up duration are limited. (Aspinall, 2013 [93]); (Grady, 2013 [94])

Ideally, treatment of HCV-infected persons who inject drugs should be delivered in a multidisciplinary care setting with services to reduce the risk of reinfection and for management of the common social and psychiatric comorbidities in this population. Regardless of the treatment setting, recent and active IDU should not be seen as an absolute contraindication to HCV therapy. There is strong evidence from various settings in which persons who inject drugs have demonstrated adherence to treatment and low rates of reinfection, countering arguments that have been commonly used to limit access to this patient population. (Aspinall, 2013 [93]); (Hellard, 2014 [95]); (Grebely, 2011 [96]) Indeed, combining HCV treatment

with needle exchange and opioid replacement programs in this population with a high prevalence of HCV infection has shown great value in decreasing the burden of HCV disease. Elegant modeling studies illustrate the high return on the modest investment of addressing this often-ignored segment of the HCV-infected population. (Martin, 2013b [86]) These conclusions were drawn before the introduction of the latest DAA regimens. Conversely, there are no data to support the utility of pretreatment screening for illicit drug or alcohol use in identifying a population more likely to successfully complete HCV therapy. These requirements should be abandoned, because they create barriers to treatment, add unnecessary cost and effort, and potentially exclude populations that are likely to obtain substantial benefit from therapy. Scale up of HCV treatment in persons who inject drugs is necessary to positively impact the HCV epidemic in the United States and globally.

HIV-infected men who have sex with men (MSM) who engage in high-risk sexual practices. Over the past decade, a dramatic increase in incident HCV infections among HIV-infected MSM who did not report IDU as a risk factor has been demonstrated in several US cities. (van de Laar, 2010 [97]) Recognition and treatment of HCV infection (including acute infection) in this population may represent an important step in preventing subsequent infections. As with persons who inject drugs, HIV/HCV-coinfected MSM who engage in ongoing high-risk sexual practices should be treated for their HCV infection in conjunction with continued education on risk-reduction strategies. In particular, safer-sex strategies should be emphasized given the high rates of reinfection after SVR, which may approach 30% over 2 years, in HIV-infected MSM with acute HCV infection. (Lambers, 2011 [98])

Incarcerated persons. Among incarcerated individuals, the rate of HCV seroprevalence ranges from 30% to 60% (Post, 2013 [99]) and the rate of acute infection is approximately 1%. (Larney, 2013 [100]) Screening for HCV infection is relatively uncommon in state prison systems. Treatment uptake has been limited in part because of the toxic effects and long treatment duration of older IFN-based therapies as well as concerns about cost. (Spaulding, 2006 [101]) In particular, truncation of HCV treatment owing to release from prison has been cited as a major limitation to widespread, effective HCV treatment in correctional facilities. (Post, 2013 [99]); (Chew, 2009 [102]) Shorter (12- to 24-week) HCV therapies reduce duration of stay-related barriers to HCV treatment in prisons. Likewise, the improved safety of newer, all-oral regimens diminishes concerns of toxic effects. Coordinated treatment efforts within prison systems would likely rapidly decrease the prevalence of HCV infection in this at-risk population, although research is needed in this area.

Persons on hemodialysis. The prevalence rate of HCV infection is markedly elevated in persons on hemodialysis and ranged from 2.6% to 22.9% in a large multinational study. (Fissell, 2004 [103]) Studies in the United States found a similarly elevated prevalence rate of 7.8% to 8.9%. (Centers for Disease Control and Prevention, 2001 [104]); (Finelli, 2005 [105]) Importantly, the seroprevalence of HCV was found to increase with time on dialysis, suggesting that nosocomial transmission, among other risk factors, plays a role in HCV acquisition in these patients. (Fissell, 2004 [103]) Improved education and strict adherence to universal precautions can drastically reduce nosocomial HCV transmission risks for persons on hemodialysis, (Jadoul, 1998 [106]) but clearance of HCV viremia through treatment-induced SVR eliminates the potential for transmission.

HCV-infected persons on hemodialysis have a decreased quality of life and increased mortality compared with uninfected persons on hemodialysis. (Fabrizi, 2002 [107]); (Fabrizi, 2007 [108]); (Fabrizi, 2009 [109]) HCV infection in this population also has a deleterious impact on kidney transplantation outcomes with decreased patient and graft survival. (Fabrizi, 2014 [110]) The increased risk for nosocomial transmission and the substantial clinical impact of HCV infection in those on hemodialysis are compelling arguments

for HCV therapy as effective antiviral regimens that can be used in persons with advanced renal failure become available.

Populations Unlikely to Benefit From HCV Treatment

Patients with a limited life expectancy that cannot be remediated by treating HCV, by transplantation, or by other directed therapy do not require treatment. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert. Chronic hepatitis C is associated with a wide range of comorbid conditions. (Butt, 2011 [111]); (Louie, 2012 [112]) Little evidence exists to support initiation of HCV treatment in patients with limited life expectancy (less than 12 months) owing to non–liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized and palliative care strategies should take precedence. (Holmes, 2006 [113]); (Maddison, 2011 [114])

Recommendations for pretreatment assessment

An assessment of the degree of hepatic fibrosis, using noninvasive testing or liver biopsy, is recommended.

Rating: Class I, Level A

An accurate assessment of fibrosis remains vital, as degree of hepatic fibrosis is one of the most robust prognostic factors used to predict HCV disease progression and clinical outcomes. (Everhart, 2010 [115]) Individuals with severe fibrosis require surveillance monitoring for liver cancer, esophageal varices, and hepatic function. (Garcia-Tsao, 2007 [116]); (Bruix, 2011 [117]) In some instances, the recommended duration of treatment is also longer [118].

Although liver biopsy is the diagnostic standard, sampling error and observer variability limit test performance, particularly when inadequate sampling occurs. Up to one-third of bilobar biopsies had a difference of at least 1 stage between the lobes. (Bedossa, 2003 [119]) In addition, the test is invasive and minor complications are common, limiting patient and practitioner acceptance. Serious complications such as bleeding, although rare, are well recognized.

Noninvasive tests to stage the degree of fibrosis in patients with chronic HCV infection include models incorporating indirect serum biomarkers (routine tests), direct serum biomarkers (components of the extracellular matrix produced by activated hepatic stellate cells), and vibration-controlled transient liver elastography. No single method is recognized to have high accuracy alone and each test must be interpreted carefully. A recent publication of the Agency for Healthcare Research and Quality found evidence in support of a number of blood tests; however, at best, they are only moderately useful for identifying clinically significant fibrosis or cirrhosis. (Selph, 2014 [120])

Vibration-controlled transient liver elastography is a noninvasive way to measure liver stiffness and correlates well with measurement of substantial fibrosis or cirrhosis in patients with chronic HCV infection. The measurement range does overlap between stages. (Ziol, 2005 [121]); (Afdhal, 2015 [122]); (Castera, 2005 [123])

The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography. (Boursier, 2012 [124]); (European Association for the Study of the Liver and Asociacion Latinoamericana para el Estudio del Higado, 2015 [125]) A biopsy should be considered for any patient who has discordant results between the 2 modalities that would affect clinical decision making. For example, one shows cirrhosis and the other does not. The need for liver biopsy with this approach is markedly reduced.

Alternatively, if direct biomarkers or vibration-controlled transient liver elastography are not available, the AST-to-platelet ratio index (APRI) or FIB-4 index score can help, (Sebastiani, 2009 [126]); (Castera, 2010 [127]); (Chou, 2013b [128]) although neither test is sensitive enough to rule out substantial fibrosis. (Chou, 2013b [128]) Biopsy should be considered in those in whom more accurate fibrosis staging would impact treatment decisions. Individuals with clinically evident cirrhosis do not require additional staging (biopsy or noninvasive assessment).

Recommendation for repeat liver disease assessment

Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.

Rating: Class I, Level C

When therapy is deferred, it is especially important to monitor liver disease in these patients. In line with evidence-driven recommendations for treatment of nearly all HCV-infected patients, several factors must be taken into consideration if treatment deferral is entertained or mandated by lack of medication access. As noted, strong and accumulating evidence argue against deferral because of decreased all-cause morbidity and mortality, prevention of onward transmission, and quality-of-life improvements for patients treated regardless of baseline fibrosis. Additionally, treatment of HCV infection may improve or prevent extraheptatic complications, including diabetes mellitus, cardiovascular disease, renal disease, and B-cell non-Hodgkin lymphoma, (Conjeevaram, 2011 [129]); (Hsu, 2015 [130]); (Torres, 2015 [131]) which are not tied to fibrosis stage. (Allison, 2015 [132]); (Petta, 2015 [133]) Deferral practices based on fibrosis stage alone are inadequate and shortsighted.

Fibrosis progression varies markedly between individuals based on host, environmental, and viral factors (**Table 1** [134]). (Feld, 2006 [135]) Fibrosis may not progress linearly. Some individuals (often those aged ≥50 years) may progress slowly for many years followed by an acceleration of fibrosis progression. Others may never develop substantial liver fibrosis despite longstanding infection. The presence of existing fibrosis is a strong risk factor for future fibrosis progression. Fibrosis results from chronic hepatic necroinflammation, and thus a higher activity grade on liver biopsy and higher serum transaminase values are associated with more rapid fibrosis progression. (Ghany, 2003 [136]) However, even patients with normal ALT levels may develop substantial liver fibrosis over time. (Pradat, 2002 [137]); (Nutt, 2000 [138]) The limitations of transient elastography and liver biopsy in ascertaining the progression of fibrosis must be recognized.

Host factors associated with more rapid fibrosis progression include male sex, longer duration of infection, and older age at the time of infection. (Poynard, 2001 [139]) Many patients have concomitant nonalcoholic fatty liver disease, and the presence of hepatic steatosis with or without steatohepatitis on

liver biopsy, elevated body mass index, insulin resistance, and iron overload are associated with fibrosis progression. (Konerman, 2014 [51]); (Everhart, 2009 [140]) Chronic alcohol use is an important risk factor because alcohol consumption has been associated with more rapid fibrosis progression. (Feld, 2006 [135]) A safe amount of alcohol consumption has not been established. Cigarette smoking may also lead to more rapid fibrosis progression.

Immunosuppression leads to more rapid fibrosis progression, particularly HIV/HCV coinfection and solid organ transplantation. (Macias, 2009 [50]); (Konerman, 2014 [51]); (Berenguer, 2013 [141]) Therefore, immunocompromised patients should be treated even if they have mild liver fibrosis at presentation.

Level of HCV RNA does not correlate with stage of disease (degree of inflammation or fibrosis). Available data suggest that fibrosis progression occurs most rapidly in patients with HCV genotype 3 infection. (Kanwal, 2014 [142]) (Bochud, 2009 [143]) Aside from coinfection with HBV or HIV, no other viral factors are consistently associated with disease progression.

Although an ideal interval for assessment has not been established, annual evaluation is appropriate to discuss modifiable risk factors and to update testing for hepatic function and markers for disease progression. For all individuals with advanced fibrosis, liver cancer screening dictates a minimum of evaluation every 6 months.

When and in Whom to Initiate HCV Therapy Table 1. Factors Associated With Accelerated Fibrosis Progression

Host	Viral
Nonmodifiable	HCV genotype 3
Fibrosis stage	Coinfection with hepatitis B virus or HIV
Inflammation grade	
Older age at time of infection	
Male sex	
Organ transplant	
Modifiable	
Alcohol consumption	
Nonalcoholic fatty liver disease	
Obesity	
Insulin resistance	

Changes made on October 22, 2015.

Links
[1] http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-hivhcv-coinfection
[2] http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-cirrhosis
[3]

http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-who-develop-recurrent-hcv-infection-post–liver
[4] http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-renal-impairment
[5] http://www.hcvguidelines.org/node/11
[6] http://www.hcvguidelines.org/node/145
[7] http://www.hcvguidelines.org/full-report/references#swain2010
[8] http://www.hcvguidelines.org/full-report/references#manns2013
[9] http://www.hcvguidelines.org/full-report/references#marcellin1997
[10] http://www.hcvguidelines.org/full-report/references#coppola2013
[11] http://www.hcvguidelines.org/full-report/references#garcia-bengoechea1999
[12] http://www.hcvguidelines.org/full-report/references#poynard2002b
[13] http://www.hcvguidelines.org/full-report/references#morgan2013
[14] http://www.hcvguidelines.org/full-report/references#vandermeer2012
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[26] http://www.hcvguidelines.org/full-report/references#jezequel2015
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October 2015

Hepatitis C Guidance Underscores the Importance of Treating HCV Infection: Panel Recommends Direct-Acting Drugs for Nearly All Patients with Chronic Hepatitis C

Experts at the American Association for the Study for Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) have updated HCVguidelines.org, a website developed in collaboration with the International Antiviral Society-USA (IAS-USA) to provide up-to-date guidance on the treatment of hepatitis C virus (HCV). Based on expanded "real-world" experience with the tolerability and efficacy of newer HCV medications, the section on "When and in Whom to Initiate HCV Therapy" no longer includes tables that offer recommendations on how to prioritize patients for treatment.

"When the direct-acting medications were first introduced, all our knowledge about how these drugs worked came from clinical trials. We needed to gain more experience with their safety before we encouraged all infected persons to initiate therapy. We now have that experience," said panel co-chair David Thomas, MD.
According to the guidance, successful hepatitis C treatment results in sustained virologic response—or virologic cure—and thus would benefit nearly all of those chronically infected with HCV. Previously, the panel of experts who write the guidance had prioritized treatment with the direct-acting anti-virals for those with the greatest need, particularly those with severe liver disease.

Since the panel's initial recommendation, there have been opportunities to treat many of the highest-risk patients and to learn more about the new medications. "There are also expanding data on the benefits of HCV treatment for patients with all stages of disease, including mild liver disease," added panel co-chair Raymond Chung, MD.

Because of the cost of the new drugs, or regional availability of appropriate health care providers, a practitioner may still need to decide which patients should be treated first. Additionally, those with short life expectancies unrelated to HCV infection are not recommended for treatment with these newer therapies, according to the guidance. "However, the goal is to treat all patients as promptly as feasible to improve health and to reduce HCV transmission" said panel co-chair Henry Masur, MD.

"A good relationship between doctor and patient is crucial to achieving the best outcomes with direct-acting therapies. The physician needs to make an assessment of a patient's understanding of the treatment goals and provide education on the importance of adherence to the therapy and follow-up care," added panel co-chair Gary Davis, MD.
Visit www.HCVguidelines.org for updates to this and other sections of the guidance.

About the AASLD

AASLD is a medical subspecialty society representing clinicians and researchers in liver disease. The work of our members has laid the foundation for the development of drugs used to treat patients with viral hepatitis. Access to care and support of liver disease research are at the center of AASLD's advocacy efforts.

AASLD is the leading organization of scientists and healthcare professionals committed to preventing and curing liver disease. AASLD was founded in 1950 by a small group of leading liver specialists and has grown to an international society responsible for all aspects of hepatology.

Press releases and additional information about AASLD are available online at www.aasld.org

About IDSA

The Infectious Diseases Society of America (IDSA) is an organization of physicians, scientists, and other health care professionals dedicated to promoting health through excellence in infectious diseases research, education, prevention, and patient care. The Society, which has nearly 10,000 members, was founded in 1963 and is based in Arlington, VA. For more information, see www.idsociety.org.

Visit www.idsociety.org/HCV/ to access IDSA's extensive collection of resources on hepatitis C, including the Society's Core Curriculum for HCV at www.idsociety.org/HCV_Curriculum/#Introduction.

About IAS-USA

The International Antiviral Society – USA (IAS-USA) serves as a collaborating partner for the AASLD/IDSA Hepatitis C Virus (HCV) Guidance and is responsible for providing expertise and administrative support to HCV Guidance Panel members and processes. A representative from the IAS-USA serves as a co-chair of the HCV Guidance Panel. For more information, see http://iasusa.org

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MEDICAID DRUG REBATE PROGRAM NOTICE **Release No. 172**

For State Technical Contacts

ASSURING MEDICAID BENEFICIARIES ACCESS TO HEPATITIS C (HCV) DRUGS

The Centers for Medicare & Medicaid Services (CMS) remains committed to Medicaid beneficiaries continuing to have access to needed prescribed medications, a commitment we know that states share. The purpose of this letter is to advise states on the coverage of drugs for Medicaid beneficiaries living with hepatitis C virus (HCV) infections. Specifically, this letter addresses utilization of the direct-acting antiviral (DAA) drugs approved by the Food and Drug Administration (FDA) for the treatment of chronic HCV infected patients.

Rules Regarding Medicaid Drug Coverage

Coverage of prescription drugs is an optional benefit in state Medicaid programs, though all fifty (50) states and the District of Columbia currently provide this benefit. States that provide assistance for covered outpatient drugs of manufacturers that have entered into, and have in effect, rebate agreements described in section 1927(b) of the Social Security Act (the Act) under their Medicaid fee-for-service (FFS) programs or Medicaid managed care plans are required to comply with the requirements of section 1927(d)(1) and (2) of the Act.

Section 1927(d)(1) of the Act provides that a state may subject a covered outpatient drug to prior authorization, or exclude or otherwise restrict coverage of a covered outpatient drug if the prescribed use is not for a medically accepted indication as defined by section 1927(k)(6) of the Act, or the drug is included in the list of drugs or drug classes (or their medical uses), that may be excluded or otherwise restricted under section 1927(d)(2) of the Act.

Section 1927(k)(6) of the Act defines the term “medically accepted indication” as any use of a covered outpatient drug which is approved under the Food Drug And Cosmetic Act (FFDCA), 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).

When establishing formularies, states must ensure compliance with the requirements in section 1927(d)(4), including the requirements of section 1927(d)(4)(C) of the Act. Under this provision, a covered outpatient drug may only be excluded with respect to the treatment of a specific disease or condition for an identified population if, based on the drug's labeling, or in the case of a drug the prescribed use of which is not approved under the FFDCA, but is a medically accepted indication based on information from the appropriate compendia described in section 1927(k)(6), the excluded drug does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome of such treatment for such population over other drugs included in the formulary and there is a written explanation (available to the public) of the basis for the exclusion.

Accordingly, to the extent that states provide coverage of prescription drugs, they are required to provide coverage for those covered outpatient drugs of manufacturers that have entered into, and have in effect, rebate agreements described in section 1927(b) of the Act, when such drugs are prescribed for medically accepted indications, including the new DAA HCV drugs.

CMS is aware that, given the costs of these new DAA HCV drugs, states have raised concerns about the budgetary impact to their Medicaid programs and beneficiary access to needed care. The agency shares these concerns. However, the recent launch of multiple DAA HCV drugs in the marketplace is creating competition in this class that may result in downward pressure on the prices of these drugs. This competition may enhance the ability of states to negotiate supplemental rebates or other pricing arrangements with manufacturers to obtain more competitive prices for both their FFS and managed care programs, thereby reducing costs. CMS encourages states to take advantage of such opportunities.

To that end, manufacturers have a role to play in ensuring access and affordability to these medications. CMS has sent a letter to the manufacturers of these DAA HCV drugs, asking them to provide information regarding any value-based purchasing arrangements they offer for these drugs so that states might be able to participate in such arrangements.

Permissible Limitations to Medicaid Drug Coverage

CMS is concerned that some states are restricting access to DAA HCV drugs contrary to the statutory requirements in section 1927 of the Act by imposing conditions for coverage that may unreasonably restrict access to these drugs. For example, several state Medicaid programs are limiting treatment to those beneficiaries whose extent of liver damage has progressed to metavir fibrosis score F3, while a number of states are requiring metavir fibrosis scores of F4[1].

[1] The metavir scoring system is used to assess inflammation and fibrosis by histopathological evaluation of a liver biopsy of patients with hepatitis C. The stages, indicated by F0 through F4, represent the amount of fibrosis or scarring of the liver. F0 indicates no fibrosis while F4 represents cirrhosis; a chronic degenerative liver disease state in which normal liver cells are damaged and are then replaced by scar tissue. For more information about liver fibrosis please read Ramon Batallar and David A. Brenner, Liver fibrosis Journal of Clinical Investigation. 2005 Feb 1; 115(2): 209–218 by visiting http://www.ncbi.nlm.nih.gov/pmc/articles/PMC546435/

Certain states are also requiring a period of abstinence from drug and alcohol abuse as a condition for payment for DAA HCV drugs. In addition, several states are requiring that prescriptions for DAA HCV drugs must be prescribed by, or in consultation with specific provider types, like gastroenterologists, hepatologists, liver transplant specialists, or infectious disease specialists in order for payments to be provided for the drug.

While states have the discretion to establish certain limitations on the coverage of these drugs, such as preferred drug lists and use of prior authorization processes,[2] such practices must be consistent with requirements of section 1927(d) of the Act to ensure appropriate utilization.

As such, the effect of such limitations should not result in the denial of access to effective, clinically appropriate, and medically necessary treatments using DAA drugs for beneficiaries with chronic HCV infections. States should, therefore, examine their drug benefits to ensure that limitations do not unreasonably restrict coverage of effective treatment using the new DAA HCV drugs.

CMS encourages states to exercise sound clinical judgment and utilize available resources to determine their coverage policies. These resources include pharmacy and therapeutics (P&T) committees, drug utilization review (DUR) boards, and comparative analysis of the costs to treat HCV patients in light of the efficacy of these newer regimens in terms of cure rates, when compared to those of preexistent therapies. Additionally, CMS notes the availability of guidelines for states to refer to regarding testing, managing, and treating HCV put forth by the American Association for the Study of Liver Diseases (AASLD), the Infectious Diseases Society of America (IDSA), and the International Antiviral Society-USA (IAS-USA), which can be found at http://www.hcvguidelines.org/full-report-view. CMS also suggests that states consider implementing programs that provide patients on HCV treatment with supportive care that will enhance their adherence to regimens, thereby increasing the success rates.

Coverage under Medicaid Managed Care Plans

CMS is also concerned that in many states, Medicaid managed care organizations (MCOs) or other managed care arrangements' conditions for payment for DAA HCV drugs appear to be more restrictive than coverage under the states' fee-for-service (FFS) programs. Furthermore, in states with multiple MCOs or arrangements, the conditions for payment for DAA HCV drugs often differ between various plans.

CMS reminds states that the drugs under the approved state plan must be available to individuals enrolled in Medicaid managed care arrangements. As with their FFS program, states are urged to carefully monitor the DAA HCV drug coverage policies of their MCOs to ensure enrollees have appropriate access. States have the option to include these drugs in the managed care contracts and capitation rates or to "carve out" the drugs used in the treatment of chronic HCV

[2] In accordance with section 1927(d)(5) of the Act, a state plan may establish a prior authorization program as a condition of coverage or payment for a covered outpatient drug; however, the program must provide responses by telephone or other telecommunication device within 24 hours of a request for prior authorization, and, except for those drugs restricted or excluded from coverage pursuant to section 1927(d)(2) of the Act, provide for the dispensing of at least a 72-hour supply of a covered outpatient prescription drug in an emergency situation.

infections from managed care contracts and capitation rates and instead provide access to these drugs through FFS or other arrangements.

Consistent with the regulation at 42 CFR §438.210, services covered under Medicaid managed care contracts (with MCOs, prepaid inpatient health plans, and prepaid ambulatory health plans) must be furnished in an amount, duration, and scope that is no less than the amount, duration, and scope for the same services for beneficiaries under FFS Medicaid. While managed care plans may place appropriate limits on DAA HCV drugs using criteria applied under the state plan, such as medical necessity, the managed care plan may not use a standard for determining medical necessity that is more restrictive than is used in the state plan.

CMS notes that managed care plans are permitted to use other utilization controls provided that the services, as controlled under the health plan's policies, can be reasonably expected to achieve their purpose. However, states should carefully monitor utilization controls and the HCV coverage policies of their managed care plans to ensure that the organizations are providing appropriate access to covered services and benefits consistent with 42 CFR §438.210.

CMS recognizes the challenges of defining policies in the face of new and innovative drug treatments. It will monitor the policies and conditions states impose for the coverage of DAA HCV drugs to ensure compliance with the requirements of the Act and access to effective, clinically appropriate, and medically necessary treatments for beneficiaries. CMS will monitor state compliance with their approved state plans, the statue, and regulations to assure that access to these medications is maintained.

CMS shares with states the common goal of ensuring access to quality care for Medicaid beneficiaries. Given the complexities that have arisen with the introduction of the DAA HCV drugs, CMS will continue to work with State Medicaid agencies to continue providing and improving care to persons infected with chronic HCV infections. If you have any questions, please contact John M. Coster, Ph.D., R.Ph., Director of the Division of Pharmacy, at John.Coster@cms.hhs.gov.

/s/

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Why We Should Be Willing to Pay for Hepatitis C Treatment

The launch of oral direct-acting antivirals (DAAs) to treat chronic hepatitis C virus (HCV) infection represents a significant shift in the HCV treatment paradigm. With DAAs, the sustained virologic response (SVR) (ie, efficacy of treatment) has increased to more than 90%, treatment duration has decreased to as few as 8 weeks, and these regimens have no major side effects. Coupled with the updates in HCV screening guidelines, use of new DAAs could make HCV a rare disease in the next 20 years in the United States.[1]

However, the high price of DAAs is a barrier, and has drawn criticism from patients and payers.[2–4] Challenged with a budget needed to treat all HCV patients, Medicaid has restricted these treatments in at least 30 US states to patients with advanced fibrosis stage.[5] With more than a million patients needing HCV treatment in the next 3 to 5 years in the United States, the high price of DAAs could impact the budget of private payers and government. On the other hand, several recent studies have shown that these drugs provide a good value for the money. Furthermore, the price of DAAs has decreased since their first availability. For example, the average discounts on sofosbuvir-based regimens in 2015 have been 46%.[6] As additional antiviral drugs become available in the near future, drug prices may decrease even further.

Here, we discuss the value of HCV treatment with oral DAAs considering new discounts, the importance of treating all HCV patients, and how HCV treatment costs and value compare with that of human immunodeficiency (HIV) treatment.

Value of Hepatitis C Virus Treatment

Recently published cost-effectiveness studies have shown that HCV regimens based on sofosbuvir, ledipasvir, and simeprevir are cost effective for most patients.[7–12] The incremental cost-effectiveness ratios (ICERs) of these regimens (when compared with the old standard of care) ranged from $10,000 to $284,000 per quality-adjusted life-year (QALY) depending on the patient's status with respect to treatment history, HCV genotype, and cirrhosis status. The average ICER for all HCV patients was $55,400 per QALY.[7] The ICERs of treatment with older therapies based on first-generation protease inhibitors, boceprevir and telaprevir, were between $17,000 and $103,000 per QALY, depending on disease stage.[13–17] The ICERs of peginterferon-ribavirin (in comparison with peginterferon) were between $26,000 and $64,000 per QALY. In general, the ICERs were higher in patients with early stages of liver fibrosis than in patients with advanced fibrosis. Collectively, these data show that throughout its history, compared with the previous standard, overall the "new" HCV treatment costs an additional approximately $50,000 to $100,000 for 1 additional QALY gained and the DAAs are no exception.

Hepatitis C Virus Treatment Now Is Cost Saving

With recent rebates on drug prices, sofosbuvir-based treatment in 2015, on average, costs 54% of the wholesale acquisition cost.[6] Applying these discounted drug prices to our previously published simulation model,[7] we evaluated the cost effectiveness of DAAs. We found that compared with treatment with telaprevir/boceprevir or peginterferon-based therapies, treatment with sofosbuvir–ledipasvir regimens is cost saving in the majority of patients (ie, these regimens increased QALYs and saved health care costs) (Figure 1). This effect was most prominent in patients with genotype 1 infection. Treatment was not cost saving, although it was cost effective, in patients with other genotypes.

Decreased Cost per Sustained Virologic Response

Although the cost of antiviral treatment increased with the availability of new therapies, the cost per SVR has decreased. As shown in Figure 2, the cost of treating HCV genotype 1 with peginterferon–ribavirin, first-generation protease inhibitors, and sofosbuvir–ledipasvir (at wholesale acquisition cost) increased from $43,000 to $103,000 per patient. However, the corresponding costs per SVR decreased from $213,000 to $108,000. After applying the recent discounts (46%), the cost of treatment decreased to $56,000, which is less expensive than boceprevir- and telaprevir-based therapies, and the cost per SVR decreased to $58,000.

Health Economics of Hepatitis C Virus Versus Human Immunodeficiency Virus Treatment

HCV has superseded HIV as a cause of death in the United States since 2007.[18] Therefore, to put the health economics of HCV into perspective, we can compare the cost of HCV treatment with DAAs with the

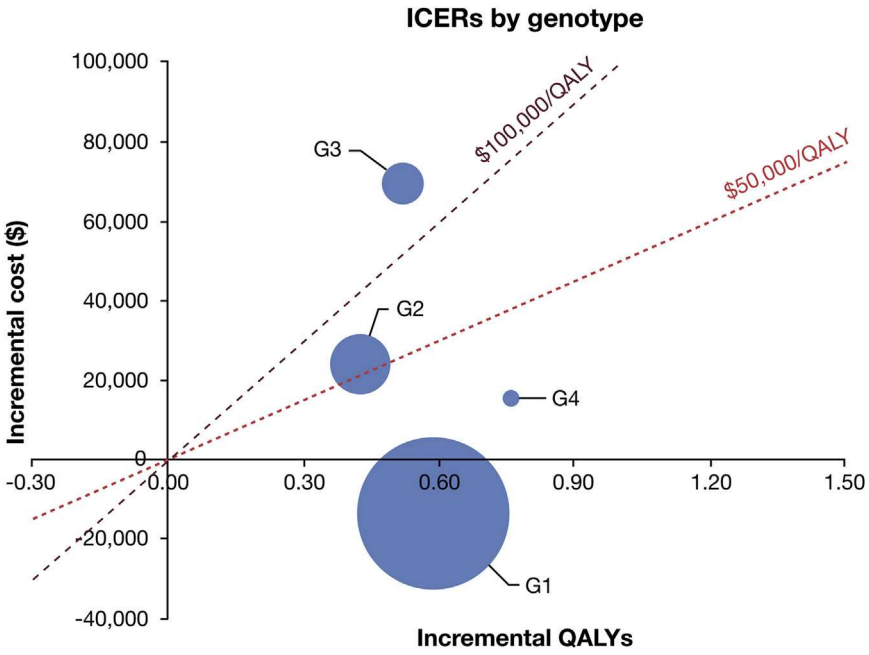

Figure 1. Incremental cost and effectiveness of new antiviral regimens in comparison with old standard of care by HCV genotype. The size of each *bubble* represents the relative population size needing treatment. The center of the bubble represents the incremental costs and QALYs of sofosbuvir/ledipasvir-based therapies in comparison with the old standard of care. *Bubbles* below the *red line* are cost effective at that threshold, and *bubbles* below the *green line* are cost-saving strategies. For instance, treatment of genotype 1 patients with sofosbuvir–ledipasvir in comparison with telaprevir/boceprevir will increase QALYs and decease costs (ie, cost-saving strategy). Treatment of genotype 4 patients will increase both QALYs and costs, but is still cost effective at a $100,000 willingness-to-pay threshold. The weighted average of the results across all genotypes is cost saving.

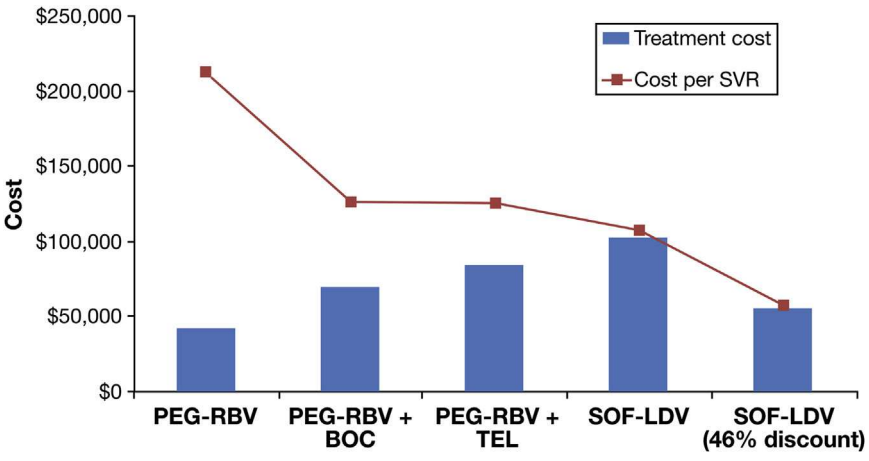

Figure 2. Cost and cost per SVR of different antiviral regimens to treat patients with hepatitis C virus genotype 1. The cost of treatment increased from peginterferon–ribavirin (PEG-RBV) to sofosbuvir–ledipasvir (SOF-LDV) in genotype 1 patients, however, the corresponding costs per SVR decreased at the same time. Furthermore, at 46% discounts, both costs and cost per SVR of SOF–LDV were lower than boceprevir (BOC)- and telaprevir (TEL)-based therapies, the old standard of care.

cost of treating HIV. The discounted lifetime cost of treating 1 person with HIV in the United States is $315,000 in 2014 US dollars.[19] The corresponding cost of curing HCV with oral DAAs is $58,000–which is only 18% of the total HIV treatment cost. HIV antiretroviral treatment is cost effective in the United States,[20] HCV treatment is cost saving.

The total federal budget requested for HIV and acquired immune deficiency syndrome in 2015 was $24.2 billion, of which $17.5 billion was allocated to HIV treatment and care.[21] Ryan White's Acquired Immune Deficiency Syndrome Drug Assistance Program, which provides access to HIV-related medications to people with HIV, was funded at $900 million. The federal spending on HCV treatment is unknown. However, using a simulation model, we predicted that the maximum 5-year budget needed to treat all patients (by private as well as government payers) who are candidates for HCV treatment would be $37 billion (ie, $7.4 billion per year).[7] Of note, unlike HIV, HCV treatment offers a cure; therefore, annual spending on HCV treatment would decrease sharply in subsequent years.

Why We Should Be Willing to Pay for Hepatitis C Virus Treatment

The cost of HCV treatment with the available oral DAAs has decreased substantially since their first availability in 2014. Furthermore, we anticipate more discounts with increased competition from other manufacturers in the near future. The overall budget needed to treat HCV is not huge and is reasonable when compared with that of HIV. Therefore, HCV treatment should be not be restricted only to

patients in advanced fibrosis stages. We have an opportunity to eliminate hepatitis C by taking appropriate and timely steps. We as a society should be willing to pay for the current HCV therapies by providing additional resources and giving the attention to hepatitis C that it deserves.

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Viral Hepatitis in Oregon

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Oregon Health Authority
PUBLIC HEALTH DIVISION
Acute and Communicable Disease Program

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Executive summary

Purpose

The purpose of Oregon's first viral hepatitis epidemiologic profile is to document the burden of disease associated with viral hepatitis in Oregon. This report focuses on chronic infection with hepatitis B (HBV) and hepatitis C virus (HCV) because they cause the greatest morbidity and mortality. The goals are to:

- Increase public and professional awareness of screening recommendations for treatment of HCV;
- Provide useful data to local health departments, other state agencies, and health care providers and systems for planning purposes; and
- Inform policies for viral hepatitis prevention and care.

The Acute and Communicable Disease Prevention (ACDP) Program in the Public Health Division of the Oregon Health Authority (OHA) developed this profile in collaboration with an advisory group made up of both internal partners and external stakeholders. The advisory group included other OHA programs and state agencies, local health departments, academic partners, health systems, community-based agencies and community members. This group was instrumental in guiding the report's organization and design. From the outset, our goal was to develop a report to be used for education and planning.

This report is divided into three sections. The chapters in each section are organized to stand alone, so some sections repeat information.

The first section provides an overview of chronic hepatitis due to HBV and HCV, starting with chapters covering prevalence, natural history of the two viruses and risk factors for infection. A third chapter discusses CDC's rationale for its recent recommendation for a one-time HCV screening of all persons born between 1945 and 1965.

The middle section describes the burden of disease in Oregon, providing data on the incidence of acute and chronic viral hepatitis, hospitalizations, liver cancer, liver transplant, and mortality. This section generally focuses on the most recent five years of available data.

The last section has chapters that discuss different populations at high risk or with special needs: Asians and Pacific Islanders (PIs), blacks and African Americans, American Indians and Alaska Natives (AI/ANs), persons who inject drugs (PWIDs), and incarcerated populations.

The hepatitis A virus (HAV), HBV and HCV are the three most common causes of viral hepatitis. Each has a distinct mode of transmission, populations affected, prevention strategies and treatments although there is some overlap between the viruses.

Findings

Hepatitis A

From a high of nearly 3,000 cases reported in 2005, new infections (acute cases) due to hepatitis A virus (HAV) have declined with the availability of HAV vaccine, averaging only 20 cases a year between 2009 and 2013. In the past five years, infections were rare in children, and occurred most commonly in persons aged 30–59. HAV is transmitted by eating contaminated foods or having close contact with another person with HAV. International travelers or household contacts of travelers have been most commonly affected in the past five years.

Hepatitis B

Similarly, Oregon's case counts of acute HBV have fallen dramatically since universal vaccination of infants began in 1991. Between 2009 and 2013, only 2% of acute HBV cases occurred in persons under 20 years of age. Just over half (53%) of cases occurred in persons in their 40s and 50s. Men in this age group were twice as likely to be infected as women were. Sexual transmission, injection drug use and potential health care exposures were the most commonly identified risk factors.

In contrast, rates of chronic infection with HBV have varied little over time. The OHA received an annual average of 440 laboratory reports consistent with chronic HBV between 2009 and 2013. Seventy-five percent of cases were foreign-born, with the highest rates seen in Asians and Pacific Islanders (PIs), who had rates 41 and 44 times higher, respectively, than whites in Oregon, followed by blacks and African Americans, whose rate is 21 times higher than that of whites.

Hepatitis C

Rates of acute infection with HCV (for which no vaccine is available) between 2009 and 2013 were stable over the same period. HCV infections were most common in younger adults; nearly half of the cases were in persons less than 30 years of age. Injection drug use was the predominant route of transmission, accounting for 64% of interviewed cases. The average rate of acute HCV in Oregon was 50% higher than the national rate in 2007–2011. The highest rates were in AI/ANs (2.1 cases/100,000), who had rates three times higher than whites (0.6 cases/100,000) and blacks and African Americans (0.6 cases/100,000) in Oregon.

The volume of laboratory reports of positive HCV tests is more than 10 times higher than for chronic HBV, averaging 5,087 reports per year in the last five years. The majority of cases are male (61%) and over the age of 40 (79%); both AI/ANs and blacks and African Americans had rates of positive HCV laboratory reports that were twice as high as in whites. Like acute cases, the majority of persons interviewed reported injection drug use at some point in their lives.

Hospitalizations

Between 2008 and 2012, 3,917 persons with HCV were hospitalized and had a discharge diagnosis consistent with advanced liver disease. The number of hospitalizations averaged 783 per year, and the average length of stay was five days. Only 8% occurred in persons under the age of 45 years, while 70% occurred in persons aged 50–64. Two-thirds occurred in men. The most common liver-related discharge diagnoses were cirrhosis (75%) and decompensated cirrhosis (76%), followed by liver cancer (15%), chronic liver disease (22%) and liver transplant (3%).

Liver cancer

Between 1996 and 2012, 3,395 cases of hepatocellular carcinoma (HCC) were reported to the Oregon State Cancer Registry (OSCaR). Of those, 959 (28%) were attributable to chronic viral hepatitis; 196 (6%) were in persons reported to the Oregon Health Authority with chronic HBV (reported between 1988 and 2012); and 763 (22%) had chronic HCV (reported 2005–2012). By the year 2012, 8% of liver cancer cases had chronic HBV, while 47% had chronic HCV. The highest rates of HBV-associated liver cancer were seen in Asians and Pacific Islanders and in blacks and African Americans; for HCV-related liver cancer, the highest rates were seen in American Indians and Alaska Natives, and blacks and African Americans.

Liver transplants

Between 2009 and 2013, 169 liver transplants were performed at Oregon Health & Science University (OHSU), which translates into 34 cases annually. Of those, between one and two were attributable to chronic HBV each year. An average of 18 liver transplants were performed annually on patients with chronic HCV, which accounted for 54% of liver transplant cases.

Mortality

Deaths from HCV in Oregon have risen steadily over the last decade, surpassing the death rate from HIV in 2000, and averaging 441 deaths annually in Oregon during the last five years (2009–2013). The mortality rate from HCV is more than six times higher than mortality from HIV in Oregon. HCV mortality was also 81% higher in Oregon than in the United States as a whole. Most deaths (71%) were in men and persons aged 45–64 (79%). There were marked racial disparities; AI/ANs (17.4 deaths/100,000) and blacks and African Americans (16.1 deaths/100,000) had roughly twice the mortality rate of whites (8.9 deaths/100,000).

Recommendations

Until recently, Oregon has largely underappreciated the impact of viral hepatitis on the health outcomes of those infected, the considerable burden hepatitis B and C place on health systems, and the significant health disparities experienced by disproportionately affected communities and populations. Actions are needed to increase awareness, prevent transmission, and support access to care and treatment. Otherwise, Oregonians will continue on the trajectory of disproportionate rates of viral hepatitis, advanced liver disease and death. The economic costs and burden of viral hepatitis on health care and social services will increase and the opportunity to decrease human suffering will be lost.

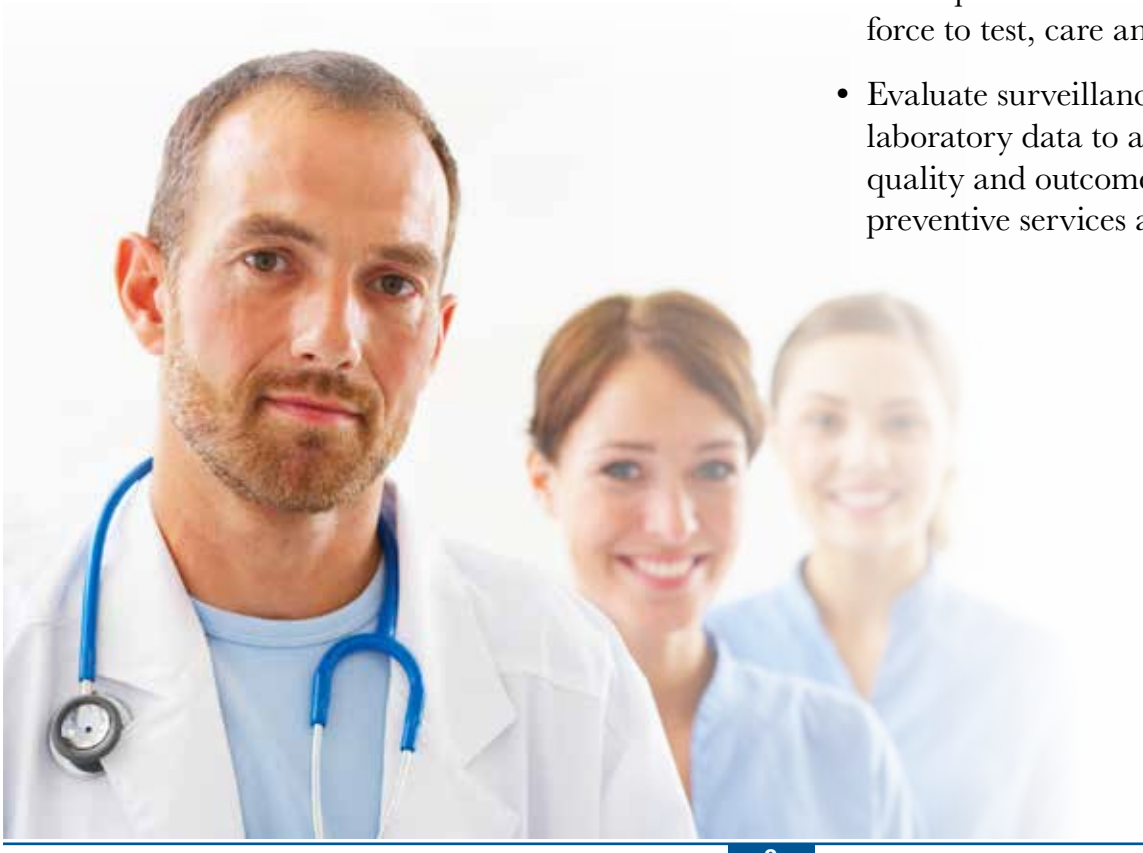
While the size and impact of viral hepatitis in Oregon looms large, public health actions and evidence-based strategies can support the prevention of new infections, improve health outcomes, decrease community and population health disparities, and decrease future medical care costs. Oregon needs to comprehensively address viral hepatitis through community partnerships and strategic actions across multiple state and local systems. Public health recommendations for addressing the problem of chronic viral hepatitis in Oregon include the following:

Assessment

- Monitor trends in hepatitis incidence and prevalence, liver cancer and mortality.
- Investigate epidemiologic trends, respond to outbreaks and study health disparities.

Policy development

- Develop evidence-based policies to prevent viral hepatitis, identify persons early in their infection and link them to care and treatment.
- Target populations with increased prevalence, immediate risks of advanced liver disease, and ongoing transmission risks.
- Support efforts to address opiate dependency and prevent it from progressing to injection drug use.
- Conduct culturally appropriate education to raise awareness about viral hepatitis, its risks and the benefits of testing, care and treatment.
- Develop culturally appropriate health promotion interventions to reduce barriers to testing, care and treatment.



Assurance

- Enforce laws and regulations that mandate hepatitis surveillance, promote health care safety and expand access to hepatitis testing and other preventive services.
- Support equitable syringe access and education about safe injection practices and safe syringe disposal through local health departments, community-based organizations and pharmacies.
- Ensure priority access to drug and alcohol treatment programs for people with viral hepatitis.
- Promote linkage to care by integrating viral hepatitis services with other public health services; collaborate with substance treatment and health care providers to promote hepatitis testing and ensure appropriate care; provide surveillance data to support registries linking infected individuals to care.
- Train public health and health care work force to test, care and treat for HCV.
- Evaluate surveillance, clinical and laboratory data to assess accessibility, quality and outcomes of hepatitis preventive services and care.

Background

Overview of chronic HCV infection in the United States

Hepatitis C virus (HCV) is common in the United States; data from a recent national study conducted from 2003 to 2010 suggest that 3.6 million Americans (1.3%) have ever been infected with HCV, and 1.0% (corresponding to 2.7 million Americans) are chronically infected with HCV.[2] Infected persons were more likely to be aged 40–59, male, non-Hispanic black, and to have less education and lower family income. Risk factors included history of injection drug use and having a transfusion before 1992. Of note, 49% of persons with HCV infection did not report either risk factor, suggesting that screening strategies based purely on risk factors may be ineffective.

The majority of those infected will experience no symptoms at the time of infection, and although the first screening test was developed in 1989, more than half of persons infected with HCV are unaware of their infection.[3] It is generally accepted that 25% to 30% of those infected will develop cirrhosis 20 to 30 years later.[4] Once cirrhosis is present, the estimated annual rate of developing any complication is 6.4%; the risk of developing hepatocellular carcinoma (HCC) is 3.4% per year, and the death or transplantation rate is 4.6% per year.[5] The rate of progression to cirrhosis or liver cancer can be influenced by several factors: age of more than 40 years at the time of initial infection, male gender, alcohol use, and presence of other underlying medical conditions (nonalcoholic steatohepatitis, hemochromatosis and co-infection with HIV or HBV).[4]

The number of new infections occurring annually peaked in the late 1980s, when CDC estimated more than 200,000 cases occurred each year in the United States. In 2011, the most recent year for which national estimates are available, there were an estimated 16,000 new infections after accounting for asymptomatic, undetected and unreported infections.[6]

Although the number of new infections has dropped, morbidity and mortality remain high in the age group most commonly affected by HCV. In one study of patients enrolled in four HMOs in the United States, 13% of patients with HCV were hospitalized each year.[7] Deaths from HCV increased 50% from 1999 to 2007, while HIV deaths declined during that time; nationally, HCV deaths became more common than HIV in 2007, and 73% of the deaths occurred in persons aged 45–64.[8]

Before universal antibody screening of blood donors began in 1992, many HCV infections were acquired through blood, tissue and organ donation. Although this source of infection accounts for many of the estimated 3 million Americans in the baby boom generation with chronic HCV, effective interventions to screen blood, tissue and organs prior to donation have dramatically reduced the risk.[9] Unfortunately, transmission in health care settings still occurs. A well-publicized outbreak in a Las Vegas gastroenterology practice, attributed to contamination of single-use medication vials that were used for multiple patients, led the CDC to review known outbreaks of HCV in health care

settings.[10] The authors identified 33 outbreaks in nonhospital health care settings between 1998 and 2008: 12 in outpatient clinics, six in hemodialysis centers, and 15 in long-term care facilities. The outbreaks resulted in 448 persons acquiring HBV or HCV infection. In each setting, the mechanism of infection was patient-to-patient transmission through failure of health care personnel to adhere to fundamental principles of infection control and aseptic technique, including reuse of syringes and lancing devices.[11]

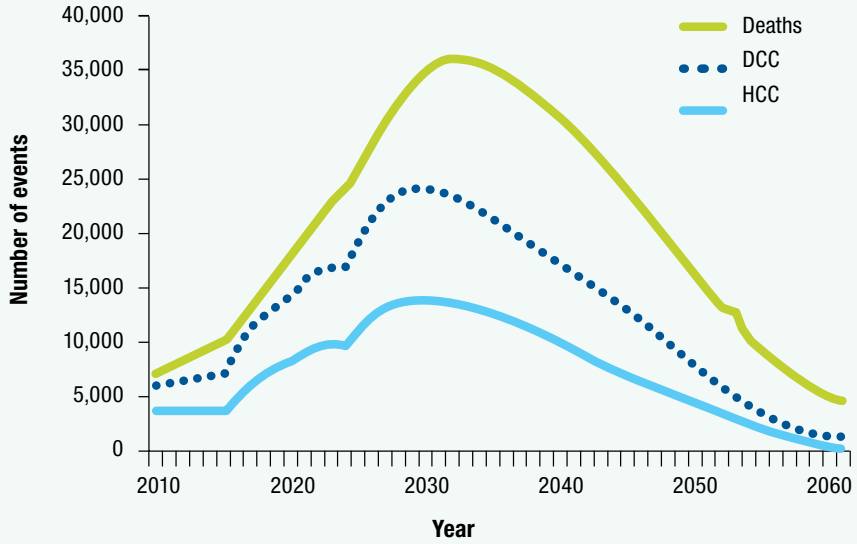
In the past two decades, the predominant route of infection in developed countries has been injection drug use, with young persons who inject typically acquiring HCV infection within 3.4 years of injection initiation.[12] In 2011, 60% of persons reported to CDC with acute HCV reported injection drug use. However, this is likely an underestimate because many persons with acute HCV are not interviewed or are not willing to answer questions about risk.

Although overall trends in incidence of acute HCV have declined over the last two decades, a recent disturbing trend is the emergence of a new cohort of young PWIDs who are acquiring HCV. These new injectors share certain characteristics that are atypical of PWIDS at risk for HCV described previously; they are usually less than 25 years old, white, reside in rural areas, and have typically used oral prescription opiates prior to initiating injection drug use.[13,14]

HCV is rarely transmitted between heterosexual partners. Cases have been reported in men who have sex with men (MSM). The risk of sexual transmission in heterosexual women with HIV is higher than in women not infected with HIV.

HCV-associated disease is the leading indication for liver transplantation in the United States and accounts for 50% of liver cancer cases.[15] Liver cancer and cirrhosis have been increasing among persons infected with HCV, and these outcomes are projected to increase substantially in the coming decades if left untreated.[16] Forecasts predict that in 2030, there will be 14,300 cases of liver cancer in the United States attributable to HCV. There will also likely be 3,100 liver transplants and 34,900 deaths.

Figure A. Future burden of HCV-related morbidity and mortality in the United States



DCC is defined as decompensated cirrhosis and HCC as hepatocellular carcinoma.
Adapted from Ward JW.[17]

Recommendations for HCV screening

Facts at a glance

- 81% of U.S. residents infected with HCV were born between 1945 and 1965.
- At least 50% of persons infected with HCV are unaware of their infection.
- HCV testing, followed by appropriate care and treatment, can reduce risk for liver cancer by 70% and mortality by 50%.
- In terms of cost effectiveness, screening followed by treatment ranks favorably with screening for breast cancer and high cholesterol.

Baby boomer recommendation

Since 1998, the CDC has recommended HCV testing for persons at high risk for HCV (see box).[18] However, 15 years after these recommendations were published, the CDC estimates that approximately 50% of those infected have not been tested for HCV.[3] Given the limited effectiveness of this risk-based strategy, in 2013, CDC recommended an additional testing strategy: a one-time screening of all persons born between 1945 and 1965.[19]

The focus on this age group is based on results of periodic studies looking at prevalence of HCV in the United States. The most recent study of the U.S. non-institutionalized civilian population between 2003 and 2010 found that 1%, or 2.7 million persons, are chronically infected with HCV, and 81% of all cases were born between 1945 and 1965.[2] The high prevalence of HCV among persons in this birth cohort reflects the substantial number of incident infections throughout the 1970s and 1980s and the persistence of HCV as a chronic infection. Implementation of this one-time screening is expected to identify 800,000 persons currently unaware of their infection and potentially avert 120,000 U.S. deaths.

Cost-effectiveness of screening and treating

Identifying persons with HCV is a critically important first step in public health efforts to reduce morbidity and mortality from HCV. HCV testing, followed by appropriate care and treatment, can reduce risk for liver cancer by 70% and mortality by 50%.[20,21] Studies have found that the cost per quality-adjusted life year (QALY) of the baby boomer screening recommendation using standard treatment (pegylated interferon + ribavirin) is comparable to other commonly recommended preventive services such as screening for high blood pressure, colon cancer and influenza vaccination of adults over 50 years of age. Screening followed by use of a first generation direct-acting agent (telaprevir) plus standard treatment is more expensive, but in terms of cost-effectiveness still ranks favorably with screening for breast cancer and high cholesterol.[22,23]

Summary of CDC recommendations for screening for HCV

HCV testing is recommended for those who:

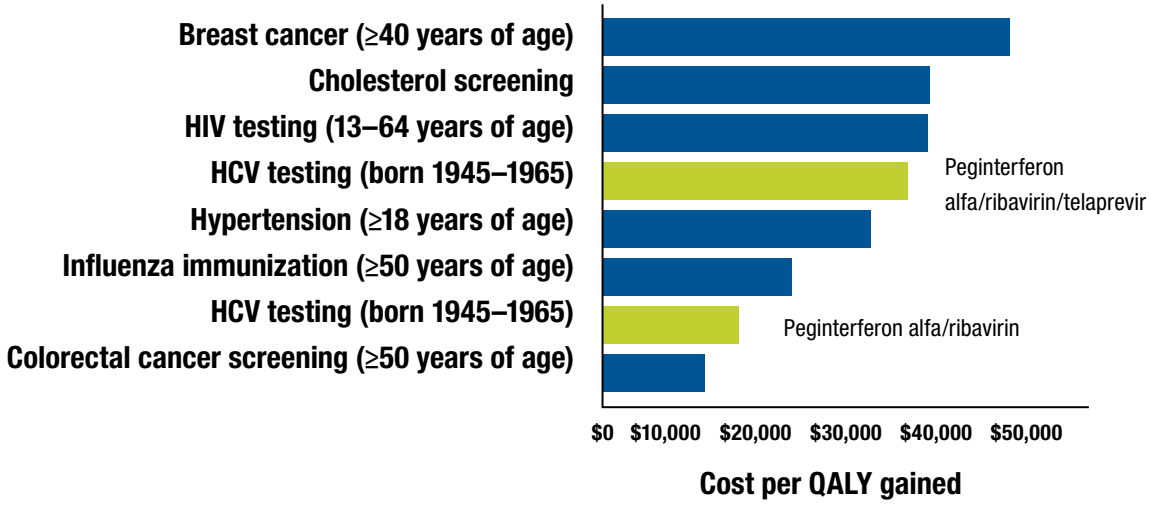
- Currently inject drugs;
- Ever injected drugs, including those who injected once or a few times many years ago;
- Have certain medical conditions, including persons:
  - » Who received clotting factor concentrates produced before 1987;
  - » Who were ever on long-term hemodialysis;
  - » With persistently abnormal alanine aminotransferase levels (ALT);
  - » Who have HIV infection.
- Were 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, blood components or an organ transplant before July 1992.

HCV testing based on a recognized exposure is recommended for:

- Health care, emergency medical and public safety workers after needle sticks, sharps or mucosal exposures to HCV-positive blood;
- Children born to HCV-positive women.

Added in 2012: one-time testing of persons born between 1945 and 1965 (without ascertainment of risk factors).

Figure B. Comparison of cost-effectiveness of HCV screening with other routine preventive services. QALY indicates quality-adjusted life year. Adapted from Ward JW.[17]



Overview of chronic HBV infection in the United States

CDC estimates that 700,000 to 1.4 million persons are living with chronic HBV infection in the United States. Like HCV, 65% do not know they are infected.[30,31] HBV is transmitted by percutaneous or mucosal exposure to the blood or body fluids of an infected person. This usually occurs through injection drug use, from sexual contact with an infected person, or from an infected mother transferring HBV to her newborn during childbirth. Transmission also can occur among persons who have prolonged but nonsexual interpersonal contact with someone who is HBV-infected (e.g., household contacts).[32]

The national strategy for preventing new HBV infection in infants and children includes routine screening of pregnant women and universal vaccination of children and adolescents. As a result, chronic HBV infection in infants and acute HBV infection in young people of all races and ethnicities have drastically decreased. Nationally, the number of new infections decreased 64% between 2000 and 2011. The 2,890 acute cases reported in the United States, after adjusting for asymptomatic infections and under-reporting, represent approximately 18,800 cases. These acute infections are most common in men and in persons 30–39 years old. Persons less than 20 years of age had the lowest rates. Acute HBV rates were highest in blacks and African Americans and lowest in Asians and Pacific Islanders (PIs) and in Hispanics.[6]

The risk for chronic HBV infection decreases with increasing age at infection. As many as 90% of infants who acquire HBV at birth become chronically infected. However, 30%–50% of children infected at 1–5 years of age become chronically infected. This percentage is smaller among adults, in whom approximately 5% of all acute HBV infections progress to chronic infection.[32] Approximately half of all chronic HBV infections in the United States occur among persons born in Asia or in Asian-Americans born in the United States to HBV-infected mothers.[30,33] In a study conducted by four HMOs that tracked patients with chronic viral hepatitis between 2006 to 2010, more than 9% of patients with chronic HBV were hospitalized each year and 2.1% required liver transplant during the five-year follow-up period.[7]

Like HCV, persons with chronic HBV are at risk for cirrhosis and end stage liver disease; an estimated 10% to 15% of patients will die from this complication. Twenty percent to 40% of men and 15% of women who are infected early in life develop liver cancer, and the risk increases with age, heavy alcohol use, smoking and increasing viral load.[34] The risk also increases in persons co-infected with HIV or HCV. The risks of HCC and cirrhosis are low in those under 35 years of age, but they rise rapidly in men over 40 and women over 50.

In 2010, the mortality rate for hepatitis B was 0.5 deaths per 100,000 population (n=1,792 deaths). Persons aged 55–64 (1.7 deaths per 100,000 population), Asians and PIs (3.0 deaths per 100,000 population) and males (0.8 deaths per 100,000 population) had the highest mortality rates by age, race/ethnicity and sex.[6]

Burden of disease from viral hepatitis in Oregon

Acute hepatitis A viral infections

An effective vaccine has caused rates of new infections (referred to as "acute cases) due to HAV to dramatically decline in recent years. From a high of nearly 3,000 acute cases reported in 1995 in Oregon, the annual number of acute cases of HAV dropped to under 100 in 2002. Fewer than 20 acute cases occurred annually over the last five years. HAV is often transmitted through eating contaminated foods or being in close contact with another person with HAV. Universal vaccination of children starting at age 1 year has significantly reduced the incidence in children in Oregon. The most common risk factor reported by cases during 2009–2013 was foreign travel (44%), most commonly to Latin America. Only 7% of cases during the period 2009–2013 occurred in persons under age 20, while 50% of cases were in persons aged 30–59. HAV risk among different racial and ethnic groups in Oregon varies only slightly.

Hepatitis A vaccination is recommended for the following:

- All children at age 1 year;
- Travelers to countries where hepatitis A is common;
- Family and caregivers of recent adoptees from countries where Hepatitis A is common;
- Men who have sex with men (MSM);
- Users of recreational drugs, whether injected or not;
- People with chronic or long-term liver disease, including hepatitis B or hepatitis C;
- Persons who work with HAV-infected primates or with HAV in a research laboratory;
- People with clotting-factor disorder.

Facts at a glance

- Routine vaccination of children has dramatically reduced the rate of HAV infection.
- The most common risk factor for HAV was foreign travel in the period 2009–2013.

Incidence of acute hepatitis A, Oregon, 1993–2013

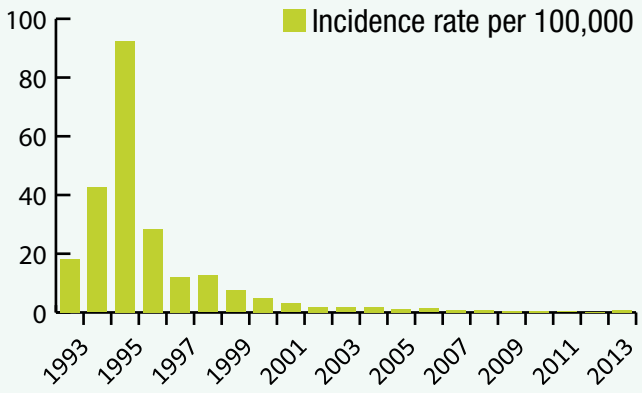


Figure 1 (See Table 1 in the Appendix section for details.)

Acute hepatitis B viral infections

Similarly, in the early 1990s, Oregon case counts of acute HBV topped 200 annually. However, counts have fallen dramatically since the universal vaccination of infants began in 1991. In the last five years, counts have averaged fewer than 40 cases a year. Acute HBV cases are rare in children and young adults in the post-vaccine era; in 2009–2013 fewer than 2% of cases occurred in persons under 20 years, and only 10% of cases occurred in persons in their 20s. Acute HBV cases were most common among persons in their 40s and 50s (53% of reported cases), and men in this age range were twice as likely to acquire infection as women were. Like acute HAV, there were no marked differences in rates of acute HBV by race or ethnicity. Behavioral risks for acute HBV included sexual transmission (16% of cases occurred in MSM and 31% in persons reporting multiple sex partners during the previous six months) and injection drug use (12%). Twelve percent of cases had a potential health care source such as dialysis, transfusion, other injection or surgery.

Hepatitis B vaccination is recommended for the following:

- Routine vaccination of all infants.
- Catch-up vaccination of children and adolescents who did not receive vaccination as infants.
- Sexual exposures
  - » Sex partners of chronic HBV carriers;
  - » Sexually active persons not in a long-term, mutually monogamous relationship;
  - » Persons seeking evaluation for a sexually transmitted disease;
  - » Men who have sex with men (MSM).
- Exposure to blood
  - » Current or recent person who injects drugs (PWIDs);
  - » Household contacts of HBV chronic carriers;
  - » Residents and staff of facilities for developmentally disabled persons;
  - » Health care and public safety workers with risk for exposure to blood;
  - » Persons with end-stage kidney disease;
  - » Persons with diabetes mellitus.
- Other groups
  - » International travelers to regions with high or intermediate levels of HBV infection in the population (prevalence> 2%);
  - » Persons with HIV infection.

Facts at a glance

- Similar to HAV, a vaccine given routinely to children and offered to high-risk adults has decreased the number of new infections.
- New infections with HBV were most common in people aged 40–59 years.
- Behavioral risk factors for acute HBV infection in adults in Oregon include sexual transmission and injection drug use.

Incidence of acute hepatitis B, Oregon, 1993–2013

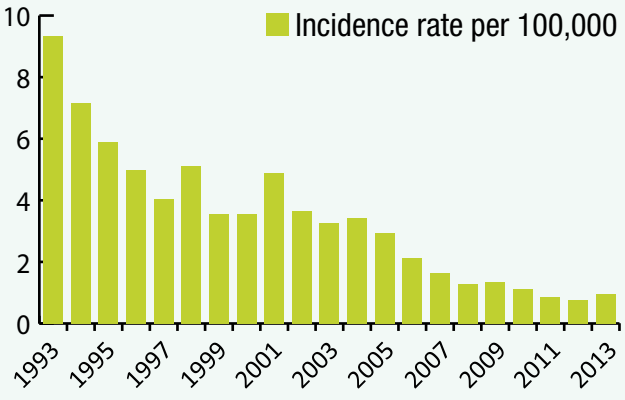


Figure 2 (See Table 2 in the Appendix section for details.)

Acute hepatitis C viral infections

Nationally, reported cases of acute HCV infection peaked in the 1980s when the CDC estimates more than 200,000 cases occurred.[35] Rates of acute cases have fallen dramatically since then, with 16,500 cases reported in 2011 in the United States. In contrast, the annual numbers of acute cases in Oregon have remained fairly stable since 1993, with an average of 25 acute cases per year between 2009 and 2013. After accounting for asymptomatic cases and under-reporting, these 25 cases likely represent 332 acute cases of HCV in Oregon each year because most new infections are not reported. Rates of acute HCV cases in Oregon were 50% higher than the national rate during 2007–2011 (2011 is the most recent year for which national data are available).[6] In contrast to acute HAV and HBV, acute HCV infection is common in younger patients: nearly half of cases occurred in persons under 30 years of age and 68% of cases were in persons under age 40. Compared to HBV, the number of new HCV infections was more evenly matched between men and women, with 56% of cases from 2009-2013 occurring in men. The highest rates of acute HCV in Oregon occurred in American Indians and Alaskan Natives (AI/ANs), with a rate of 2.1 cases per 100,000, compared to a rate of 0.6 cases for both whites and blacks and African Americans (no cases were identified in Asians or Pacific Islanders during 2009–2013). Rates of acute HCV were lower in Hispanics than non-Hispanics (0.2 cases/100,000 vs. 0.6 cases/100,000). Persons who injected drugs accounted for the majority of new infections (64%).

Facts at a glance

- Rates of acute HCV cases in Oregon were 50% higher than the national rate during 2007–2011.
- Injection drug use accounted for the majority of new HCV infections in Oregon.
- Rates of acute HCV in Oregon were four times higher in AI/ANs than in any other racial group.

Incidence of acute hepatitis C, Oregon, 2000–2013

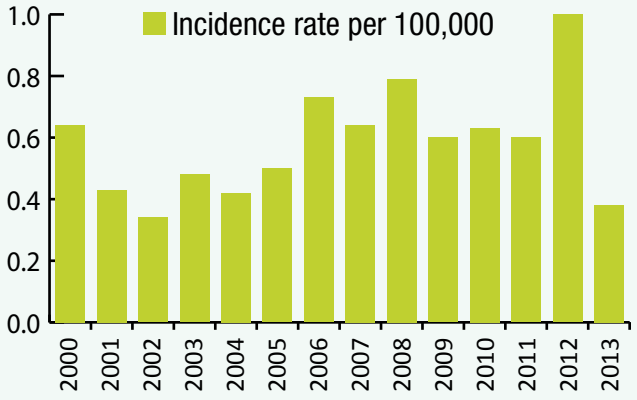


Figure 3 (See Table 3 in the Appendix section for details.)

Chronic hepatitis B viral infections

Annual numbers of laboratory reports consistent with chronic HBV have been stable at 440 cases for the past five years. The majority of cases were identified among persons aged 30–59 (64%). Among cases in their 20s and 30s, 52% occurred in females, while most chronic HBV cases (65%) over the age of 40 occurred in males. One-third of cases reported having contact with another person with hepatitis B, while fewer than 10% occurred in MSM or persons who inject drugs (PWIDs).

The majority of chronic B cases (75%) occurred in persons born outside of the United States. The highest rates were seen in Asians and PIs, who have rates 41 and 44 times higher than whites in Oregon (Asians, 131.4 cases/100,000; PIs, 139.8 cases/100,000; whites, 3.2 cases/100,000). The next highest rates were seen in blacks and African Americans, with a rate of 39.9 cases/100,000. Rates in Hispanics (2.7 cases/100,000) were lower than in non-Hispanics (10.0 cases/100,000).

Facts at a glance

- The majority of chronic HBV cases (75%) occurred in persons born outside of the United States.
- Asians and PIs had the highest rates, followed by blacks and African Americans.

Incidence of chronic hepatitis B, Oregon, 1993–2013

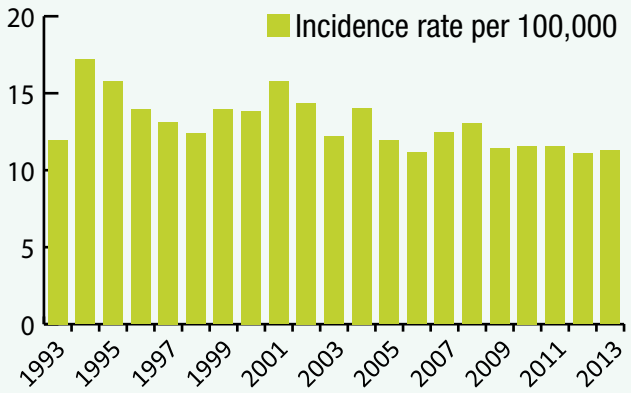
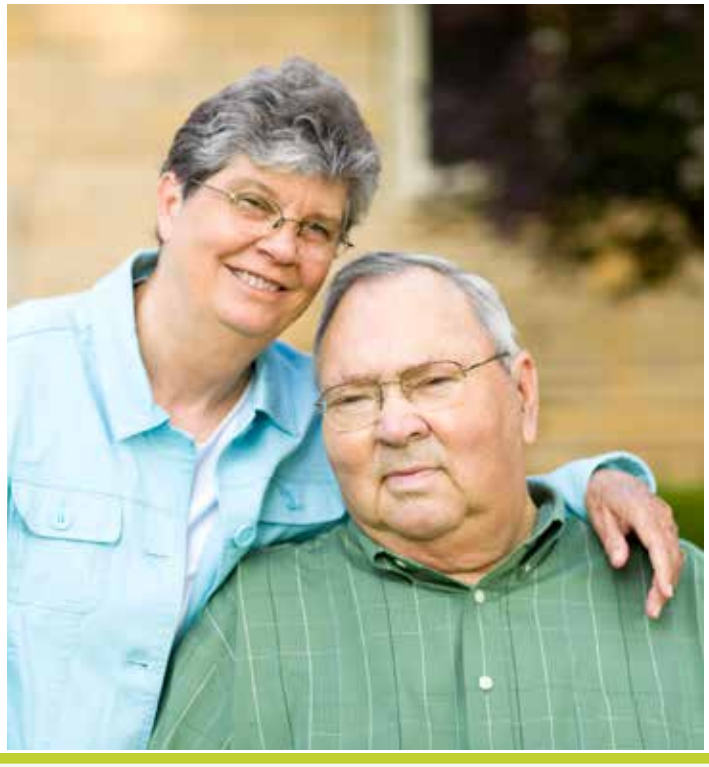


Figure 4 (See Table 4 in the Appendix section for details.)

Chronic hepatitis C viral infections

In 2005, positive laboratory test results of HCV (referred to as "chronic" infections, likely representing persons who acquired HCV sometime in the past) became reportable in Oregon. Between 2009 and 2013, Acute and Communicable Disease Prevention received 25,437 reports of persons with positive laboratory HCV tests, with an average annual number of 5,087. Compared to acute cases of HCV, persons with positive laboratory reports were more likely to be male (61%) and over age 40 (79%). AI/ANs and blacks and African Americans had the highest rates of HCV laboratory reports in this time; their rates (127.7 cases /100,000 and 124.4 cases/100,000) were both more than twice the rate seen in whites during the same time (57.5 cases/100,000). The lowest rates were found among Hispanics (20.8 cases/100,000). Neither the OHA nor local health departments typically have resources to investigate persons reported with positive laboratory tests for HCV. However, a study conducted in Lane, Marion and Multnomah counties in 2011–2012 found that 77% of persons with positive laboratory reports who received follow-up investigation reported injection drug use.



Facts at a glance

- More than 5,000 persons with positive HCV tests are reported each year in Oregon.
- Rates of chronic HCV infection are twice as high in AI/ANs and in blacks and African Americans compared to whites.

Incidence of chronic hepatitis C, Oregon, 2005–2013

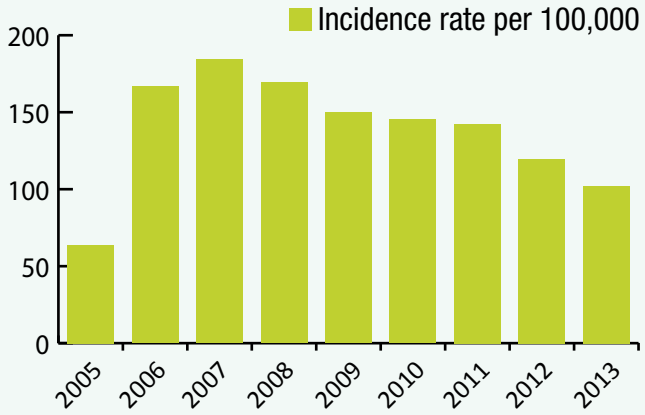


Figure 5 (See Table 5 in the Appendix section for details.)

Hospitalizations

Several published studies, looking at state Medicaid and managed care organization databases, have identified HCV hospitalization costs as the major driver of costs associated with the care of HCV.[36,37] One study using state hospital discharge data found that the cost of hospitalizations in which HCV was the primary discharge diagnosis tripled between 2007 and 2009; 70% of the costs were charged to government sources.[38]

For 2008–2012 (2012 is the most recent year for which Oregon data are available), 3,917 hospitalizations of HCV patients were identified who also had a discharge diagnosis consistent with advanced liver disease (chronic liver disease, cirrhosis, decompensated cirrhosis, liver cancer or liver transplant).* The number of hospitalizations in Oregon averaged 783 per year and ranged from 764 to 838 annually during this period; the average length of stay was five days. Only 8% occurred in persons under age 45 years, while 70% occurred in persons aged 50–64. Two-thirds of the HCV hospitalizations occurred in men. The most common liver discharge diagnoses were cirrhosis (75%) and decompensated cirrhosis (76%), followed by liver cancer (15%), chronic liver disease (22%) and liver transplant (3%).** A majority of HCV hospitalizations (62%) were in persons whose insurance payer was either Medicare or Medicaid. During this five-year period, the average charges per patient discharge were $26, 961, and the total charges per year for these hospitalizations averaged $21,149,111.

Facts at a glance

- In Oregon, from 2008 to 2012, 70% of HCV hospitalizations occurred in persons aged 50–64, and the average charges per hospitalization were $26,961.
- Most hospitalizations (62%) were in persons whose insurance payer was either Medicare or Medicaid.

Table 1. Lengths of stay and total charges related to HCV hospitalizations, by category of liver disease,* Oregon 2008–2012 (n=3,917)

Condition**	Mean length of hospital stay in days					Mean health care charges per admission
(n = 3,917)	2008	2009	2010	2011	2012	5-year average
Cirrhosis	4.6	4.5	4.4	4.1	4.1	$23,942
Decompensated cirrhosis	4.9	5.0	4.9	4.8	4.8	$27,234
Other chronic liver disease	4.7	5.0	4.1	4.4	4.1	$22,230
Liver cancer	5.3	5.5	4.6	4.1	5.7	$52,345
Liver transplant	5.7	11.7	7.1	4.9	5.1	$34,281
Total	**4.9**	**5.0**	**4.7**	**4.6**	**4.6**	**$26,961**

(See Table 48 in the Appendix section for details.)

* See Table 45 in the Appendix section for list of ICD9 codes used to classify patients as having chronic liver disease, cirrhosis, decompensated cirrhosis, liver cancer or liver transplant

**These categories are not mutually exclusive, because patients can have more than one discharge diagnosis consistent with advanced liver disease.

Liver cancer

Globally, hepatocellular carcinoma (HCC) is the main type of liver cancer associated with chronic viral hepatitis. It is highest in less developed countries; the highest incidence rates are in Eastern and Southeastern Asia, followed by Northern and Western Africa. In 2012, it was the fifth most common cancer in men and the ninth most common in women. It was the second most common cause of death from cancer.[39]

In the United States, liver cancer is not in the top 10 causes of new cases of cancer. However, U.S. liver cancer rates have doubled since the 1980s.[40,41] Liver cancer is predicted to be the fifth most common cause of cancer deaths in the United States in 2014 for men, and the ninth most common cause in women. This rate is largely due to a poor prognosis: The overall five-year survival rate is 16%.

Between 1996 and 2012, 3,395 cases of HCC were reported to the Oregon State Cancer Registry (OSCaR). Of those, 959 (28%) were attributable to chronic viral hepatitis: 196 (6%) were in persons reported to ACDP with chronic HBV (reported between 1988 and 2012), and 763 (22%) occurred in persons reported with chronic HCV (reported between 2005 and 2012). The proportion of cases due to chronic viral hepatitis each year has risen dramatically since 2005, when chronic HCV first became reportable in Oregon. Liver cancer in persons with HCV in Oregon undoubtedly occurred before 2005. However, because it was not reportable until 2005, liver cancer in persons with HCV would not have been detected by our surveillance systems. Because Oregon's liver cancer rates were rising before 2005, the increase is likely due to an increase in the prevalence of persons with long-standing HCV infection. By 2012, 8% of liver cancer cases had chronic HBV, while 47% had chronic HCV.

More than three-quarters of liver cancer cases linked to chronic viral hepatitis occurred in men for both HBV and HCV between 2008 and 2012. The main difference between the two hepatitis viruses lies in the age distribution. Nearly a third of cases of liver cancer in persons with HBV were detected below the age of 50, while fewer than 10% of liver cancer cases in persons with HCV

Facts at a glance

- The annual number of liver cancer cases in Oregon has doubled in the last 10 years. Chronic viral hepatitis caused more than half of the cases by 2012.
- More than half (60%) of liver cancer cases associated with HBV infection in Oregon were among APIs.
- In Oregon, AI/ANs were twice as likely to suffer from liver cancer or die from HCV as whites.

Cases of liver cancer by year, with and without chronic viral hepatitis, Oregon, 1996–2012 (n=3,395)

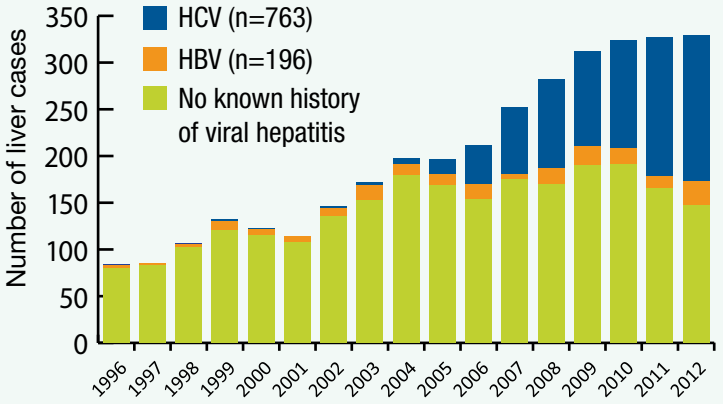


Figure 6 (See Table 49 in the Appendix section for details.)

Facts at a glance

- Half of liver transplants performed at OHSU in the past five years were due to HCV.

occurred before age 50; 53% of persons with liver cancer due to HCV were aged 50–59; and 33% were in persons aged 60–69. It is notable among cases of HBV-associated liver cancer that 59% of males were diagnosed before the age of 60, while only 33% of women developed liver cancer before the age of 60.

Most Oregon cases of HBV-associated HCC in 2008–2012 occurred in Asians and PIs (60%). The risk of HBV-associated HCC in Oregon was 32 times higher in Asians and PIs compared to white persons living in Oregon (6.3 cases/100,000 vs. 0.2 cases/100,000). The next highest rates were seen in blacks and African Americans (1.5 cases/100,000). For HCV, the highest rates of HCC were seen in AI/ANs (4.1 cases/100,000) and blacks and African Americans (5.1 cases/100,000), followed by whites (3.1/100,000) and Asians and PIs (2.7 cases/100,000).

Transplants

Major advances have occurred in antiviral therapy for chronic viral hepatitis. However, chronic infections with HBV and HCV remain a common indication for liver transplantation, most commonly for HCC or end-stage liver disease (ESLD). Over a 20-year period from 1985 to 2006, data on waiting list registrants in the United States obtained from the Organ Procurement and Transplantation Network indicated that 4% and 36% were classified to have HBV and HCV, respectively.[42] The number of waiting list registrations increased dramatically in the 1990s, from under 3,000 individuals in 1990 to 8,382 in 1999. It has stabilized at more than 8,000 individuals awaiting transplant annually. The most consistent trend during this time was the decline in transplants in the United States performed for the indication of ESLD. This is likely due to increasing use of antiviral medications for HBV during this time.

In the five-year period from 2009 to 2013, 169 liver transplants were performed at OHSU. This translates into 34 cases annually in Oregon. Of those, between one and two were attributable to chronic HBV each year, while 18 patients with chronic HCV had liver transplants each year, which accounted for 54% of liver transplant cases during those five years.

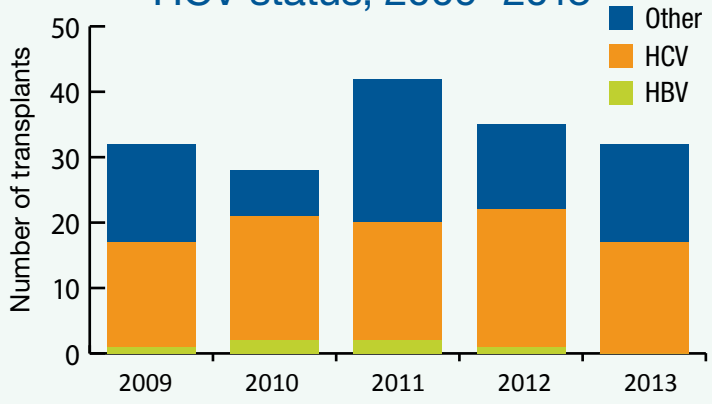


Figure 7 (See Table 54 in the Appendix section for details.)

Deaths

Analysis of 1999–2007 U.S. mortality data from the National Center for Health Statistics found that deaths from HCV in the United States increased significantly to 15,106 in 2007. However, deaths from HIV declined to 12,734 by 2007.[8] Factors associated with HCV-related deaths included chronic liver disease, HBV co-infection, alcohol-related conditions, minority status and HIV co-infection. Factors that increased odds of HBV-related death included chronic liver disease, HCV co-infection, Asian or Pacific Islander descent, HIV co-infection and alcohol-related conditions. In 2007, 59% of HBV deaths and 73% of HCV deaths occurred in persons aged 45–64.

Mirroring national trends, deaths from HCV in Oregon have risen steadily over the last decade, averaging more than 400 deaths annually in Oregon during the last five years. Oregon's HCV mortality rate during 2009–2013 is more than six times higher than Oregon's HIV mortality rate. HCV mortality is also higher in Oregon than in the United States as a whole; in 2011, the most recent year of available national data, the age-adjusted Oregon mortality rate was 8.7 deaths per 100,000 persons, compared to the national mortality rate of 4.8 deaths per 100,000.

In contrast, mortality from HBV has declined, with an average of 32 deaths per year in the last five years (2009–2013). Numbers of deaths related to HBV are too small to analyze. However, HCV-related deaths from 2009–2013 are similar to national trends: The majority of deaths occurred in men (71%) and in persons aged 45–64 (80%). By race, the highest mortality rates occurred in AI/ANs (17.4 deaths/100,000) and

Facts at a glance

- Between 2009 and 2013, the highest mortality rates from HCV occurred in two groups: AI/ANs and blacks and African Americans. Both were roughly twice the rate of whites.
- The mortality rate in Oregon from HCV was nearly twice the national average in 2011.

Age-adjusted mortality rates for HIV and HCV, Oregon and U.S., 1999–2013

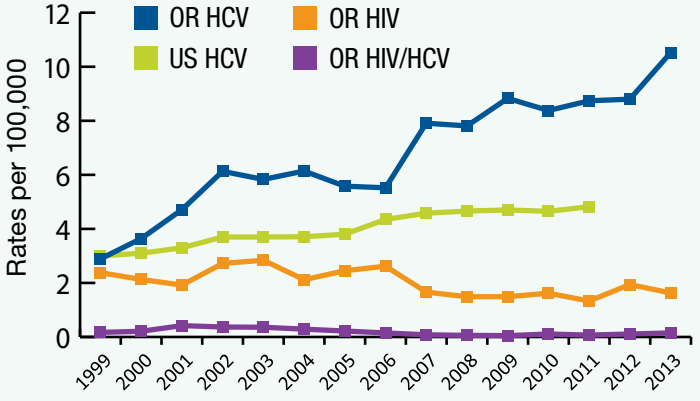


Figure 8 (See Table 56 in the Appendix section for details.)

blacks and African Americans (16.1 deaths/100,000) during this time period and both were roughly twice the rate in whites (8.9 deaths/100,000).

Public health implications

The long-term consequences of chronic HBV or HCV diagnosis are substantial morbidity and mortality. These findings highlight the need to promote HBV and HCV screening programs and HAV and HBV vaccination programs within communities and populations at high risk for viral hepatitis. Improved linkage to care and treatment for persons diagnosed with chronic HBV and HCV will also be critical in efforts to improve health outcomes and decrease cost.

Secondly, significant health disparities exist in Oregon for hepatitis B and C. There is clearly a need to:

- Educate providers and communities at risk about viral hepatitis prevention and screening; and
- Support access to culturally competent care and treatment for disproportionately affected populations including AI/ANs, Asians and PIs, blacks and African Americans, persons who inject drugs and incarcerated populations.

Special populations

HBV in Asians and Pacific Islanders

Background in the United States

Although Asian and Pacific Islanders (PIs) currently comprise about 5% of the U.S. population, they represent more than 50% of persons chronically infected with HBV.[43] Nearly 70% of Asians and PIs living in the United States were born or have parents who were born in countries where HBV is endemic. They were infected as infants or young children. The highest rates of chronic HBV infection in the world are found in Africa and Eastern and Southeastern Asia.[32] In contrast, rates of acute hepatitis A, B and C and chronic HCV are generally no higher in Asians and PIs living in the United States than in the general U.S. population.[6]

Risk of morbidity and mortality from HBV is also more common in Asians and PIs. During 2001–2006, the incidence of hepatocellular carcinoma (HCC) was higher among Asians and PIs than any other racial or ethnic group in the United States.[41] HBV-related mortality rates were 10 times higher in Asians and PIs than whites in the United States in 2010.[6]

HBV in Asians and PIs in Oregon

Data from Oregon match the national trends. Of the 2,130 laboratory reports consistent with chronic HBV reported in Oregon during 2009–2013, race is known for 1,815 (85%); 59% of cases occurred in Asians and PIs. Among the 1,024

Facts at a glance

- The majority of Oregon HBV chronic cases occur in persons born outside of the United States and were likely acquired at birth or in childhood.
- In 2009–2013, 59% of Oregon's chronic HBV cases occurred in Asians and PIs.
- Chronic HBV is more common in Asian and PI women than in women of other races.
- Nearly two-thirds (63%) of Oregon's liver cancer cases associated with HBV infection were among Asians and PIs.
- Asians and PIs accounted for a quarter of deaths from HBV infection between 2008 and 2012.

Birth countries of chronic hepatitis B cases, Oregon, 2009–2013

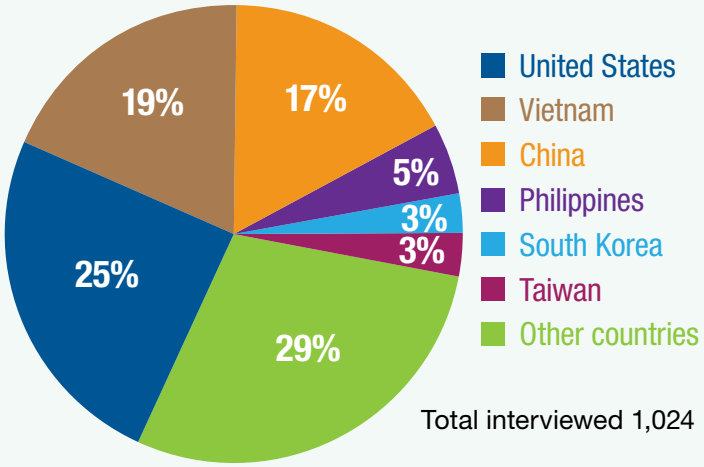


Figure 9 (See Table 40 in the Appendix section for details.)

interviewed cases whose birthplace was known, 770 (75%) reported being born outside of the United States. Five countries accounted for 47% of the cases: Vietnam (19%), China (17%), Philippines (5%), South Korea (3%) and Taiwan (3%). The rate of chronic HBV infection among Asians and PIs (131.4 and 139.8 cases per 100,000, respectively) are 41 and 44 times higher than rates in whites (3.2/100,000). Compared to persons of other races, Asians and PIs were more likely to be diagnosed at a younger age: In 2009–2013, 52% of chronic HBV laboratory reports for Asians and PIs were in persons less than 40 years of age, compared to only 30% of whites. Chronic HBV is also more common in Asian and PI women than in women of other races. More than half (52%) of chronic HBV laboratory reports in Asians and PIs occurred in females, while only 32% of cases in all other races combined occurred in females during this time period.

Of the 93 cases of persons with hepatocellular carcinoma (HCC) related to chronic HBV identified in Oregon between 2008 and 2012, 56 (60%) occurred in Asians and PIs. The risk of HBV-associated HCC in Oregon is 32 times higher in Asians and PIs compared to white persons. Oregon mortality data show that Asians disproportionately die from chronic HBV; of 159 deaths from HBV occurring in 2009–2013, 23% were in Asians and PIs.

Public health implications

Foreign-born Asians and PIs in Oregon carry a high risk of chronic HBV infection and the resulting sequelae of chronic liver disease, liver cancer and death. Lack of knowledge and awareness likely contribute to low testing rates in this population. Additionally, many immigrants may fear the stigma associated with HBV infection, and persons with limited English ability may avoid or delay visits to health care providers.

Partnerships with community-based agencies are necessary to provide ongoing prevention education, screening and vaccination services to the diverse Asian and PI communities affected by HBV. Providers also need training in culturally proficient care and treatment for persons living with chronic HBV.

Incidence of chronic hepatitis B by sex and race/ethnicity, Oregon, 2009–2013

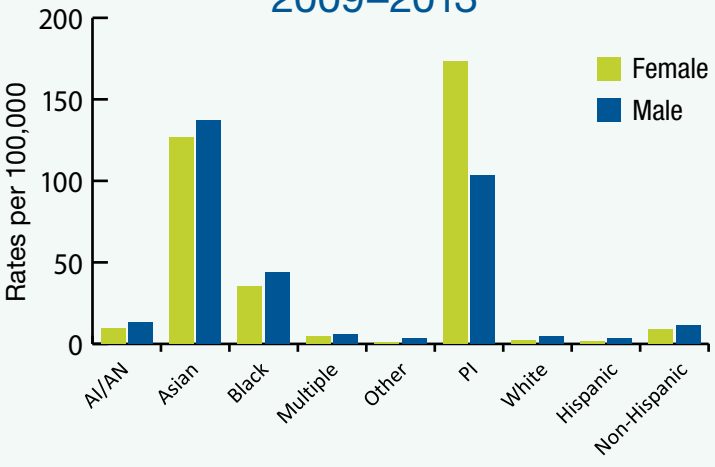


Figure 10 (See Table 30 in the Appendix section for details.)

Incidence of liver cancer associated with chronic hepatitis B, by race/ethnicity, Oregon, 2008–2012

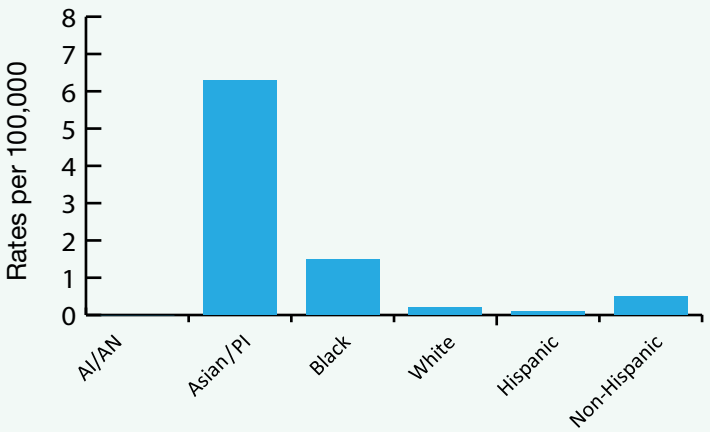


Figure 11 (See Table 52 in the Appendix section for details.)

Chronic viral hepatitis in blacks and African Americans

HBV in the United States in blacks and African Americans

Blacks and African Americans are disproportionately affected by chronic viral hepatitis. According to data reported to CDC's National Notifiable Diseases Surveillance System (NNDS), blacks and African Americans had higher rates of acute HBV than any other racial or ethnic group in 2011. Although reported cases of chronic infection due to HBV were most common in Asians and Pacific Islanders (PIs), more cases were reported in blacks and African Americans than in whites.[6] A national study from 1999 to 2006 found a high prevalence of past infection (12.2%) among non-Hispanic blacks and African Americans, and the prevalence of chronic HBV infection (0.89%) was nearly 10-fold higher than the prevalence in whites living in the United States (0.09%).[30] Lastly, deaths from HBV in 2010 were three times higher in blacks and African Americans than in whites.[6]

Facts at a glance

- Rates of acute HBV among blacks and African Americans in Oregon from 2009–2013 did not differ from other racial or ethnic groups. However, chronic HBV was more than 20 times higher in blacks and African Americans than in whites.
- The majority of cases of chronic HBV among blacks and African Americans in Oregon are among persons born in Africa (78%).
- Cases of chronic HBV and liver cancer associated with HBV are more common in blacks and African Americans than in whites in Oregon.
- Chronic HCV infection is more common in blacks and African Americans than in whites in Oregon.
- Among blacks and African Americans, 64% of chronic HCV cases occur in men and 67% in persons aged 40–59.
- Liver cancer and deaths from HCV are nearly twice as common in blacks and African Americans compared to whites.

Although the national rates of acute HCV are no higher in blacks and African Americans than in other racial or ethnic groups, chronic infection with HCV is more common in blacks and African Americans. The most recent national prevalence estimates found that blacks and African Americans have the highest risk of any racial group in the United States.[2] Rates of liver cancer and liver cancer deaths, which could be due to either HBV or HCV, are also consistently higher in blacks and African Americans compared to whites. Between 2006 and 2010, rates of deaths from HCV among blacks and African Americans averaged 79% higher than HCV deaths among whites.[6,40]

There are some well-recognized differences in the natural course of infection with HCV in blacks and African Americans. Although they have a lower prevalence of cirrhosis than whites, blacks and African Americans do not respond to treatment with antiviral medications as well as whites and have been underrepresented in clinical trials.[44] Blacks and African Americans are most commonly infected with HCV genotype 1, which is difficult to treat but does not explain the difference in response to treatment. Compared to whites with genotype 1, blacks and African Americans are still 50% less likely to clear the virus. One contributing factor is that blacks and African Americans are less likely to carry a variant of the IL-28B gene. This gene typically correlates with a better response to treatment. However, this genetic factor still does not fully explain treatment response differences between whites and blacks.

HBV in Oregon

Rates of acute HBV in blacks and African Americans in Oregon during 2009–2013 were not different from other racial or ethnic groups. Nevertheless, chronic HBV reports during this time were more than 12 times higher among blacks and African Americans than among whites in Oregon (39.9 cases per 100,000 vs. 3.2 cases per 100,000). However, HBV reports for blacks and African Americans were lower than in Asians and PIs. The majority of chronic HBV cases among blacks and African Americans occurred in men (59%). Chronic HBV cases were also more commonly found in persons under the age of 40 (64%, in contrast to only 30% of cases in whites occurring in persons under the age of 40). As with Asians and PIs, the main risk factor is foreign birth, which accounted for 78% of cases in blacks and African Americans during 2009–2013.

Similar to the trend seen in chronic HBV infections in Oregon, rates of liver cancer due to HBV were more than seven times higher in blacks and African Americans than in whites (1.5 cases per 100,000 vs. 0.2 cases per 100,000). The incidence of liver cancer due to HBV in blacks and African Americans was the second highest among any racial group in Oregon after Asians and PIs.

HCV in Oregon

Rates of acute infection in Oregon and nationally during the period 2009–2013 are the same in blacks and African Americans and in whites (0.6 cases per 100,000). In contrast, rates of positive HCV laboratory reports are 2.1 times higher in blacks and African Americans than in whites (124.4 cases per 100,000 vs. 57.5 cases per 100,000, respectively). Blacks and African Americans have the second highest incidence of HCV among racial groups in Oregon, with American Indians/Alaska Natives (AI/AN) having the highest rates. The age and sex of chronic HCV infection cases in blacks and African Americans are similar to other racial groups in Oregon, with 65% of cases occurring in men and 67% of cases in persons aged 40–59. Almost half (46%) were in persons aged 50–59. Like other racial and ethnic groups in Oregon, the most common route of transmission was injection drug use (76%).

The rate of liver cancer associated with HCV is 1.6 times higher in blacks and African Americans than in whites. Blacks and African Americans' incidence rate is 5.1 cases per 100,000. Mortality from HCV is also higher in blacks and African Americans than in whites and comparable to the rates in AI/ANs (blacks and African Americans, 16.1/100,000; whites, 8.9/100,000; AI/ANs, 17.4/100,000). All but one of the deaths in blacks and African Americans occurred in persons over age 45, with 20% in persons 45–54 years of age, 48% in 55–64 year-olds, and 25% in 65–74 year-olds.

Public health implications

Significant health disparities exist in Oregon for black communities in HBV and HCV infection, chronic liver disease, liver cancer and death. Providers and the group at risk may be unaware of the need to:

- Screen African Americans and foreign-born blacks for chronic HBV infection;
- Increase awareness of the existence of viral hepatitis health disparities; and
- Implement culturally appropriate prevention programs.

Birth cohort and risk-based HCV screenings for blacks and African Americans are also critical. More research into the differences in natural history and response to treatment in blacks and African Americans is needed, and efforts must be made to include blacks and African Americans in clinical trials of new antiviral medications.

Table 2. Disparities in incidence rate of viral hepatitis, liver cancer associated with viral hepatitis, and mortality from HCV between blacks and African Americans and whites in Oregon

Condition	Incidence rate in whites per 100,000	Incidence rate in blacks and African Americans per 100,000
Chronic HBV infection, 2009–2013	2.2	39.9
Chronic HCV infection, 2009–2013	57.5	124.4
HBV-associated liver cancer, 2008–2012	0.2	1.5
HCV-associated liver cancer, 2008–2012	3.1	5.1
Mortality from HCV, 2009–2013	8.9	16.1

HCV in American Indians and Alaska Natives

Background on HCV in American Indians and Alaska Natives

In 2010, chronic liver disease (CLD) was the fifth leading cause of death among American Indians and Alaska Natives (AI/ANs). In contrast, CLD was not in the top 10 causes of death in the United States overall and ranked 11th among whites.[45] Two studies evaluated the etiology of CLD among AI/AN populations. One study was in two regions of the southwestern United States and the second was in Alaska. Both found a high prevalence of alcoholic liver disease, HCV and non-alcoholic fatty liver disease in persons diagnosed with CLD.[46,47] The prevalence of HCV as an etiology of CLD was 6% and 24% in two medical centers in Arizona and California, respectively; it was 26% in the Alaskan study. AI/ANs also have elevated rates of liver cancer and mortality from liver cancer compared to other racial and ethnic groups in the United States. Their rates are second only to Asians and Pacific Islanders (PIs).[40]

Recent trends in national surveillance data reported to CDC's National Notifiable Diseases Surveillance System suggest that AI/ANs are not at higher risk of acute HAV, acute HBV or chronic HBV than other racial or ethnic groups. However, the highest U.S. rates of acute HCV between 2002 and 2011 occurred in AI/ANs.[6] In 2010, AI/ANs had the highest mortality rate of any race or ethnicity from HCV at 9.9 deaths per 100,000; this is more than twice the rate in whites (4.0 deaths /100,000).

One study that reviewed hospital discharge data from the Indian Health Service National Patient Information Reporting System found a three-fold increase in HCV-related hospitalizations between 1995 and 2007.[48] The hospitalization rate was highest among people aged 45–64, males, and those in the Alaska region. Another study of an Alaskan cohort found the highest prevalence in persons 40–59 years of age, males and urban residents.[49] A majority of infections with HCV were in people injecting drugs (61%) in this cohort, followed by those who received a transfusion (14%).

Facts at a glance

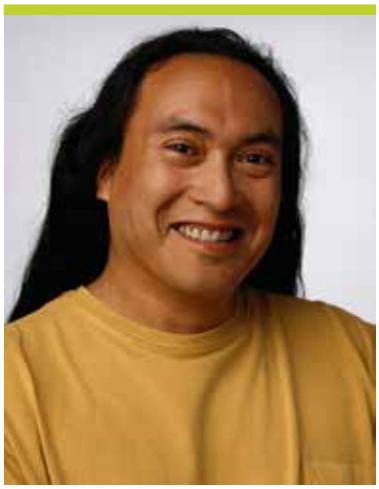
- Rates of acute HCV in Oregon are more than three times higher in AI/ANs than any other racial group.
- The highest rates of chronic HCV in Oregon are seen in AI/ANs and blacks and African Americans.
- Hospital discharge data from the Indian Health Service (IHS) found a three-fold increase in HCV-related hospitalizations between 1995 and 2007.
- In Oregon, AI/ANs are twice as likely to die from HCV as whites.

Table 3. Disparities in incidence rates of viral hepatitis, liver cancer associated with viral hepatitis, and mortality from HCV in American Indians and Alaska Natives in Oregon

Condition	Incidence rates in AI/ANs per 100,000	Incidence rates in whites per 100,000
Chronic HCV infection, 2009–2013	127.7	57.5
HCV-associated liver cancer, 2008–2012	4.1	3.1
Mortality from HCV, 2009–2013	17.4	8.9

HCV in AI/ANs in Oregon

AI/ANs are more likely to acquire acute HCV than any other racial or ethnic group in Oregon, with a rate of 2.1/100,000 persons in 2009–2013. This is nearly four times higher than the rate in whites and in blacks and African Americans (0.6 cases/100,000). For chronic HCV, the rate of laboratory-reported cases of HCV in AI/ANs during the same time was 127.7 cases /100,000. The AI/AN rate is similar to the rate in blacks and African Americans (124.4 cases/100,000) and more than twice the rate in whites (57.5 cases/100,000). AI/AN cases were predominantly male (58%), and 65% occurred in persons aged 40–59, which is similar to other racial groups in Oregon. Expanded surveillance in Lane, Marion and Multnomah counties from 2011 to 2012 identified injection drug use as the predominant risk factor in all racial groups; 76% of those for whom race and risk factor data were available reported injection drug use. These numbers did not vary by race: 80% of AI/AN respondents reported injection drug use.



AI/ANs also had the second highest rate after blacks and African Americans of hepatocellular carcinoma (HCC, the type of liver cancer commonly due to viral hepatitis) due to HCV in Oregon in 2008–2012. AI/ANs' rate of 4.1 cases/100,000 compares to 5.1 cases/100,000 in blacks and African Americans and 3.1 cases/100,000 in whites. AI/ANs and blacks and African Americans also had the highest mortality rates from HCV in Oregon during 2009–2013 (17.4 and 16.1 cases per 100,000, respectively). Misclassification of race and ethnicity (in which AI/ANs are misclassified as either white, Asian or Hispanic) has been documented in several public health datasets, suggesting that these disparities may be even bigger than described here.[50-52]

Public health implications

AI/ANs experience some of the highest rates of HCV infection, liver cancer and death in Oregon. Studies of this population in other parts of the United States suggest that their course of HCV is often complicated by a high prevalence of other conditions that can damage the liver, such as alcoholism and fatty liver disease. Culturally appropriate efforts to raise awareness, support prevention efforts and promote birth cohort and risk-based HCV screenings are critical in this population. It is especially important to monitor screening efforts, linkage to care and access to treatment in this population because of the high risk of HCV progression to ESLD in persons with other co-morbidities affecting the liver.

Persons who inject drugs and viral hepatitis

Hepatitis A

HAV is an acute infection transmitted by the fecal-oral route. The infection may come from contaminated food or beverages or from sexual activity with an infected person. HAV transmission among persons who inject drugs (PWIDs) has been reported in the United States, including Oregon, where injection drug use fueled a large outbreak in Portland in the mid-1980s.[53] PWIDs who are homeless may be at increased risk of HAV infection because of their restricted access to sanitary bathroom and hand-washing facilities.[54] Although it has not been a common risk factor in Oregon in the last five years, in 2006 Multnomah County reported a cluster of six HAV cases among homeless PWIDs 20–49 years of age.

Facts at a glance

- Injection drug use accounts for 12% of new infections with acute HBV and 64% of new infections with acute HCV in Oregon.
- Prevalence of HCV in persons who inject ranges from 8% in persons under 20 years old to 58% in persons aged 50–54.
- Interviews with young persons being screened for HCV who inject drugs found that 50% reported sharing needles with someone with HCV.
- National trends suggest the pathway to injection drug use starts with misuse of prescription opioids. Oregon had the highest rate of use in the nation of non-medical prescription pain relievers in 2012.

Because persons with chronic liver disease are at higher risk for developing severe illness with HAV, the CDC recommends HAV vaccine for persons chronically infected with HBV or HCV, a group that often includes PWIDs.[55,56]

Hepatitis B and C among PWIDs in the United States

HBV is easily transmitted through infected blood and body fluids. In a study of the seroprevalence of HBV infection among young PWIDs in Seattle from 1994–2004, 27% had serologic evidence of past HBV infection. Seroprevalence of HBV ranged from 43% in 1994 to 15% in 2004. The decline in prevalence may have been due to increasing rates of HBV vaccination.[57] Review of U.S. cases of acute HBV reported to the CDC in 2011 reveal that sexual risk factors were the most common route of transmission, with 19% of cases occurring in men who have sex with men (MSM) and 7% reporting having sex with someone with HBV in the previous six months. Eighteen percent also reported injection drug use.[58]

In contrast, HCV is transmitted primarily through infected blood. Sexual transmission plays a much smaller role. Injection drug use accounted for most acute HCV infections (60%) reported in the United States in 2011. Thirteen percent of cases reported having sex with someone with HCV in the previous six months. Four percent were MSM. In the most recent national prevalence study, 51% of persons with chronic HCV aged 20–59 reported prior injection drug use.[2]

Syringe sharing has declined among PWIDs since the emergence of HIV. However, sharing and reusing drug preparation equipment are still often reported in the United States. The 2009 National HIV Behavioral Surveillance System conducts

surveys of PWIDs in urban areas. It reports a high proportion of participants sharing previously used syringes (35%). This holds true for receptive sharing of other injection equipment, such as cookers, cotton or water (58%) as well as syringes to divide drugs (35%).[59,60] The percentage of receptive sharing of syringes and equipment to inject drugs was highest among participants aged 18–29 and those who had been arrested during the past year. This is of particular concern because the level of HCV infection risk by sharing drug preparation equipment is just as high as the HCV transmission risk from sharing syringes.[61]

Recent national reports have described an increase in HCV infection among PWIDs in multiple states. The cases have commonly been under the age of 30, white and residents of suburban or rural areas.[14,62] Studies of young persons who inject drugs report misuse of prescription opiates as a common pathway to injecting drugs. They often obtain prescriptions themselves for opiates or get them from their friends or family members.[13,63]

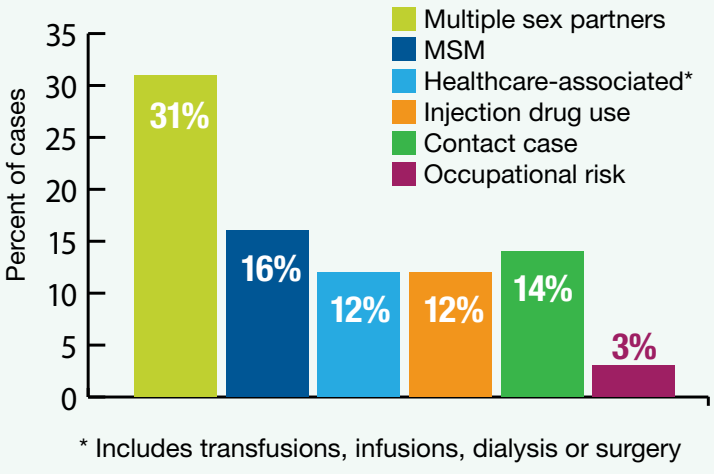
HBV in PWIDs in Oregon

In Oregon from 2009 to 2013, sexual risk factors were common among persons reported with acute HBV (31% reported multiple sex partners and 16% occurred in MSM.) However, 12% of acute HBV cases reported injection drug use (IDU). Among the 18 persons who reported IDU, 11 (61%) were male, and 44% (8/18) were aged 30–39. Only three (17%) were under age 30. Most of the HBV cases reported in Oregon with chronic HBV infection from 2009 to 2013 were persons born in endemic countries who likely acquired their infection at birth or in early childhood (75%); only 7% reported IDU.

HCV in PWIDs in Oregon

IDU is the predominant route of transmission of HCV in Oregon and nationally. Of the 81 acute HCV cases interviewed in Oregon from 2009 to 2013, 64% reported IDU. Among Oregon's acute HCV cases who reported IDU risk, 56% were male and, in marked contrast to acute HBV cases in Oregon, 55% were under age 30. Rates

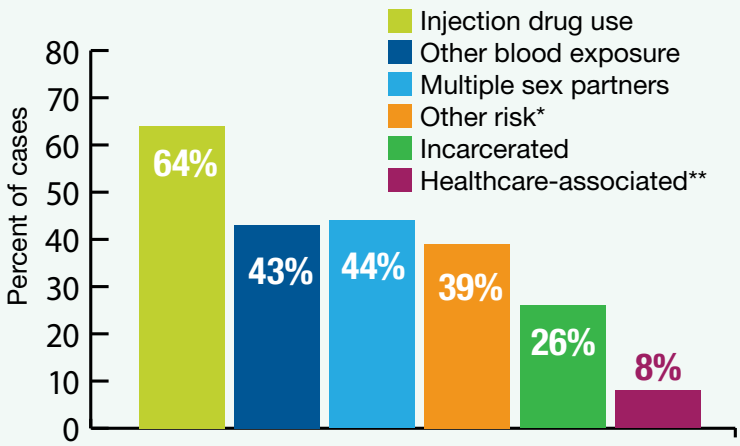
Risk factors among acute cases of HBV, 2009–2013, Oregon



* Includes transfusions, infusions, dialysis or surgery

Figure 12 (See Table 37 in the Appendix section for details.)

Risk factors among acute cases of HCV, 2009–2013, Oregon



* Includes needlesticks, tattoos and piercings
** Includes transfusions, infusions, dialysis or surgery

Figure 13 (See Table 41 in the Appendix section for details.)

of persons newly reported with chronic HCV infection have declined in Oregon since 2008. However, rates in persons under age 30 have increased steadily in the past two years, and have increased 27% since 2006.

Most local health departments do not have resources to investigate reported cases of chronic HCV infection. However, Lane, Marion and Multnomah counties participated in an expanded surveillance project in 2011–2012. Of the 1,778 chronic HCV cases from those three counties with IDU risk data available (representing 38% of the cases reported in that time), 77% reported IDU. Among chronic HCV cases reporting IDU in Lane, Marion and Multnomah counties, 64% were male, and 58% were in the 40–59 year-old age group. There were 1,519 chronic cases of HCV from the three counties in 2011–2012 for whom race and injection drug risks were known. Of these, 80% of AI/ANs, 76% of blacks and African Americans and 78% of whites reported IDU. This suggests little variation by race in the route of transmission.

Prevalence of HCV in current injection drug users by age, Oregon Adult High Risk Screening Project, 2007–2013

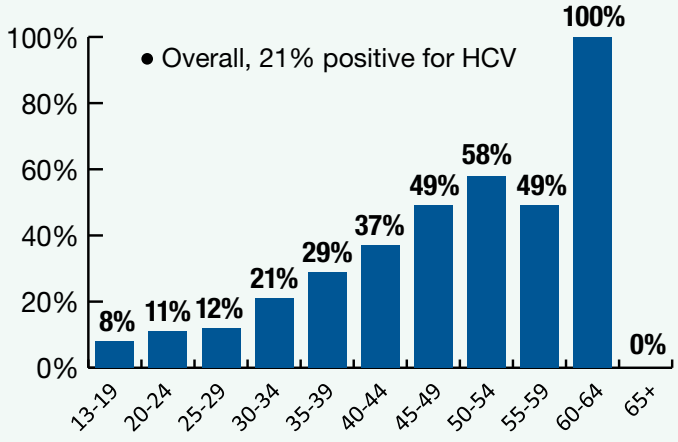


Figure 14 (See Table 65 in the Appendix section for details.)

High-risk behaviors in PWIDs in Oregon

Oregon has collected information about HCV behavior risk among persons tested for HCV through the state's High Risk Adult HCV Screening Project. Between 2007 and 2013, the screening project performed 4,027 HCV tests among persons who reported risk factors for HCV. Twenty local health departments and four syringe exchange programs participated in the screening.

Overall, 16% of the persons screened and 21% of persons who reported IDU were positive for HCV. The prevalence of HCV increased with age, ranging from 6% in persons less than 20 years of age to 39% in persons aged 50–54. The prevalence of HCV did not vary by sex or by race in this population.

Since the screening program targets persons at highest risk for HCV, the majority tested (72%) reported IDU at some point in their lives. Those with injection drug use risk reported methamphetamine and heroin as the primary drug injected (74% and 21% respectively). HCV prevalence between users of these two drugs did not vary. Of the 2,467 who reported IDU and responded to a question about their most recent drug use, 85% said they had injected within the past three years. This sub-group of recent injectors was young: 52% were under age 30. Half reported sharing needles with someone who had HCV, 54% lived with someone with HCV, and 46% reported having sex with someone with HCV. The prevalence of HCV antibodies in this group of recent injectors under the age of 30 was only 11%. This suggests that intervention in this age group could be effective in preventing further transmission.

More detailed data on injection practices came from a 2013 Lane County study of a fungal bloodstream infection outbreak in PWIDs using heroin. ACDP staff conducted in-depth interviews with 32 heroin users living in Lane County and found that 34% shared syringes, 63% shared cottons and 84% reported shared preparation surfaces.[64]

Data from a report published by the Injury and Prevention Section of the Oregon Health Authority on drug overdose deaths and hospitalizations in Oregon suggests that Oregon's rates of prescription opioid misuse and heroin abuse are very high.[65] The rate of unintentional and undetermined overdose deaths associated with prescription opioids has declined in Oregon since peaking in 2006. However, the rate of deaths (4.2/100,000) in 2012 was still higher than it was in 2000. Oregon also had the highest rate of non-medical use of prescription pain relievers in the nation in 2012.[66] Meanwhile, heroin overdose deaths in Oregon have increased three-fold since 2000. Hospitalizations due to unintentional and undetermined overdoses related to prescription opioids have increased five-fold between 2000 and 2012. Hospitalizations due to heroin poisoning have doubled during that same time. The biggest increases in heroin-associated hospitalizations have been in males 15–24 years of age, followed by 25–34 year-old males.

Public health implications

Viral hepatitis is a significant public health issue among PWIDs in Oregon and nationally. Most persons diagnosed with chronic HCV infection are over the age of 40 and likely acquired their infection decades earlier. However, Oregon has growing numbers of cases in young PWIDs. This is likely fueled by high rates of prescription opioid misuse and injection drug use.

Persons with injection drug use risk often have additional complex health and social issues. They experience marginalization, stigma and barriers to accessing social, behavioral and health care services.[67] These challenges contribute to PWIDs' continued viral hepatitis transmission and significant morbidity and mortality from viral hepatitis-related liver disease.

System level collaborations are needed among OHA's Public Health Division (PHD), Addictions and Mental Health Division (AMH) and the Medical Assistance Programs (MAP). Collaborations with state and local partners serving PWIDs — such as the Oregon Department of Corrections, coordinating care organizations, local health departments and community-based organizations (CBOs) — are also important. These partnerships can increase community and provider awareness, train providers across disciplines, and support screening and HAV/HBV vaccination efforts. Successfully reducing transmission of viral hepatitis between PWIDs requires combined interventions involving opiate substitution therapy programs, high coverage syringe exchange programs, pharmacy syringe access, and access to care and treatment.[68,69]

Viral hepatitis in incarcerated populations

Background

The criminal justice system includes jails, prisons, probation, parole and other forms of community supervision. An estimated one in six people in the United States passes through the criminal justice system each year.[70] Nationally, 13%–47% of incarcerated persons have past or current HBV infection. Chronic HBV infection affects from 1% to 3.7% of incarcerated persons.[71] The prevalence of HCV is higher, with evidence of past or current HCV infection reported in 16%–41% of incarcerated populations. Confirmed chronic HCV infection ranges from 12% to 35%.[71] These estimates compare to 0.27% for chronic HBV, and 1.0% for chronic HCV among civilian non-institutionalized persons.[2,30] In Oregon, 26% of cases of acute HCV between 2009 and 2013 reported a history of incarceration (either jail or prison) in the six months prior to their onset of hepatitis symptoms.

Studies have demonstrated that inmates rarely acquire these infections while incarcerated. The chronic infection is usually present at the time of entrance.[71,72] Several factors such as substance abuse, dependency, addiction and mental health issues contribute to the higher prevalence of HBV and HCV among persons formerly or currently incarcerated.[73,74]

Given this high prevalence of viral hepatitis, the CDC recommends that correctional facilities ask about risk factors for HBV and HCV infections during prison admission medical evaluations.[71] The facilities should offer HBV and HCV antibody screening tests to persons reporting risk factors. Persons who screen positive for HBV or HCV should be further evaluated for a chronic infection. If an infection is present, the extent of liver disease should also be evaluated.

Facts at a glance

- In Oregon, 30% of persons incarcerated in state prisons are thought to have chronic hepatitis C infection.[1]
- Between 2009 and 2013, one-quarter of acute HCV cases in Oregon reported a history of incarceration in the previous six months.
- Although the majority of persons jailed in Oregon are repeat offenders, only half have ever been offered HCV screening while in jail.
- Although screening programs in jails are limited, one study suggests that 11% of jail detainees in Oregon were infected with HCV at the time of entrance.

Number of new inmates tested for HCV and proportion positive as part of voluntary screening, Oregon Department of Corrections, 2009–2012

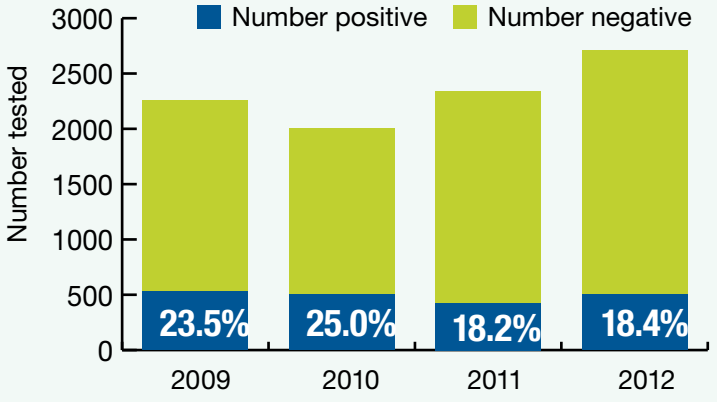


Figure 15 (See Table 66 in the Appendix section for details.)

Viral hepatitis in Oregon's prisons

The Oregon Department of Corrections (ODOC) reports a high prevalence of substance abuse and mental health issues among persons incarcerated in the state prison system. In 2013, close to 80% of persons incarcerated in Oregon state prisons reported substance abuse, dependence or addiction issues. Half of the state's incarcerated population had existing mental health treatment needs; 23% had severe or high need.[75] Like prisons in other parts of the country, ODOC reports a high prevalence of HBV and HCV in its facilities. It offers voluntary HBV and HCV screening at the time of entrance. Between 2009 and 2012, approximately half of persons who requested HBV screening were found to be immune to HBV, either through vaccination or past infection; 1.5% were chronically infected with HBV. During the same time, the prevalence of HCV among the 2,300 persons screened annually ranged from 18% to 25%. Additionally, persons are diagnosed during the course of medical care while incarcerated and persons aware of their viral hepatitis status may report this to ODOC health services staff at intake or any time during incarceration. The ODOC experienced a 29% increase in identified HCV cases between 2006 and 2012 (from 1,402 to 1,804 HCV cases, respectively).[76] The ODOC used these two sources of data (voluntary screening, identification of infected individuals as part of their medical care) and a 2006 unpublished seroprevalence study to estimate in June 2014 that 140 persons were infected with chronic HBV and between 3,600 and 4,400 incarcerated persons were infected with chronic HCV.[1] These estimates of 1% for HBV and 30% for HCV are consistent with the published national prison population estimates of HBV and HCV infection.[71,72]

Viral hepatitis in Oregon's jails

Nationally and in Oregon, health screening and behavioral risk factor data for jail populations is limited.[70] Oregon jails do not report the number of persons with HBV and HCV diagnoses detained within Oregon's county jail facilities each year. The limited data that exist about jail populations in Oregon come from the Oregon High Risk Adult HCV Screening Project, conducted by local health departments and syringe exchange programs. Jail settings were added as a test setting to the screening risk questionnaire in 2012 in five counties, and 11% of the 255 rapid HCV antibody screening tests in jail settings from 2012 to 2013 were positive in Oregon.

In the Deschutes County Jail, the HIV/HCV Health Education and Screening Program collected additional data on incarceration history and risk behavior of persons who participated

Jails vs. prisons

Most people do not distinguish between jails and prisons, but the two systems differ.

Jails are locally operated and hold persons awaiting trial or sentencing. They also hold convicted persons sentenced to a term of one year or less. Jails have high bed turnover, with stays usually lasting less than 48 hours. Jails have a higher prevalence of persons with acute intoxication and uncontrolled mental illness.

Prisons are state or federally operated and hold convicted persons with sentences of one year or longer. Persons arrive at prison relatively stable and the intake process may take several weeks.

Effective interventions in jails must be limited in scope and occur within a very narrow time frame.[48]

in an HIV/HCV education class in 2011–2012. Of the 111 respondents who provided complete responses, 92% had been jailed at least once before the current episode; 60% had been jailed more than six times. Forty-eight percent reported receiving testing at least once for HCV. The probability of being tested increased with the number of times the individual had been jailed, but it was not statistically significant (42% of those jailed between two and five times compared to 54% of those jailed six or more times). Those with a history of incarceration in a state prison were more than twice as likely to have been tested previously.

Public health perspective

Incarcerated settings have concentrated numbers of persons at risk of or living with chronic HBV and HCV. These settings present opportunities for public health partnerships and efforts, such as the vaccination campaign described below in state correctional facilities.[79] Early detection, liver health education and treatment can slow disease progression and reduce morbidity and mortality.

Almost half of the state prison population is scheduled for release within 24 months; addressing the health needs of persons in Oregon's prisons and linking people to care after release benefits communities. Most of the cost savings of prevention, detection and treatment will occur after incarceration.[80]

Table 4. Screening for HCV in Deschutes County Jail, 2010–2011 (n=111)

Opportunity for screening for HCV	Number screened	Percent screened
Number of times detained in a county jail		
First time	2/8	25
Two to five times	15/36	42
Six or more times	36/67	54
Overall	53/111	48
Ever incarcerated in state prison		
Yes	31/45	69
No	21/65	32

Example of successful collaboration between Public Health and Department of Corrections: Hepatitis B vaccination of adults during incarceration in Oregon

The Advisory Committee on Immunization Practices (ACIP) recommends HBV vaccination for adults in correctional settings because of their increased risk for infection;[77] vaccination of persons incarcerated in state prison systems has been found feasible and cost saving.[77,78]

ODOC collaborated with the Oregon Health Authority to implement the ACIP recommendations. ODOC offers the three-dose (zero, one-month and six-month) hepatitis B vaccination series to inmates. The ODOC health clinic staff document the vaccinations in the state's electronic vaccination registry so that individuals returning to the community have record of HBV vaccination. In 2013, the program provided 2,593 doses to 1,569 persons, with 83% of persons who received a first dose in 2013 reported as also receiving a second dose. Sixty percent of persons who received a second dose in 2003 also reported a third dose. Thirty-four percent of persons who initiated the HBV series in ODOC during 2013 completed the three dose series within the same year.

Appendix: Supporting data tables

Table 1. Incidence of acute hepatitis A, Oregon, 1993–2013

Source: Orpheus hepatitis A surveillance and American Community Survey, June 2014

Year	Oregon population	Cases	Incidence rate per 100,000
1993	3,059,110	559	18.27
1994	3,119,940	1,328	42.56
1995	3,182,690	2,943	92.47
1996	3,245,100	918	28.29
1997	3,302,140	399	12.08
1998	3,350,080	422	12.60
1999	3,393,410	254	7.49
2000	3,431,085	170	4.95
2001	3,470,385	106	3.05
2002	3,502,588	64	1.83
2003	3,538,591	60	1.70
2004	3,578,895	70	1.96
2005	3,626,938	41	1.13
2006	3,685,206	50	1.36
2007	3,739,359	35	0.94
2008	3,784,182	28	0.74
2009	3,815,775	19	0.50
2010	3,837,300	17	0.44
2011	3,857,625	13	0.34
2012	3,883,735	8	0.21
2013	3,930,065	31	0.79

Table 2. Incidence of acute hepatitis B, Oregon, 1993–2013

Source: Orpheus hepatitis B surveillance and American Community Survey, June 2014

Year	Oregon population	Cases	Incidence rate per 100,000
1993	3,059,110	286	9.35
1994	3,119,940	223	7.15
1995	3,182,690	187	5.88
1996	3,245,100	162	4.99
1997	3,302,140	133	4.03
1998	3,350,080	171	5.10
1999	3,393,410	120	3.54
2000	3,431,085	122	3.56
2001	3,470,385	170	4.90
2002	3,502,588	128	3.65
2003	3,538,591	115	3.25
2004	3,578,895	122	3.41
2005	3,626,938	107	2.95
2006	3,685,206	79	2.14
2007	3,739,359	61	1.63
2008	3,784,182	48	1.27
2009	3,815,775	51	1.34
2010	3,837,300	43	1.12
2011	3,857,625	33	0.86
2012	3,883,735	30	0.77
2013	3,930,065	38	0.97

Table 3. Incidence of acute hepatitis C, Oregon, 1993–2013

Source: Orpheus hepatitis C surveillance and American Community Survey, June 2014

Year	Oregon population	Cases	Incidence rate per 100,000
1993	3,059,110	0	0.00
1994	3,119,940	1	0.03
1995	3,182,690	6	0.19
1996	3,245,100	25	0.77
1997	3,302,140	11	0.33
1998	3,350,080	7	0.21
1999	3,393,410	24	0.71
2000	3,431,085	22	0.64
2001	3,470,385	15	0.43
2002	3,502,588	12	0.34
2003	3,538,591	17	0.48
2004	3,578,895	15	0.42
2005	3,626,938	18	0.50
2006	3,685,206	27	0.73
2007	3,739,359	24	0.64
2008	3,784,182	30	0.79
2009	3,815,775	23	0.60
2010	3,837,300	24	0.63
2011	3,857,625	23	0.60
2012	3,883,735	39	1.00
2013	3,930,065	15	0.38

Table 4. Incidence of chronic hepatitis B, Oregon, 1993–2013

Source: Orpheus hepatitis B surveillance and American Community Survey, June 2014

Year	Oregon population	Cases	Incidence rate per 100,000
1993	3,059,110	366	11.96
1994	3,119,940	537	17.21
1995	3,182,690	503	15.80
1996	3,245,100	452	13.93
1997	3,302,140	434	13.14
1998	3,350,080	415	12.39
1999	3,393,410	473	13.94
2000	3,431,085	475	13.84
2001	3,470,385	547	15.76
2002	3,502,588	503	14.36
2003	3,538,591	432	12.21
2004	3,578,895	502	14.03
2005	3,626,938	433	11.94
2006	3,685,206	410	11.13
2007	3,739,359	466	12.46
2008	3,784,182	494	13.05
2009	3,815,775	435	11.40
2010	3,837,300	444	11.57
2011	3,857,625	446	11.56
2012	3,883,735	431	11.10
2013	3,930,065	444	11.30

Table 5. Incidence of chronic hepatitis C, Oregon, 1993–2013*

Source: Orpheus hepatitis C surveillance and American Community Survey, June 2014

Year	Oregon population	Cases	Incidence rate per 100,000
1993	3,059,110	6	0.20
1994	3,119,940	5	0.16
1995	3,182,690	6	0.19
1996	3,245,100	8	0.25
1997	3,302,140	5	0.15
1998	3,350,080	9	0.27
1999	3,393,410	14	0.41
2000	3,431,085	28	0.82
2001	3,470,385	18	0.52
2002	3,502,588	37	1.06
2003	3,538,591	110	3.11
2004	3,578,895	164	4.58
2005	3,631,440	2,318	63.83
2006	3,690,505	6,155	166.78
2007	3,745,455	6,898	184.17
2008	3,791,075	6,424	169.45
2009	3,815,775	5,723	149.98
2010	3,837,300	5,567	145.08
2011	3,857,625	5,495	142.45
2012	3,883,735	4,649	119.70
2013	3,919,020	4,003	102.14

*First made reportable in 2005

Table 6. Incidence of acute hepatitis A by county, Oregon, 2009–2013

Source: Orpheus hepatitis A surveillance and American Community Survey, June 2014
Hepatitis A counts and rates per 100,000 residents

	2009		2010		2011		2012		2013		2009–2013	
County	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
Baker	0	0	0	0	0	0	0	0	2	12	2	2.46
Benton	1	1	0	0	0	0	0	0	1	1	2	0.46
Clackamas	0	0	3	1	1	0	2	1	2	1	8	0.42
Clatsop	0	0	0	0	0	0	0	0	0	0	0	0.00
Columbia	0	0	0	0	0	0	0	0	0	0	0	0.00
Coos	0	0	0	0	0	0	0	0	1	2	1	0.32
Crook	0	0	0	0	0	0	0	0	0	0	0	0.00
Curry	0	0	0	0	0	0	0	0	0	0	0	0.00
Deschutes	2	1	2	1	1	1	0	0	0	0	5	0.63
Douglas	0	0	1	1	0	0	0	0	0	0	1	0.19
Gilliam	0	0	0	0	0	0	0	0	0	0	0	0.00
Grant	0	0	0	0	0	0	0	0	0	0	0	0.00
Harney	0	0	0	0	0	0	0	0	0	0	0	0.00
Hood River	0	0	0	0	2	9	0	0	0	0	2	1.77
Jackson	2	1	1	0	0	0	1	0	2	1	6	0.59
Jefferson	0	0	0	0	0	0	0	0	0	0	0	0.00
Josephine	0	0	0	0	0	0	0	0	0	0	0	0.00
Klamath	1	2	0	0	1	2	1	1	0	0	3	0.90
Lake	0	0	0	0	0	0	0	0	0	0	0	0.00
Lane	3	1	3	1	0	0	0	0	4	1	10	0.57
Lincoln	0	0	0	0	0	0	0	0	1	2	1	0.43
Linn	0	0	0	0	0	0	0	0	0	0	0	0.00
Malheur	0	0	0	0	1	3	0	0	0	0	1	0.64
Marion	1	0	1	0	0	0	1	0	2	1	5	0.31
Morrow	0	0	0	0	0	0	1	9	0	0	1	1.77
Multnomah	4	1	2	0	4	1	0	0	4	1	14	0.38
Polk	0	0	1	1	0	0	0	0	0	0	1	0.26
Sherman	0	0	0	0	0	0	0	0	0	0	0	0.00
Tillamook	0	0	0	0	0	0	0	0	0	0	0	0.00
Umatilla	0	0	0	0	0	0	1	1	0	0	1	0.26
Union	0	0	0	0	0	0	0	0	3	11	3	2.28
Wallowa	0	0	0	0	0	0	0	0	0	0	0	0.00
Wasco	0	0	0	0	0	0	0	0	0	0	0	0.00
Washington	5	1	3	1	2	0	2	0	8	1	20	0.74
Wheeler	0	0	0	0	0	0	0	0	0	0	0	0.00
Yamhill	0	0	0	0	0	0	0	0	0	0	0	0.00

Table 7. Incidence of acute hepatitis B by county, Oregon, 2009–2013

Source: Orpheus hepatitis B surveillance and American Community Survey, June 2014
Acute hepatitis B counts and rates per 100,000 residents

	2009		2010		2011		2012		2013		2009–2013	
County	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
Baker	0	0	0	0	0	0	0	0	0	0	0	0.00
Benton	1	1	0	0	0	0	0	0	1	1	2	0.46
Clackamas	4	1	6	2	5	1	1	0	1	0	17	0.90
Clatsop	1	3	0	0	1	3	0	0	1	3	3	1.61
Columbia	0	0	0	0	0	0	1	2	4	8	5	2.01
Coos	0	0	1	2	0	0	1	2	0	0	2	0.64
Crook	0	0	1	5	0	0	0	0	0	0	1	0.95
Curry	0	0	0	0	0	0	0	0		0	0	0.00
Deschutes	4	3	3	2	1	1	0	0	0	0	8	1.01
Douglas	2	2	1	1	0	0	2	2	0	0	5	0.93
Gilliam	0	0	0	0	0	0	0	0	0	0	0	0.00
Grant	0	0	0	0	0	0	0	0	0	0	0	0.00
Harney	0	0	0	0	0	0	0	0	0	0	0	0.00
Hood River	0	0	0	0	0	0	0	0	0	0	0	0.00
Jackson	3	1	1	0	1	0	0	0	3	1	8	0.78
Jefferson	0	0	0	0	0	0	0	0	0	0	0	0.00
Josephine	0	0	0	0	0	0	0	0	2	2	2	0.48
Klamath	1	2	0	0	0	0	0	0	0	0	1	0.30
Lake	0	0	0	0	0	0	0	0	0	0	0	0.00
Lane	4	1	4	1	3	1	5	1	1	0	17	0.96
Lincoln	0	0	0	0	0	0	1	2	0	0	1	0.43
Linn	0	0	3	3	1	1	2	2	0	0	6	1.02
Malheur	1	3	0	0	1	3	0	0	0	0	2	1.28
Marion	4	1	4	1	2	1	1	0	3	1	14	0.88
Morrow	0	0	0	0	0	0	0	0	0	0	0	0.00
Multnomah	14	2	8	1	9	1	5	1	13	2	49	1.32
Polk	0	0	2	3	1	1	0	0	0	0	3	0.79
Sherman	0	0	0	0	0	0	0	0	0	0	0	0.00
Tillamook	0	0	1	4	0	0	0	0	0	0	1	0.79
Umatilla	0	0	0	0	0	0	1	1	0	0	1	0.26
Union	0	0	0	0	1	4	1	4	0	0	2	1.53
Wallowa	0	0	0	0	0	0	0	0	0	0	0	0.00
Wasco	0	0	3	12	2	8	0	0	1	4	6	4.73
Washington	11	2	5	1	5	1	6	1	5	1	32	1.20
Wheeler	0	0	0	0	0	0	0	0	0	0	0	0.00
Yamhill	0	0	1	1	0	0	1	1	2	2	4	0.79

Table 8. Incidence of chronic hepatitis B by county, Oregon, 2009–2013

Source: Orpheus hepatitis B surveillance and American Community Survey, June 2014
Chronic hepatitis B counts and rates per 100,000 residents

	2009		2010		2011		2012		2013		2009–2013	
County	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
Baker	1	6	0	0	0	0	0	0	0	0	1	1.24
Benton	4	5	5	6	5	6	10	12	8	9	32	7.39
Clackamas	39	10	30	8	38	10	31	8	42	11	180	9.48
Clatsop	2	5	1	3	1	3	3	8	6	16	13	6.99
Columbia	2	4	4	8	2	4	0	0	5	10	13	5.24
Coos	2	3	2	3	4	6	2	3	4	6	14	4.45
Crook	1	5	0	0	0	0	0	0	1	5	2	1.91
Curry	2	9	0	0	1	4	1	4	0	0	4	3.57
Deschutes	6	4	5	3	9	6	6	4	5	3	32	3.89
Douglas	7	6	8	7	6	6	4	4	5	5	30	5.56
Gilliam	0	0	0	0	1	53	1	53	0	0	2	21.16
Grant	0	0	0	0	0	0	0	0	0	0	0	0.00
Harney	0	0	1	13	1	14	0	0	0	0	2	5.40
Hood River	1	4	0	0	0	0	1	4	3	13	5	4.35
Jackson	8	4	12	6	11	5	5	2	8	4	44	4.31
Jefferson	0	0	1	5	1	5	1	5	3	14	6	5.47
Josephine	3	4	3	4	2	2	4	5	4	5	16	3.87
Klamath	1	2	8	12	4	6	1	1	3	4	17	5.11
Lake	0	0	0	0	1	13	0	0	1	13	2	5.06
Lane	18	5	14	4	21	6	17	5	30	8	100	5.66
Lincoln	4	9	4	9	4	9	2	4	1	2	15	6.50
Linn	7	6	7	6	5	4	5	4	3	3	27	4.61
Malheur	3	10	1	3	2	6	4	13	2	6	12	7.65
Marion	23	7	30	9	27	8	27	8	28	9	135	8.48
Morrow	2	18	1	9	0	0	2	18	1	9	6	10.66
Multnomah	182	25	181	25	198	27	168	22	199	26	928	24.98
Polk	2	3	6	8	0	0	4	5	5	6	17	4.47
Sherman	0	0	0	0	0	0	0	0	0	0	0	0.00
Tillamook	0	0	1	4	1	4	2	8	2	8	6	4.74
Umatilla	4	5	4	5	4	5	3	4	4	5	19	4.96
Union	1	4	1	4	2	8	4	15	0	0	8	6.15
Wallowa	0	0	1	14	0	0	0	0	0	0	1	2.86
Wasco	2	8	2	8	0	0	2	8	3	12	9	7.07
Washington	83	16	86	16	68	13	88	16	87	16	412	15.33
Wheeler	0	0	0	0	0	0	0	0	0	0	0	0.00
Yamhill	4	4	2	2	7	7	3	3	4	4	20	4.00

Table 9. Incidence of acute hepatitis C by county, Oregon, 2009–2013

Source: Orpheus hepatitis C surveillance and American Community Survey, June 2014
Acute hepatitis C counts and rates per 100,000 residents

	2009		2010		2011		2012		2013		2009–2013	
County	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
Baker	0	0		0		0		0		0	0	0
Benton	0	0	0	0	0	0	2	2	0	0	2	0
Clackamas	3	1	2	1	1	0	3	1	5	1	14	1
Clatsop	1	3	0	0	0	0	0	0	0	0	0	1
Columbia	0	0	0	0	0	0	0	0	1	2	1	0
Coos	0	0	0	0	0	0	0	0	0	0	0	0
Crook	0	0	0	0	0	0	0	0	0	0	0	0
Curry	0	0	0	0	0	0	0	0	0	0	0	0
Deschutes	0	0	1	1	1	1	2	1	1	1	5	1
Douglas	2	2	5	5	2	2	4	4	0	0	13	2
Gilliam	0	0	0	0	0	0	0	0	0	0	0	0
Grant	0	0	0	0	0	0	0	0	0	0	0	0
Harney	0	0	1	13	0	0	1	14	0	0	2	5
Hood River	0	0	2	9	0	0	0	0	0	0	2	2
Jackson	2	1	0	0	0	0	0	0	1	0	3	0
Jefferson	1	5	0	0	0	0	0	0	0	0	1	1
Josephine	1	1	0	0	0	0	1	1	0	0	2	0
Klamath	4	6	0	0	2	3	1	1	0	0	7	2
Lake	0	0	0	0	0	0	0	0	0	0	0	0
Lane	5	1	4	1	5	1	5	1	3	1	22	1
Lincoln	0	0	0	0	0	0	0	0	1	2	1	0
Linn	0	0	0	0	1	1	0	0	0	0	1	0
Malheur	0	0	0	0	0	0	0	0	0	0	0	0
Marion	1	0	3	1	3	1	6	2	1	0	14	1
Morrow	0	0	0	0	0	0	0	0	0	0	0	0
Multnomah	1	0	3	0	5	1	12	2	0	0	21	1
Polk	1	1	0	0	1	1	0	0	0	0	2	1
Sherman	0	0	0	0	0	0	0	0	0	0	0	0
Tillamook	0	0	0	0	0	0	0	0	0	0	0	0
Umatilla	2	3	1	1	1	1	1	1	0	0	5	1
Union	0	0	0	0	0	0	0	0	0	0	0	0
Wallowa	0	0	0	0	0	0	0	0	0	0	0	0
Wasco	0	0	0	0	0	0	0	0	0	0	0	0
Washington	0	0	0	0	1	0	1	0	1	0	3	0
Wheeler	0	0	0	0	0	0	0	0	0	0	0	0
Yamhill	0	0	0	0	0	0	0	0	0	0	0	0

Table 10. Incidence of chronic hepatitis C by county, Oregon, 2009–2013

Source: Orpheus hepatitis C surveillance and American Community Survey, June 2014
Chronic hepatitis C counts and rates per 100,000 residents

	2009		2010		2011		2012		2013		2009–2013	
County	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
Baker	29	180	16	99	15	93	20	123	22	135	102	126
Benton	74	87	57	66	57	66	38	44	38	43	264	61
Clackamas	348	93	283	75	315	83	281	74	327	85	1,554	82
Clatsop	61	165	61	165	63	170	55	148	36	97	276	149
Columbia	51	104	76	154	65	131	64	129	33	66	289	117
Coos	157	249	143	227	133	211	132	210	52	83	617	196
Crook	16	76	23	109	20	96	30	145	13	63	102	98
Curry	62	276	53	237	37	166	38	170	25	112	215	192
Deschutes	164	104	159	101	215	135	195	122	168	103	901	113
Douglas	192	178	202	188	239	222	160	148	134	123	927	172
Gilliam	2	107	3	160	3	160	1	53	2	103	11	116
Grant	6	80	4	54	7	94	0	0	5	67	22	59
Harney	5	67	8	107	10	136	8	109	8	110	39	106
Hood River	11	49	9	40	8	35	15	66	6	26	49	43
Jackson	346	171	281	138	331	162	239	117	224	109	1,418	139
Jefferson	48	222	48	221	51	233	57	260	72	327	276	252
Josephine	187	226	176	213	172	208	105	127	101	122	741	179
Klamath	142	214	119	179	104	156	70	105	71	106	506	152
Lake	14	177	15	190	12	152	13	164	15	189	69	174
Lane	632	180	590	168	550	156	470	133	419	118	2,661	151
Lincoln	62	135	69	150	101	219	88	190	79	170	399	173
Linn	229	197	224	192	188	160	149	126	142	120	932	159
Malheur	115	368	80	255	82	261	63	201	33	105	373	238
Marion	504	161	540	171	500	157	412	129	329	102	2,285	144
Morrow	0	0	2	18	10	89	8	71	2	18	22	39
Multnomah	1,360	186	1,469	199	1,430	193	1,266	169	938	124	6,463	174
Polk	80	107	71	94	72	95	46	60	59	77	328	86
Sherman	1	56	1	57	0	0	3	170	1	56	6	68
Tillamook	30	119	34	135	47	186	27	107	20	79	158	125
Umatilla	196	259	169	222	97	127	106	137	90	116	658	172
Union	39	152	19	74	41	158	13	50	14	53	126	97
Wallowa	2	28	7	100	6	86	1	14	7	99	23	66
Wasco	25	99	26	103	27	107	30	118	21	81	129	102
Washington	438	83	438	82	379	71	324	60	388	70	1,967	73
Wheeler	4	277	0	0	0	0	2	140	1	70	7	98
Yamhill	91	92	91	92	108	108	122	121	107	106	519	104

Table 11. Cases of hepatitis A by age group and sex, Oregon, 2009–2013

Source: Orpheus hepatitis A surveillance

	Female		Male		Total	
Age	Count	Percent	Count	Percent	Count	Percent
0–19 years	3	7%	3	7%	6	7%
20s	6	15%	8	17%	14	16%
30s	6	15%	6	13%	12	14%
40s	4	10%	8	17%	12	14%
50s	10	24%	9	20%	19	22%
60s	6	15%	5	11%	11	13%
70s	4	10%	5	11%	9	10%
80+	2	5%	2	4%	4	5%
Total	41	47%	46	53%	87	100%

Note: 87/87 (100%) data available.

Table 12. Cases of acute hepatitis B by age group and sex, Oregon, 2009–2013

Source: Orpheus hepatitis B surveillance

	Female		Male		Total	
Age	Count	Percent	Count	Percent	Count	Percent
0–19 years	2	3%	1	1%	3	2%
20s	6	10%	14	11%	20	10%
30s	16	27%	20	15%	36	19%
40s	18	30%	39	30%	57	30%
50s	10	17%	34	26%	44	23%
60s	6	10%	17	13%	23	12%
70s	1	2%	6	5%	7	4%
80+	1	2%	1	1%	2	1%
Total	60	31%	132	69%	192	100%

Note: 192/192 (100%) data available.

Table 13. Cases of chronic hepatitis B by age group and sex, Oregon, 2009–2013

Source: Orpheus hepatitis B surveillance

	Unknowns excluded					
	Female		Male		Total	
Age	Count	Percent	Count	Percent	Count	Percent
0–19 years	59	6%	33	3%	92	4%
20s	206	22%	151	13%	357	17%
30s	241	26%	261	22%	502	24%
40s	157	17%	307	25%	464	22%
50s	130	14%	269	22%	399	19%
60s	84	9%	132	11%	216	10%
70s	29	3%	42	3%	71	3%
80+	12	1%	12	1%	24	1%
Total	918	43%	1,207	57%	2,125	100%

Note: 2,125/2,130 (99.8%) data available.

Table 14. Cases of acute hepatitis C by age group and sex, Oregon, 2009–2013

Source: Orpheus hepatitis C surveillance

	Female		Male		Total	
Age	**Count**	**Percent**	**Count**	**Percent**	**Count**	**Percent**
0–19 years	6	11%	8	12%	14	11%
20s	20	37%	21	31%	41	34%
30s	10	19%	18	26%	28	23%
40s	12	22%	11	16%	23	19%
50s	5	9%	9	13%	14	11%
60s	1	2%	0	0%	1	1%
70s	0	0%	1	1%	1	1%
Total	54	44%	68	56%	122	100%

Note: 122/122 (100%) data available.

Table 15. Cases of chronic hepatitis C by age group and sex, Oregon, 2009–2013

Source: Orpheus hepatitis C surveillance

	Unknowns excluded					
	Female		Male		Total	
Age	**Count**	**Percent**	**Count**	**Percent**	**Count**	**Percent**
0–19 years	166	2%	117	1%	283	1%
20s	1,012	10%	976	6%	1,990	8%
30s	1,342	14%	1,738	11%	3,100	12%
40s	2,473	25%	3,825	25%	6,323	25%
50s	3,365	35%	6,107	39%	9,513	37%
60s	1,124	12%	2,437	16%	3,572	14%
70s	188	2%	278	2%	468	2%
80+	64	1%	66	0%	131	1%
Total	9,734	38%	15,544	61%	25,380	100%

Note: 25,380/25,437 (99.8%) data available.

Table 16. Incidence of acute hepatitis A by sex and age, Oregon, 2009–2013

Source: Orpheus hepatitis A surveillance and the American Community Survey, June 2014

Average incidence rates per 100,000 Oregon residents, 2009–2013			
Age	**Female**	**Male**	**Total**
0–19	0.13	0.12	0.12
20s	0.46	0.60	0.53
30s	0.47	0.46	0.47
40s	0.31	0.62	0.47
50s	0.71	0.68	0.69
60s	0.52	0.49	0.51
70s	0.67	0.99	0.82
80+	0.41	0.69	0.52
Total	**0.42**	**0.48**	**0.45**

Table 17. Incidence of acute hepatitis B by sex and age, Oregon, 2009–2013

Source: Orpheus hepatitis B surveillance and the American Community Survey, June 2014

Average incidence rates per 100,000 Oregon residents, 2009–2013			
Age	**Female**	**Male**	**Total**
0-19	0.09	0.04	0.06
20s	0.36	0.94	0.76
30s	1.26	1.52	1.41
40s	1.41	3.03	2.22
50s	0.75	2.60	1.61
60s	0.53	1.51	1.09
70s	0.09	1.05	0.62
80+	0.22	0.19	0.26
Total	**0.62**	**1.38**	**0.99**

Table 18. Incidence of chronic hepatitis B by sex and age, Oregon, 2009–2013

Source: Orpheus hepatitis B surveillance and the American Community Survey, June 2014

Average incidence rates per 100,000 Oregon residents, 2009–2013			
Age	**Female**	**Male**	**Total**
0-19	2.52	1.32	1.90
20s	15.75	11.38	13.55
30s	19.09	19.99	19.54
40s	12.26	23.81	18.16
50s	9.24	20.19	14.56
60s	7.58	12.78	10.17
70s	4.81	8.21	6.38
80+	2.51	4.07	3.10
Total	**9.40**	**12.58**	**11.00**

Table 19. Incidence of acute hepatitis C by sex and age, Oregon, 2009–2013

Source: Orpheus hepatitis C surveillance and the American Community Survey, June 2014

Average incidence rates per 100,000 Oregon residents, 2009–2013			
Age	**Female**	**Male**	**Total**
0-19	0.25	0.32	0.29
20s	1.53	1.59	1.56
30s	0.79	1.37	1.09
40s	0.94	0.85	0.90
50s	0.36	0.67	0.51
60s	0.09	0.00	0.04
70s	0.00	0.18	0.09
80+	0.00	0.00	0.00
Total	**0.55**	**0.71**	**0.63**

Table 20. Incidence of chronic hepatitis C by sex and age, Oregon, 2009–2013

Source: Orpheus hepatitis C surveillance and the American Community Survey, June 2014

Average incidence rates per 100,000 Oregon residents, 2009–2013			
Age	**Female**	**Male**	**Total**
0-19	7.08	4.69	5.84
20s	77.36	73.54	75.50
30s	106.29	133.37	120.81
40s	192.72	296.49	245.72
50s	239.04	458.97	347.39
60s	102.64	234.62	167.46
70s	31.96	54.49	42.58
80+	13.39	22.53	17.02
Total	**99.89**	**162.62**	**131.5234012**

Table 21. Hepatitis A cases by sex and race/ethnicity, Oregon, 2009–2013

Source: Orpheus hepatitis A surveillance
Unknowns excluded

	Hepatitis A cases by race, 2009–2013					
	Female		Male		Total	
Race	Count	Percent	Count	Percent	Count	Percent
AI/AN	0	0%	1	2%	1	1%
Asian/PI	1	3%	3	7%	4	5%
Black	1	3%	1	2%	2	2%
Other	0	0%	2	4%	2	2%
White	38	95%	37	82%	75	88%
Multiple	0	0%	1	2%	1	1%
Total	40	47%	45	53%	85	100%

*85/87 (98%) data available

	Hepatitis A cases by ethnicity, 2009–2013					
	Female		Male		Total	
Hispanic	Count	Percent	Count	Percent	Count	Percent
No	35	97%	35	83%	70	90%
Yes	1	2%	7	17%	8	10%
Total	36	46%	42	54%	78	100%

Note: 78/87 (90%) data available

Table 22. Acute hepatitis B cases by sex and race/ethnicity, Oregon, 2009–2013

Source: Orpheus hepatitis B surveillance

	Acute hepatitis B cases by race and sex, 2009–2013					
	Female		Male		Total	
Race	Count	Percent	Count	Percent	Count	Percent
AI/AN	0	0%	1	1%	1	1%
Asian	1	2%	4	3%	5	3%
Black	2	4%	1	1%	3	2%
Multiple	2	4%	3	2%	5	3%
Other	0	0%	2	2%	2	1%
PI	1	2%	0	0%	1	1%
White	49	89%	114	91%	163	91%
Total	55	31%	125	69%	180	100%

*180/192 (94%) data available

	Acute hepatitis B cases by ethnicity and sex, 2009–2013					
	Female		Male		Total	
Hispanic	Count	Percent	Count	Percent	Count	Percent
No	52	93%	111	90%	163	91%
Yes	4	7%	13	10%	17	9%
Total	56	31%	124	69%	180	100%

Note: 180/192 (94%) data available

Table 23. Chronic hepatitis B cases by sex and race/ethnicity, Oregon, 2009–2013

Source: Orpheus hepatitis B surveillance

	Chronic hepatitis B cases by race and sex, 2009–2013					
	Female		Male		Total	
Race	Count	Percent	Count	Percent	Count	Percent
AI/AN	11	1%	17	2%	28	2%
Asian	504	62%	456	46%	960	53%
Black	57	7%	82	8%	139	8%
Multiple	17	2%	20	2%	37	2%
Other	4	0%	13	1%	17	1%
PI	66	8%	37	4%	103	6%
White	155	19%	376	38%	531	29%
Total	814	45%	1001	55%	1,815	100%

*1,815/2,130 (85%) data available

	Chronic hepatitis B cases by ethnicity and sex, 2009–2013					
	Female		Male		Total	
Hispanic	Count	Percent	Count	Percent	Count	Percent
No	761	83%	948	79%	1709	97%
Yes	17	2%	44	4%	61	3%
Total	778	44%	992	56%	1,770	100%

Note: 1,770/2,130 (83%) data available

Table 24. Acute hepatitis C cases by sex and race/ethnicity, Oregon, 2009–2013

Source: Orpheus hepatitis C surveillance

	Acute hepatitis C cases by race and sex, 2009–2013					
	Female		Male		Total	
Race	Count	Percent	Count	Percent	Count	Percent
AI/AN	1	2%	4	7%	5	5%
Black	1	2%	1	2%	2	2%
Multiple	1	2%	0	0%	1	1%
Other	0	0%	1	2%	1	1%
White	46	94%	48	89%	94	91%
Total	49	48%	54	52%	103	100%

*103/122 (84%) data available

	Acute hepatitis C cases by ethnicity and sex, 2009–2013					
	Female		Male		Total	
Hispanic	Count	Percent	Count	Percent	Count	Percent
No	47	100%	51	91%	98	95%
Yes	0	0%	5	9%	5	5%
Total	47	46%	56	54%	103	100%

Note: 103/122 (84%) data available

Table 25. Chronic hepatitis C cases by sex and race/ethnicity, Oregon, 2009–2013

Source: Orpheus hepatitis C surveillance

	Chronic hepatitis C cases by race and sex, 2009–2013					
	Female		Male		Total	
Race	Count	Percent	Count	Percent	Count	Percent
AI/AN	131	3%	182	3%	313	3%
Asian	61	1%	105	2%	166	2%
Black	152	4%	282	4%	434	4%
Multiple	29	1%	49	1%	78	1%
Other	50	1%	86	1%	136	1%
PI	6	0%	18	0%	24	0%
White	3,885	90%	5,584	89%	9,469	89%
Total	4,314	41%	6,306	59%	10,620	100%

*10,620/25,437 (42%) data available

	Chronic hepatitis C cases by ethnicity and sex, 2009–2013					
	Female		Male		Total	
Hispanic	Count	Percent	Count	Percent	Count	Percent
No	3,951	97%	5,734	94%	9,685	95%
Yes	142	3%	337	6%	479	5%
Total	4,093	40%	6,071	60%	10,164	100%

Note: 10,164/25,437 (40%) data available

Table 26. Incidence of acute hepatitis A by sex and race/ethnicity, Oregon, 2009–2013

Source: Orpheus hepatitis A surveillance and the American Community Survey, June 2014

Average incidence rate per 100,000 Oregon residents, 2009–2013			
Race	Female	Male	Total
AI/AN	0.00	0.83	0.42
Asian	0.27	0.89	0.55
Black	0.61	0.53	0.57
Multiple	0.00	0.30	0.15
Other	0.00	0.47	0.26
PI	0.00	0.00	0.00
White	0.45	0.45	0.48

Note: 85/87(98%) data available

Ethnicity	Female	Male	Total
Hispanic	0.10	0.59	0.36
Non-Hispanic	0.40	0.42	0.41
Black	0.61	0.53	0.57

Note: 78/87 (90%) data available

Table 27. Incidence of acute hepatitis B by sex and race/ethnicity, Oregon, 2009–2013

Source: Orpheus hepatitis B surveillance and the American Community Survey, June 2014

Average incidence rate per 100,000 Oregon residents, 2009–2013			
Race	Female	Male	Total
AI/AN	0.00	0.83	0.42
Asian	0.27	1.17	0.68
Black	1.23	0.54	0.86
Multiple	0.56	0.79	0.68
Other	0.00	0.49	0.26
PI	2.25	0.00	1.21
White	0.59	1.40	0.85

Note: 180/192 (94%) data available

Ethnicity	Female	Male	Total
Hispanic	0.38	1.08	0.75
Non-Hispanic	0.60	1.33	0.96
Black	0.61	0.53	0.57

Note: 180/192 (94%) data available

Table 28. Incidence of acute hepatitis C by sex and race/ethnicity, Oregon, 2009–2013

Source: Orpheus hepatitis C surveillance and the American Community Survey, June 2014

Average 2009–2013 incidence rate per 100,000			
Race	**Female**	**Male**	**Total**
AI/AN	0.86	3.18	2.07
Asian	0.00	0.00	0.00
Black	0.62	0.53	0.57
Multiple	0.30	0.00	0.15
Other	0.00	0.26	0.14
PI	0.00	0.00	0.00
White	0.55	0.59	0.57

Note: 103/122 (84%) data available

Ethnicity	**Female**	**Male**	**Total**
Hispanic	0.00	0.41	0.21
Non-Hispanic	0.54	0.61	0.57
Black	0.61	0.53	0.57

Note: 103/122 (84%) data available

Table 29. Incidence of chronic hepatitis C by sex and race/ethnicity, Oregon, 2009–2013

Source: Orpheus hepatitis C surveillance and the American Community Survey, June 2014

Average 2009–2013 incidence rate per 100,000			
Race	**Female**	**Male**	**Total**
AI/AN	112.82	143.56	127.72
Asian	15.10	31.31	22.62
Black	93.43	151.02	124.39
Multiple	8.22	13.71	11.13
Other	14.21	20.84	17.80
PI	15.13	47.70	31.36
White	46.55	68.70	57.53

Note: 10,620/25,437 (42%) data available

Ethnicity	**Female**	**Male**	**Total**
Hispanic	13.11	27.73	20.84
Non-Hispanic	45.50	68.47	56.93
Black	0.61	0.53	0.57

Note: 10,164/25,437 (40%) data available

Table 30. Incidence of chronic hepatitis B by sex and race/ethnicity, Oregon, 2009–2013

Source: Orpheus hepatitis B surveillance and the American Community Survey, June 2014

Average incidence rate per 100,000 Oregon residents, 2009–2013

Race	**Female**	**Male**	**Total**
AI/AN	9.45	13.11	11.40
Asian	126.38	136.82	131.41
Black	35.19	44.11	39.89
Multiple	4.86	5.53	5.20
Other	1.18	3.26	2.33
PI	173.30	103.55	139.78
White	1.86	4.62	3.23

Note: 1,815/2,130 (85%) data available

Ethnicity	**Female**	**Male**	**Total**
Hispanic	1.56	3.65	2.66
Non-Hispanic	8.76	11.31	10.03

Note: Ethnicity known for 1,770/2,130 (83%)

Table 31. Acute hepatitis A by age and race/ethnicity, Oregon, 2009–2013

Source: Orpheus hepatitis A surveillance

	0–19 years		20s		30s		40s		50s		60s		70s		80+		Total	
Race	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
AI/AN	0	0%	0	0%	0	0%	1	100%	0	0%	0	0%	0	0%	0	0%	1	1%
Asian/PI	0	0%	2	50%	1	25%	0	0%	0	0%	1	25%	0	0%	0	0%	4	5%
Black	1	50%	0	0%	1	50%	0	0%	0	0%	0	0%	0	0%	0	0%	2	2%
Multiple	0	0%	0	0%	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%	1	1%
Other	0	0%	2	100%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	2	2%
White	5	7%	10	13%	9	12%	10	13%	19	25%	10	13%	8	11%	4	5%	75	88%
Total	6	7%	14	16%	12	14%	11	13%	19	22%	11	13%	8	9%	4	5%	85	100%

Note: 85/87 (98%)data available

	0–19 years		20s		30s		40s		50s		60s		70s		80+		Total	
Hispanic	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
No	4	6%	11	16%	8	11%	9	13%	16	23%	10	14%	8	11%	4	6%	70	90%
Yes	2	25%	3	38%	2	25%	0	0%	1	13%	0	0%	0	0%	0	0%	8	10%
Total	6	8%	14	18%	10	13%	9	12%	17	22%	10	13%	8	10%	4	5%	78	100%

Note: 78/87 (90%) data available

Table 32. Acute hepatitis B by age and race/ethnicity, Oregon 2009–2013

Source: Orpheus hepatitis B surveillance

	0–19 years		20s		30s		40s		50s		60s		70s		80+		Total	
Race	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
AI/AN	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%	0	0%	1	1%
Asian	0	0%	2	40%	0	0%	2	40%	0	0%	1	20%	0	0%	0	0%	5	3%
Black	1	33%	0	0%	0	0%	1	33%	1	33%	0	0%	0	0%	0	0%	3	2%
Multiple	1	20%	0	0%	1	20%	1	20%	2	40%	0	0%	0	0%	0	0%	5	3%
Other	0	0%	0	0%	0	0%	1	50%	0	0%	0	0%	1	50%	0	0%	2	1%
PI	0	0%	0	0%	0	0%	1	100%	0	0%	0	0%	0	0%	0	0%	1	1%
White	1	1%	18	11%	31	19%	48	29%	38	23%	21	13%	5	3%	1	1%	163	91%
Total	3	2%	20	11%	32	18%	54	30%	41	23%	22	12%	7	4%	1	1%	180	

Note: 180/192 (94%) data available

	0–19 years		20s		30s		40s		50s		60s		70s		80+		Total	
Hispanic	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
No	3	2%	18	11%	27	17%	49	30%	38	23%	22	13%	5	3%	1	1%	163	91%
Yes	0	0%	2	12%	5	29%	5	29%	3	18%	0	0%	1	6%	1	6%	17	9%
Total	3	2%	20	11%	32	18%	54	30%	41	23%	22	12%	6	3%	2	1%	180	

Note: 180/192 (94%) data available

Table 33. Chronic hepatitis B by age and race/ethnicity, Oregon 2009–2013

Source: Orpheus hepatitis B surveillance

	0–19 years		20s		30s		40s		50s		60s		70s		80+		Total	
Race	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
AI/AN	1	4%	9	32%	5	18%	7	25%	2	7%	2	7%	1	4%	1	4%	28	2%
Asian	49	5%	165	17%	267	28%	206	21%	151	16%	88	9%	30	3%	6	1%	962	53%
Black	12	9%	42	30%	35	25%	24	17%	14	10%	9	6%	3	2%	0	0%	139	8%
Multiple	1	3%	3	8%	12	32%	13	35%	5	14%	2	5%	0	0%	1	3%	37	2%
Other	0	0%	6	35%	5	29%	1	6%	3	18%	1	6%	1	6%	0	0%	17	1%
PI	6	6%	31	30%	30	29%	18	17%	15	15%	1	1%	2	2%	0	0%	103	6%
White	15	3%	60	11%	82	15%	119	22%	139	26%	81	15%	25	5%	10	2%	531	29%
Total	84	5%	316	17%	436	24%	388	21%	329	18%	184	10%	62	3%	18	1%	1,817	100%

Note: 1,817/2,130 (85%) data available

	0–19 years		20s		30s		40s		50s		60s		70s		80+		Total	
Hispanic	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
No	77	4%	296	17%	405	24%	370	22%	311	18%	172	10%	62	4%	19	1%	1,712	97%
Yes	3	5%	9	15%	14	23%	19	31%	11	18%	4	7%	1	2%	0	0%	61	3%
Total	80	5%	305	17%	419	24%	389	22%	322	18%	176	10%	63	4%	19	1%	1,773	100%

Note: 1,773/2,130 (83%) data available

Table 34. Acute hepatitis C by age and race/ethnicity, Oregon, 2009–2013

Source: Orpheus hepatitis C surveillance

	0–19 years		20s		30s		40s		50s		60s		70s		Total	
Race	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
AI/AN	0	0%	1	20%	3	60%	0	0%	1	20%	0	0%	0	0%	5	4%
Black	0	0%	2	100%	0	0%	0	0%	0	0%	0	0%	0	0%	2	2%
Multiple	0	0%	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%	1	1%
Other	0	0%	0	0%	1	100%	0	0%	0	0%	0	0%	0	0%	1	1%
White	11	12%	32	34%	21	22%	17	18%	12	13%	0	0%	1	1%	94	77%
Total	11	11%	36	35%	25	24%	17	17%	13	13%	0	0%	1	1%	103	

Note: 103/122 (84%) data available

	0–19 years		20s		30s		40s		50s		60s		70s		Total	
Hispanic	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
No	10	10%	33	34%	25	26%	16	16%	13	13%	0	0%	1	1%	98	95%
Yes	2	40%	2	40%	1	20%	0	0%	0	0%	0	0%	0	0%	5	5%
Total	12	12%	35	34%	26	25%	16	16%	13	13%	0	0%	1	1%	103	

Note: 103/122 (84%) data available

Table 35. Chronic hepatitis C by age and race/ethnicity, Oregon 2009–2013

Source: Orpheus hepatitis C surveillance

	0–19 years		20s		30s		40s		50s		60s		70s		80+		Total	
Race	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
AI/AN	5	2%	27	9%	49	16%	105	34%	99	32%	27	9%	1	0%	0	0%	313	3%
Asian	7	4%	9	5%	15	9%	37	22%	51	31%	29	17%	11	7%	7	4%	167	2%
Black	7	2%	17	4%	22	5%	90	21%	201	46%	83	19%	10	2%	4	1%	434	4%
Multiple	3	4%	7	9%	9	11%	24	30%	28	35%	8	10%	0	0%	0	0%	79	1%
Other	1	1%	9	7%	17	13%	35	26%	48	35%	23	17%	1	1%	2	1%	136	1%
PI	0	0%	7	29%	4	17%	2	8%	6	25%	4	17%	0	0%	1	4%	24	0%
White	133	1%	971	10%	1,281	14%	2,295	24%	3,376	36%	1,218	13%	153	2%	42	0%	9,477	89%
Total	156	1%	1,047	10%	1,397	13%	2,588	24%	3,809	36%	1,392	13%	176	2%	56	1%	10,630	100%

Note: 10,630/25,437 (42%) data available

	0–19 years		20s		30s		40s		50s		60s		70s		80+		Total	
Hispanic	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
No	137	1%	988	10%	1,282	13%	2,343	24%	3,465	36%	1,268	13%	166	2%	56	1%	9,711	95%
Yes	14	3%	42	9%	86	18%	159	33%	126	26%	44	9%	6	1%	2	0%	480	5%
Total	151	1%	1,030	10%	1,368	13%	2,502	25%	3,591	35%	1,312	13%	172	2%	58	1%	10,191	100%

Note: 10,191/25,437 (40%) data available

Table 36. Hepatitis A risk factors, 2009–2013

Source: Orpheus hepatitis A surveillance
Unknown responses excluded from denominator

Hepatitis A risk factor, 2009–2013	Yes		No		Unknown	
Risks (non-mutually exclusive)	**Count**	**Percent of known cases for risk**	**Count**	**Percent of known cases for risk**	**Count**	**Percent of total investigated cases**
Travel	36	44%	46	56%	0	0%
HH travel	15	19%	63	81%	4	5%
Contact of a case	7	10%	66	90%	9	11%
Outbreak	7	25%	21	75%	54	66%
Street drugs	6	8%	74	93%	2	2%
Child care	3	4%	77	96%	2	2%
HH member works at daycare	2	3%	77	97%	3	4%
Injection drug use	1	1%	79	99%	2	2%
Total interviewed cases	**82**	Note: 82/87 (94.3%) interviewed				
Total cases	**87**					

Table 37. Acute hepatitis B risk factors, Oregon 2009–2013

Source: Orpheus hepatitis B surveillance
Unknown responses excluded from denominator

Acute hepatitis B risk factors, Oregon, 2009–2013	Yes		No		Unknown	
Risks (non-mutually exclusive)	**Count**	**Percent of known cases for risk**	**Count**	**Percent of known cases for risk**	**Count**	**Percent of total investigated cases**
Other risk*	60	65%	32	35%	66	42%
Multiple sex partners	49	31%	107	69%	2	1%
Dental care	39	26%	109	74%	10	6%
MSM	26	16%	132	84%	0	0%
Healthcare-associated**	18	12%	132	88%	8	5%
Injection drug use	18	12%	133	88%	7	4%
Contact of case	13	14%	78	86%	67	42%
Occupational risk	4	3%	151	97%	3	2%
Total interviewed cases	**158**	* Street drugs, needlestick, tattoo, piercing, other blood exposure				
Total cases	**192**	** Transfusion, infusions, dialysis, surgery Note: 158/192(82.3%) interviewed				

Table 38. Chronic hepatitis B risk factors, 2009–2013

Source: Orpheus hepatitis B surveillance
Unknown responses excluded from denominator

Chronic hepatitis B risk factors, 2009–2013	Yes		No		Unknown	
Risks (non-mutually exclusive)	**Count**	**Percent of known cases for risk**	**Count**	**Percent of known cases for risk**	**Count**	**Percent of total investigated cases**
Foreign born	770	75%	258	25%	224	18%
Contact of a case	271	35%	503	65%	278	22%
Multiple sex partners	135	43%	179	57%	938	75%
Ever STD	103	11%	822	89%	327	26%
Occupational exposure	73	16%	394	84%	785	63%
Injection drug use	71	7%	1,006	93%	175	14%
MSM	50	9%	493	91%	709	57%
Dialysis	9	1%	1,107	99%	136	11%
Total Interviewed cases	**1,252**	Note: 1,252/2,130 (58.8%) data available				
Total cases	**2,130**					

Table 39. Chronic hepatitis B race by birthplace, Oregon, 2009–2013

Source: Orpheus hepatitis B surveillance

	AI/AN		Asian		Black		Multiple		Other		PI		White		Unknown		Total	
	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
Foreign born	0	0%	529	94%	71	78%	4	25%	5	71%	67	93%	67	29%	27	75%	770	75%
United States	9	100%	36	6%	20	22%	12	75%	2	29%	5	7%	165	71%	9	25%	258	25%
Total	9	1%	565	55%	91	9%	16	2%	7	1%	72	7%	232	23%	36	4%	1,028	

Note: 1028/1252 (82.1%) foreign born data available

Table 40. Birth countries of chronic hepatitis B cases, Oregon 2009–2013

United States	258	25%
Vietnam	192	19%
China	173	17%
Philippines	48	5%
South Korea	29	3%
Taiwan	27	3%
Other countries	297	29%
Total interviewed	**1,024**	**100%**
Total cases	**2,130**	

Note: 1,024/2,130 (48.1%) country of birth data available

Table 41. Acute hepatitis C risk factors, Oregon, 2009–2013

Source: Orpheus hepatitis C surveillance/unknown responses excluded from denominator

Acute hepatitis C risk factors,Oregon, 2009–2013	Yes		No		Unknown	
Risks (non-mutually exclusive)	**Count**	**Percent of known cases for risk**	**Count**	**Percent of known cases for risk**	**Count**	**Percent of total investigated cases**
Injection drug use	52	64%	29	36%	1	1%
Street drug	39	60%	26	40%	17	21%
Other blood exposure	27	43%	36	57%	19	23%
Multiple sex partners	25	44%	32	56%	25	30%
Other risk*	24	39%	39	63%	19	23%
Incarcerated	19	26%	53	74%	10	12%
Healthcare-associated**	5	8%	61	92%	16	20%
Total interviewed cases	**82**					
Total cases	**122**					

* Needlestick, tattoo, piercing, other blood exposure
** Transfusion, infusions, dialysis, surgery
Note: 82/122 (67.2%) interviewed

Table 42. Chronic hepatitis C risk factors, Lane, Marion and Multnomah counties, Oregon, 2011–2012

Source: Orpheus hepatitis C surveillance/unknown responses excluded from denominator

Chronic hepatitis C risk factors, Lane, Marion, Multnomah counties, Oregon, 2011–2012	Yes		No		Unknown	
Risks (non-mutually exclusive)	**Count**	**Percent of known cases for risk**	**Count**	**Percent of known cases for risk**	**Count**	**Percent of total investigated cases**
Injection drug use	1,376	77%	402	23%	849	32%
Contact with case of HCV	577	74%	202	26%	1,848	70%
Ever incarcerated	553	59%	384	41%	1,690	64%
Ever have STD	257	35%	468	65%	1,902	72%
Transfusion	128	13%	895	87%	1,604	61%
Occupational exposure	85	7%	1,075	93%	1,467	56%
MSM	78	14%	483	86%	2,066	79%
Total investigated cases	**2,627**					
Total cases	**4,633**					

Note: 2,627/4,633 (56.7%) interviewed

Table 43. Race of persons with chronic HCV who reported injection drug use, Lane, Marion and Multnomah counties, Oregon, 2011–2012

	Race															
	AI/AN		**Asian**		**Black**		**Multiple**		**Other**		**PI**		**White**		**Total**	
IDU	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
Yes	37	80%	4	12%	67	76%	15	83%	5	83%	3	43%	1,027	78%	1,158	76%
No	9	20%	29	88%	21	24%	3	17%	1	17%	4	57%	294	22%	361	24%
Total	46	3%	33	2%	88	6%	18	1%	6	0%	7	0%	1,321	87%	1,519	

Notes: 1,778/2,627 (67.6%) IDU data available; 2,130/2,627 (81.1%) race data available

Table 44. Age and sex of persons with chronic HCV who reported injection drug use, Lane, Marion and Multnomah counties, Oregon, 2011–2012

	Sex					
	Female		Male		Total	
Age	Count	Percent	Count	Percent	Count	Percent
0–19	10	2%	10	1%	20	1%
20s	86	17%	117	13%	203	15%
30s	79	16%	120	14%	199	14%
40s	127	26%	219	25%	346	25%
50s	157	32%	300	34%	457	33%
60s	32	6%	107	12%	139	10%
70s	2	0%	9	1%	11	1%
Unknown	0	0%	1	0%	1	0%
Total	493	36%	883	64%	1,376	100%

Notes: 1,375/1,376 (99.9%) age data available; 1,376/1,376 (100%) sex data available

Table 45. Hospital discharges related to HCV by category of liver disease and year of discharge, Oregon, 2008–2012

	Cirrhosis*		Decompensated cirrhosis**		Other chronic liver disease***		Liver transplants#		Liver cancer##		Total
Year	Count	Percent	Count	Percent	Count	Percent	Count	Percent	Count	Percent	
2008	592	77%	590	77%	166	22%	22	3%	93	12%	764
2009	565	75%	555	73%	173	23%	26	3%	123	16%	756
2010	559	74%	575	76%	173	23%	19	3%	106	14%	758
2011	624	74%	645	77%	169	20%	15	2%	144	17%	838
2012	579	72%	604	75%	168	21%	21	3%	131	16%	801
2008–2012	**2,919**	**75%**	**2,969**	**76%**	**849**	**22%**	**103**	**3%**	**597**	**15%**	**3,917**

* Defined by the following ICD9 codes: 571.2, alcoholic cirrhosis of liver; 571.5, cirrhosis of liver without alcohol; 571.6, biliary cirrhosis

** Defined by the following ICD9 codes: 348.3x, encephalopathy not classified elsewhere; 456.0x, 456.1x, esophageal varices with/without bleeding; 456.20, 456.21, esophageal varices in diseases classified elsewhere with/without bleeding; 572.2, hepatic encephalopathy; 572.3, portal hypertension; 572.4, hepatorenal syndrome; 789.5x, ascites elsewhere with/without bleeding

*** Defined by the following ICD9 codes: 571.0 alcoholic fatty liver; 571.1 acute alcoholic hepatitis; 571.3 alcoholic liver damage unspecified; 571.40 chronic hepatitis unspecified; 571.41 chronic persistent hepatitis; 571.42 autoimmune hepatitis; 571.49 other chronic hepatitis; 571.8 other chronic nonalcoholic liver disease; 571.9 unspecified chronic liver disease without alcohol; 572.0 abscess of liver; 572.1 portal pyemia; 572.8 other sequelae of chronic liver disease; chronic passive congestion of liver; 573.1 hepatitis in viral diseases classified elsewhere; 573.2 hepatitis in other infectious diseases classified elsewhere; 573.3 hepatitis unspecified; 573.4 hepatic infarction; 573.8 other specified disorders of liver; 573.9 unspecified disorder of liver

\# Defined by the following ICD9 codes: 996.8, V42.7

Defined by the following ICD9 codes: 155.x, 197.7, and V10.07

Table 46. Hospital discharges related to HCV by categories of liver disease, Oregon, 2008–2012

		Morbidity by disease group											
		Cirrhosis		Decompensated cirrhosis		Other chronic liver disease		Liver transplants		Liver cancer		Total	
		Count	Percent	Count	Percent	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Sex	Female	944	32%	978	33%	303	36%	34	33%	121	20%	1,294	33%
	Male	1,975	68%	1,991	67%	546	64%	69	67%	476	80%	2,623	67%
	Unknown	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Age group	0–12	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
	13–19	10	0%	11	0%	3	0%	0	0%	0	0%	11	0%
	20–24	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
	25–29	0	0%	1	0%	4	0%	2	2%	0	0%	6	0%
	30–34	12	0%	14	0%	13	2%	0	0%	1	0%	24	1%
	35–39	53	2%	54	2%	27	3%	0	0%	5	1%	76	2%
	40–44	157	5%	166	6%	54	6%	4	4%	11	2%	212	5%
	45–49	380	13%	406	14%	146	17%	15	15%	31	5%	519	13%
	50–54	760	26%	750	25%	210	25%	25	24%	104	17%	955	24%
	55–59	851	29%	861	29%	214	25%	28	27%	204	34%	1,136	29%
	60–64	482	17%	478	16%	128	15%	19	18%	152	25%	655	17%
	65+	214	7%	228	8%	50	6%	10	10%	89	15%	323	8%
Race	AI/AN	167	6%	166	6%	57	7%	1	1%	18	3%	218	6%
	Asian	31	1%	31	1%	9	1%	9	9%	15	3%	49	1%
	Black	60	2%	62	2%	12	1%	3	3%	12	2%	82	2%
	Native Hawaiian/PI	5	0%	4	0%	3	0%	0	0%	3	1%	8	0%
	White	2,116	72%	2,142	72%	617	73%	80	78%	440	74%	2,849	73%
	Refused	19	1%	19	1%	7	1%	0	0%	6	1%	24	1%
	Unknown	276	9%	307	10%	83	10%	5	5%	46	8%	373	10%
	Other	245	8%	238	8%	61	7%	5	5%	57	10%	314	8%
Ethnicity	Hispanic	157	5%	147	5%	51	6%	5	5%	25	4%	201	5%
	Non-Hispanic	2,369	81%	2,404	81%	682	80%	90	87%	501	84%	3,194	82%
	Refused	20	1%	20	1%	8	1%	0	0%	6	1%	26	1%
	Unknown	373	13%	398	13%	108	13%	8	8%	65	11%	496	13%
Race/ethnicity	Hispanic	157	5%	147	5%	51	6%	5	5%	25	4%	201	5%
	AI/AN	157	5%	156	5%	52	6%	1	1%	18	3%	205	5%
	Asian/PI	36	1%	35	1%	12	1%	9	9%	18	3%	57	1%
	Black	60	2%	62	2%	12	1%	3	3%	12	2%	82	2%
	White	2,026	69%	2,061	69%	590	69%	75	73%	425	71%	2,733	70%
	Refused	19	1%	19	1%	7	1%	0	0%	6	1%	24	1%
	Unknown	269	9%	302	10%	81	10%	5	5%	45	8%	366	9%
	Other	195	7%	187	6%	44	5%	5	5%	48	8%	249	6%

Table 46 continued on next page

Table 46, continued

		Morbidity by disease group											
		Cirrhosis		Decompensated cirrhosis		Other chronic liver disease		Liver transplants		Liver cancer		Total	
		Count	Percent	Count	Percent	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Primary payer	Medicare (managed care)	244	8%	270	9%	66	8%	14	14%	73	12%	362	9%
	Medicare (fee-for-service)	583	20%	593	20%	165	19%	35	34%	130	22%	811	21%
	Medicaid (managed care)	655	22%	657	22%	177	21%	3	3%	83	14%	848	22%
	Medicaid (fee-for-service)	258	9%	241	8%	79	9%	7	7%	55	9%	330	8%
	Medicaid – out of state	56	2%	60	2%	7	1%	0	0%	6	1%	67	2%
	Department of Defense	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
	Department of Veterans Affairs	100	3%	102	3%	32	4%	2	2%	16	3%	131	3%
	Indian Health Service or tribe	13	0%	16	1%	5	1%	0	0%	1	0%	17	0%
	HRSA program	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
	State government	24	1%	26	1%	7	1%	0	0%	5	1%	29	1%
	Local government	7	0%	6	0%	2	0%	0	0%	1	0%	8	0%
	HMO/managed care	163	6%	152	5%	39	5%	13	13%	60	10%	225	6%
	Private health insurance – indemnity	14	0%	15	1%	2	0%	0	0%	1	0%	19	0%
	Regence Blue Cross managed care	127	4%	124	4%	33	4%	16	16%	57	10%	182	5%
	Regence Blue Cross indemnity	72	2%	84	3%	23	3%	3	3%	15	3%	101	3%
	Self-pay	327	11%	338	11%	131	15%	1	1%	28	5%	423	11%
	No charge	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
	Refused to pay/ bad debt	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
	Hill Burton free care	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
	Workers Compensation	3	0%	3	0%	1	0%	0	0%	0	0%	3	0%
	Other payer	29	1%	26	1%	7	1%	0	0%	6	1%	37	1%
	Tricare (Champus)	11	0%	12	0%	4	0%	0	0%	1	0%	13	0%
	Kaiser Permanente	61	2%	55	2%	14	2%	6	6%	26	4%	85	2%
	Commercial indemnity	130	4%	146	5%	36	4%	3	3%	29	5%	174	4%
	Self-insured	1	0%	1	0%	0	0%	0	0%	0	0%	1	0%
	Charity	41	1%	42	1%	19	2%	0	0%	4	1%	51	1%

Table 46 continued on next page

Table 46, continued

		Morbidity by disease group											
		Cirrhosis		Decompensated cirrhosis		Other chronic liver disease		Liver transplants		Liver cancer		Total	
		Count	Percent	Count	Percent	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Admission type	Home health	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
	ER	2,043	70%	2,114	71%	640	75%	35	34%	304	51%	2,706	69%
	Urgent	692	24%	714	24%	175	21%	59	57%	160	27%	949	24%
	Elective	179	6%	136	5%	33	4%	9	9%	131	22%	255	7%
	Newborn	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
	Trauma center	3	0%	3	0%	0	0%	0	0%	2	0%	5	0%
	Other	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
	N/A	2	0%	2	0%	1	0%	0	0%	0	0%	2	0%
Total		**2,919**		**2,969**		**849**		**103**		**597**		**3,917**	

Table 47. Rates of hospital discharges related to HCV by sex, age and race, Oregon 2008–2012

		HCV discharges		
		Count	Percent	Average annual rate per 100,000 population
Sex	Female	1,294	33%	13.5
	Male	2,623	67%	27.2
Age group	0-12	0	0%	0.0
	13-19	11	0%	0.6
	20-24	0	0%	0.0
	25-29	6	0%	0.5
	30-34	24	1%	1.9
	35-39	76	2%	6.0
	40-44	212	5%	16.9
	45-49	519	13%	39.5
	50-54	955	24%	69.0
	55-59	1,136	29%	83.1
	60-64	655	17%	54.5
	65+	323	8%	11.9
Race	AI/AN	218	6%	57.7
	Black	82	2%	17.4
	Asian/PI	57	1%	6.4
	White	2,849	73%	16.3
	Refused/unknown/other	711	18%	0.0
Ethnicity	Hispanic	201	5%	9.0
	Non-Hispanic	3,194	82%	18.8
	Refused/unknown/other	522	13%	0.0
Race/ethnicity	Hispanic	201	5%	9.0
	AI/AN	205	5%	77.7
	Asian/PI	57	1%	6.7
	Black	82	2%	19.5
	White	2,733	70%	17.7
	Refused/unknown/other	639	16%	0.0
Total		**3,917**	**100%**	**20.4**

Table 48. Lengths of stay and total charges related HCV hospital discharges, by category of liver disease, Oregon 2008–2012, n = 3,917

		Cirrhosis			Decompensated cirrhosis		
	Year	Mean*	Median	Sum	Mean	Median	Sum
Length of stay	2008	4.6	4.0	2,736	4.9	4.0	2,892
	2009	4.5	3.0	2,565	5.0	4.0	2,762
	2010	4.4	3.0	2,435	4.9	3.0	2,824
	2011	4.1	3.0	2,577	4.8	3.0	3,121
	2012	4.1	3.0	2,375	4.8	3.0	2,906
	5-year average	**4.4**			**4.9**		
Charges	2008	$21,416	$14,846	$12,678,326	$22,808	$15,651	$13,456,429
	2009	$23,782	$15,983	$13,436,843	$25,645	$16,764	$14,233,139
	2010	$25,189	$17,362	$14,080,645	$28,878	$18,764	$16,604,969
	2011	$25,103	$16,903	$15,664,406	$28,391	$18,560	$18,312,265
	2012	$24,217	$16,917	$14,021,791	$30,449	$19,465	$18,391,008
	5-year average	**$23,942**			**$27,234**		

		Other chronic liver disease			Transplants		
	Year	Mean	Median	Sum	Mean	Median	Sum
Length of stay	2008	4.7	4.0	774	5.7	6.0	126
	2009	5.0	3.0	857	11.7	6.5	305
	2010	4.1	3.0	703	7.1	5.0	134
	2011	4.4	3.0	738	4.9	4.0	73
	2012	4.1	3.0	684	5.1	3.0	108
	5-year average	**4.4**			**6.9**		
Charges	2008	$18,990	$13,043	$3,152,397	$40,407	$20,879	$888,951
	2009	$24,949	$15,140	$4,316,245	$72,900	$29,280	$1,895,390
	2010	$21,288	$15,863	$3,682,802	$63,627	$27,040	$1,208,912
	2011	$22,970	$14,243	$3,881,974	$31,883	$26,936	$478,243
	2012	$22,951	$15,565	$3,855,770	$52,911	$21,965	$1,111,135
	5-year average	**$22,230**			**$52,345**		

		Liver cancer			Total		
	Year	Mean	Median	Sum	Mean	Median	Sum
Length of stay	2008	5.3	5.0	497	4.9	4.0	3,734
	2009	5.5	4.0	679	5.0	3.5	3,777
	2010	4.6	4.0	489	4.7	3.0	3,564
	2011	4.1	3.0	583	4.6	3.0	3,882
	2012	5.7	4.0	751	4.6	3.0	3,688
	5-year average	**5.1**			**$26,961**		**$21,149,111**
Charges	2008	$30,373	$22,974	$2,824,652	$22,800	$15,379	$17,419,210
	2009	$36,164	$22,081	$4,448,217	$27,230	$16,503	$20,585,543
	2010	$29,191	$20,126	$3,094,251	$27,723	$18,076	$21,013,741
	2011	$30,000	$21,156	$4,320,012	$27,768	$17,982	$23,269,572
	2012	$45,677	$21,635	$5,983,698	$29,285	$18,248	$23,457,487
	5-year average	**$34,281**		**Total**	**$134,805**	**Total**	**$105,745,554**

* Mean or median length of stay (days) or total charge per discharge per year (in U.S. dollars)

Table 49. Cases of liver cancer by year, with and without chronic viral hepatitis, 1996–2012 (n=3,395)

Sources: Oregon State Cancer Registry (1996–2012) and Orpheus Surveillance Database (1988–2012)

Year	No known history of viral hepatitis	Percent	HBV (n=196)	Percent	HCV (n=763)	Percent	Total cases of liver cancer
1996	80	95.2%	3	3.6%	1	1.2%	84
1997	83	97.6%	2	2.4%	0	0.0%	85
1998	102	95.3%	4	3.7%	1	0.9%	107
1999	120	90.9%	10	7.6%	2	1.5%	132
2000	115	93.5%	7	5.7%	1	0.8%	123
2001	108	94.7%	6	5.3%	0	0.0%	114
2002	135	92.5%	9	6.2%	2	1.4%	146
2003	153	89.0%	16	9.3%	3	1.7%	172
2004	179	90.4%	12	6.1%	7	3.5%	198
2005	169	85.8%	11	5.6%	17	8.6%	197
2006	154	73.0%	15	7.1%	42	19.9%	211
2007	175	69.4%	6	2.4%	71	28.2%	252
2008	170	60.3%	17	6.0%	95	33.7%	282
2009	190	60.9%	21	6.7%	101	32.4%	312
2010	191	59.0%	18	5.6%	115	35.5%	324
2011	165	50.5%	13	4.0%	149	45.6%	327
2012	147	44.7%	26	7.9%	156	47.4%	329
						Total	**3,395**

Table 50. Cases of liver cancer associated with HBV, by age and sex, Oregon, 2008–2012

Sources: Orpheus Hepatitis Surveillance Database (2008–2012)

	Sex								
	Female			Male			Total		
Age	Count	Percent	Rates	Count	Percent	Rates	Count	Percent	Rates
0–19	0	0.0%	0.0	0	0.0%	0.0	0	0.0%	0.0
20s	0	0.0%	0.0	0	0.0%	0.0	0	0.0%	0.0
30s	0	0.0%	0.0	7	9.0%	0.5	7	7.5%	0.5
40s	2	13.3%	0.2	17	21.8%	1.3	19	20.4%	1.5
50s	3	20.0%	0.2	22	28.2%	1.7	25	26.9%	1.9
60s	10	66.7%	1.0	19	24.2%	2.0	29	31.2%	3.0
70s	0	0.0%	0.0	13	16.7%	1.7	13	14.0%	1.7
Total	15	16.1%	0.8	78	83.9%	4.1	93	100%	4.9

Table 51. Cases of liver cancer associated with HCV, by age and sex, Oregon, 2008–2012

Sources: Orpheus Hepatitis Surveillance Database (2008–2012)

	Sex								
	Female			Male			Total		
Age	Count	Percent	Rates	Count	Percent	Rates	Count	Percent	Rates
0–19	0	0.0%	0.0	1	0.2%	0.0	1	0.2%	0.0
20s	0	0.0%	0.0	1	0.2%	0.1	1	0.2%	0.1
30s	0	0.0%	0.0	0	0.0%	0.0	0	0.0%	0.0
40s	12	8.8%	0.9	30	6.3%	2.3	42	6.9%	3.2
50s	67	49.3%	4.9	254	53.5%	19.1	321	52.5%	24.0
60s	41	30.1%	4.1	160	33.7%	16.7	201	32.9%	20.7
70s	16	11.8%	1.6	29	6.1%	3.7	45	7.4%	5.3
Total	136	22.3%	7.0	475	77.7%	24.9	611	100.0%	31.9

Table 52. Numbers of cases and incidence of liver cancer associated with chronic HBV, by race and ethnicity, 2008–2012

Sources: Orpheus Hepatitis Surveillance Database (2008–2012)

Race	Count	Percent	Rate/100,000
AI/AN	0	0%	0.0
Asian/PI	56	60%	6.3
Black	7	8%	1.5
White	30	32%	0.2
Total	**93**	**100%**	

Race known for 93/95=98%

Ethnicity	Count	Percent	Rate/100,000
Hispanic	3	3%	0.1
Non-Hispanic	91	97%	0.5
Total	**94**		

Note: Ethnicity known for 94/95=99%

Table 53. Numbers of cases and incidence of liver cancer associated with chronic HCV, by race and ethnicity, 2008–2012

Sources: Orpheus Hepatitis Surveillance Database (2008–2012)

Race	Count	Percent	Rate/100,000
AI/AN	16	3%	4.1
Asian/PI	24	4%	2.7
Black	24	4%	5.1
White	543	89%	3.1
Total	**607**		

Race known for 607/616=99%

Ethnicity	Count	Percent	Rate/100,000
Hispanic	40	7%	1.8
Non-Hispanic	570	93%	3.4
Total	**610**		

Note: Race known for 610/616=99%

Table 54. Liver transplants performed at OHSU, by HBV and HCV status, 2009–2013

Clinical Transplant Services, Oregon Health & Science University

	2009		2010		2011		2012		2013		Totals	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent	Count	Percent	Count	Percent
HBV	1	3.1%	2	7.1%	2	4.8%	1	2.9%	0	0.0%	6	3.6%
HCV	16	50.0%	19	67.9%	18	42.9%	21	60.0%	17	53.1%	91	53.8%
Other	15	46.9%	7	25.0%	22	52.4%	13	37.1%	15	46.9%	72	42.6%
Total	**32**		**28**		**42**		**35**		**32**		**169**	

Table 55. Age-adjusted mortality rates for viral hepatitis and HIV, Oregon, 1993–2013

Source: Oregon Vital Statistics Mortality data; NCHS population estimate bridged 6/26/2014

	Age-adjusted death rate					Number of deaths				
Year	HBV	HCV	HIV	HIV/HBV	HIV/HCV	HBV	HCV	HIV	HIV/HBV	HIV/HCV
1993	0.78	0.10	9.80	0.06	0.00	25	3	306	2	0
1994	0.99	0.09	10.38	0.00	0.00	31	3	331	0	0
1995	1.12	0.06	10.15	0.22	0.00	36	2	330	7	0
1996	0.90	0.06	7.20	0.12	0.00	29	2	239	4	0
1997	0.59	0.23	2.97	0.09	0.00	20	8	100	3	0
1998	0.76	0.12	2.40	0.03	0.00	26	4	81	1	0
1999	0.55	2.89	2.38	0.09	0.17	19	101	82	3	6
2000	0.90	3.64	2.13	0.12	0.21	32	130	72	4	7
2001	1.06	4.71	1.92	0.20	0.42	38	173	67	7	15
2002	0.63	6.13	2.72	0.08	0.37	24	231	97	3	14
2003	0.83	5.83	2.84	0.02	0.36	32	223	103	1	13
2004	0.85	6.14	2.12	0.13	0.29	32	240	76	4	10
2005	0.79	5.58	2.45	0.15	0.22	30	228	89	5	8
2006	0.51	5.52	2.62	0.08	0.15	21	233	98	3	6
2007	0.52	7.91	1.66	0.00	0.08	22	348	63	0	3
2008	0.96	7.81	1.49	0.00	0.06	42	357	60	0	2
2009	0.80	8.83	1.49	0.06	0.05	35	405	62	2	2
2010	0.86	8.38	1.62	0.03	0.11	37	400	66	1	5
2011	0.59	8.74	1.33	0.03	0.07	26	425	58	2	3
2012	0.75	8.80	1.94	0.03	0.11	35	434	81	1	4
2013	0.57	10.52	1.63	0.02	0.15	26	543	70	1	6

Table 56. Age adjusted mortality rates for HIV and HCV, Oregon and U.S., 1999–2013

Year	OR HCV	US HCV	OR HIV/HCV	OR HIV
1999	2.89	3.00	0.17	2.38
2000	3.64	3.10	0.21	2.13
2001	4.71	3.30	0.42	1.92
2002	6.13	3.70	0.37	2.72
2003	5.83	3.70	0.36	2.84
2004	6.14	3.71	0.29	2.12
2005	5.58	3.80	0.22	2.45
2006	5.52	4.35	0.15	2.62
2007	7.91	4.58	0.08	1.66
2008	7.81	4.66	0.06	1.49
2009	8.83	4.70	0.05	1.49
2010	8.38	4.65	0.11	1.62
2011	8.74	4.82	0.07	1.33
2012	8.80		0.11	1.94
2013	10.52		0.15	1.63

Sources

Ly, KN, et al.[8];

Centers for Disease Control and Prevention (CDC). Number and rate of deaths with hepatitis C listed as a cause of death, U.S., 2007–2011. Retrieved May 1, 2015, from www.cdc.gov/hepatitis/Statistics/2012Surveillance/Table4.4.htm;

CDC. Number and rate of deaths with hepatitis C listed as a cause of death, U.S., 2009–2013. Retrieved May 1, 2015, from www.cdc.gov/hepatitis/Statistics/2013Surveillance/Table4.5.htm.

Mortality rates were calculated by taking the number of contributing causes of deaths for the specific disease or combination of diseases (HBV, HCV or HIV) and dividing by the Oregon population for the same time period (2009–2013), and then multiplying 100,000 to get the crude rate. The crude rate for each age group was then multiplied by a population weight in order to adjust the distribution of deaths to that of the standard U.S. population in 2000 (Direct Method).

Table 57. HBV Deaths by age, sex, race and ethnicity, 2009–2013

		Deaths		
		Count	Percent	Rate per 100,000
Sex	Female	31	19%	0.3
	Male	128	81%	1.1
Age group*	<1	0	0%	0.0
	1–4	0	0%	0.0
	5–14	0	0%	0.0
	15–24	0	0%	0.0
	25–34	3	2%	0.1
	35–44	18	11%	0.7
	45–54	45	28%	1.7
	55–64	58	36%	2.2
	65–74	22	14%	1.4
	75–84	11	7%	1.3
	85+	2	1%	0.5
Hispanic	Not Hispanic	149	94%	0.7
	Hispanic	10	6%	0.8
Race	White	107	70%	0.5
	Black	7	5%	1.8
	American Indian/Alaska Native	4	3%	1.5
	Asian/PI	35	23%	4.5
Total		**159**	**100%**	**0.7**

Table 58. HCV deaths by age, sex, race and ethnicity, 2009–2013

		Deaths		
		Count	Percent	Rate per 100,000
Sex	Female	639	29%	5.5
	Male	1,568	71%	12.6
Age group*	<1	0	0%	0.0
	1–4	0	0%	0.0
	5–14	0	0%	0.0
	15–24	1	0%	0.0
	25–34	14	1%	0.5
	35–44	86	4%	3.4
	45–54	585	27%	22.1
	55–64	1,165	53%	44.7
	65–74	264	12%	16.9
	75–84	74	3%	8.8
	85+	18	1%	4.5
Hispanic	Not Hispanic	2,115	96%	9.2
	Hispanic	92	4%	7.8
Race	White	2,018	93%	8.9
	Black	56	3%	16.1
	American Indian/Alaska Native	64	3%	17.4
	Asian/PI	38	2%	5.9
Total		**2,207**	**100%**	**9.1**

Source: Oregon Vital Statistics (exported June 2, 2014), NCHS intercensal population estimates (June 26, 2014).
Rates for sex, race and ethnicity are age-adjusted; age groups are crude rates.

Table 59. Mortality from HBV by county, Oregon, 2009–2013

	NCHS population estimates					HBV counts				
County	2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Baker	16,097	16,093	16,040	15,909	16,018	1	0	0	0	0
Benton	82,806	85,531	86,006	86,430	86,591	0	1	0	0	0
Clackamas	384,852	377,001	379,984	383,857	388,263	1	1	3	2	0
Clatsop	37,170	37,073	37,171	37,301	37,244	1	0	0	0	0
Columbia	49,557	49,339	49,357	49,286	49,344	0	0	0	0	0
Coos	62,683	63,053	62,795	62,534	62,282	0	2	0	2	0
Crook	22,623	20,896	20,662	20,729	20,815	0	1	1	0	0
Curry	21,165	22,364	22,462	22,248	22,339	0	0	0	0	0
Deschutes	158,532	157,895	160,083	162,277	165,954	0	1	1	0	1
Douglas	103,065	107,696	107,400	107,164	106,940	1	0	1	0	3
Gilliam	1,637	1,871	1,953	1,953	1,947	0	0	0	0	0
Grant	6,817	7,452	7,410	7,317	7,283	0	0	0	0	0
Harney	6,691	7,409	7,368	7,212	7,146	0	0	0	0	0
Hood River	21,916	22,435	22,414	22,584	22,675	0	1	0	0	0
Jackson	201,248	203,474	204,718	206,412	208,545	1	1	0	2	2
Jefferson	19,996	21,680	21,686	21,749	21,145	1	1	0	0	0
Josephine	80,982	82,865	82,680	82,930	83,306	0	1	0	0	0
Klamath	66,227	66,349	66,296	65,912	65,910	1	1	0	0	0
Lake	7,043	7,875	7,920	7,771	7,820	0	0	0	0	0
Lane	350,209	351,921	353,481	354,542	356,212	5	6	2	4	1
Lincoln	46,227	46,022	45,885	46,151	46,350	1	1	1	1	2
Linn	116,392	116,894	118,135	118,360	118,765	3	0	1	2	0
Malheur	30,721	31,322	30,757	30,630	30,479	0	1	0	0	0
Marion	317,192	316,025	317,826	319,985	323,614	2	3	2	3	4
Morrow	11,480	11,202	11,181	11,244	11,336	0	0	0	1	0
Multnomah	727,990	737,492	748,091	759,256	766,135	14	8	10	11	6
Polk	77,846	75,612	75,996	76,353	76,794	1	2	0	2	1
Sherman	1,709	1,770	1,734	1,732	1,731	0	0	0	0	1
Tillamook	24,899	25,265	25,389	25,287	25,317	0	0	0	0	0
Umatilla	73,525	76,054	76,668	76,820	76,720	0	0	1	1	0
Union	25,285	25,761	25,775	25,759	25,652	0	0	0	0	0
Wallowa	6,848	7,025	6,995	6,821	6,814	0	0	0	0	0
Wasco	24,098	25,254	25,228	25,487	25,477	0	0	0	0	1
Washington	536,920	531,440	539,464	547,672	554,996	2	4	3	4	4
Wheeler	1,375	1,447	1,419	1,424	1,381	0	0	0	0	0
Yamhill	99,235	99,355	99,800	100,255	100,725	0	1	0	0	0

Table 59 continued on next page

Table 59, continued

	HBV rates/100,000 population					NCHS	County	HBV Rate/100,000
County	2009	2010	2011	2012	2013	5-year average	5-year average	5-year average
Baker	6.21	0.00	0.00	0.00	0.00	16,031	0.2	1.25
Benton	0.00	1.17	0.00	0.00	0.00	85,473	0.2	0.23
Clackamas	0.26	0.27	0.79	0.52	0.00	382,791	1.4	0.37
Clatsop	2.69	0.00	0.00	0.00	0.00	37,192	0.2	0.54
Columbia	0.00	0.00	0.00	0.00	0.00	49,377	0.0	0.00
Coos	0.00	3.17	0.00	3.20	0.00	62,669	0.8	1.28
Crook	0.00	4.79	4.84	0.00	0.00	21,145	0.4	1.89
Curry	0.00	0.00	0.00	0.00	0.00	22,116	0.0	0.00
Deschutes	0.00	0.63	0.62	0.00	0.60	160,948	0.6	0.37
Douglas	0.97	0.00	0.93	0.00	2.81	106,453	1.0	0.94
Gilliam	0.00	0.00	0.00	0.00	0.00	1,872	0.0	0.00
Grant	0.00	0.00	0.00	0.00	0.00	7,256	0.0	0.00
Harney	0.00	0.00	0.00	0.00	0.00	7,165	0.0	0.00
Hood River	0.00	4.46	0.00	0.00	0.00	22,405	0.2	0.89
Jackson	0.50	0.49	0.00	0.97	0.96	204,879	1.2	0.59
Jefferson	5.00	4.61	0.00	0.00	0.00	21,251	0.4	1.88
Josephine	0.00	1.21	0.00	0.00	0.00	82,553	0.2	0.24
Klamath	1.51	1.51	0.00	0.00	0.00	66,139	0.4	0.60
Lake	0.00	0.00	0.00	0.00	0.00	7,686	0.0	0.00
Lane	1.43	1.70	0.57	1.13	0.28	353,273	3.6	1.02
Lincoln	2.16	2.17	2.18	2.17	4.31	46,127	1.2	2.60
Linn	2.58	0.00	0.85	1.69	0.00	117,709	1.2	1.02
Malheur	0.00	3.19	0.00	0.00	0.00	30,782	0.2	0.65
Marion	0.63	0.95	0.63	0.94	1.24	318,928	2.8	0.88
Morrow	0.00	0.00	0.00	8.89	0.00	11,289	0.2	1.77
Multnomah	1.92	1.08	1.34	1.45	0.78	747,793	9.8	1.31
Polk	1.28	2.65	0.00	2.62	1.30	76,520	1.2	1.57
Sherman	0.00	0.00	0.00	0.00	57.77	1,735	0.2	11.53
Tillamook	0.00	0.00	0.00	0.00	0.00	25,231	0.0	0.00
Umatilla	0.00	0.00	1.30	1.30	0.00	75,957	0.4	0.53
Union	0.00	0.00	0.00	0.00	0.00	25,646	0.0	0.00
Wallowa	0.00	0.00	0.00	0.00	0.00	6,901	0.0	0.00
Wasco	0.00	0.00	0.00	0.00	3.93	25,109	0.2	0.80
Washington	0.37	0.75	0.56	0.73	0.72	542,098	3.4	0.63
Wheeler	0.00	0.00	0.00	0.00	0.00	1,409	0.0	0.00
Yamhill	0.00	1.01	0.00	0.00	0.00	99,874	0.2	0.20

Table 60. Mortality from HCV by county, Oregon, 2009–2013

	NCHS population estimates					HCV counts				
County	2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Baker	16,097	16,093	16,040	15,909	16,018	2	1	0	1	3
Benton	82,806	85,531	86,006	86,430	86,591	9	7	5	3	1
Clackamas	384,852	377,001	379,984	383,857	388,263	27	30	26	33	41
Clatsop	37,170	37,073	37,171	37,301	37,244	5	7	4	7	9
Columbia	49,557	49,339	49,357	49,286	49,344	7	6	5	2	7
Coos	62,683	63,053	62,795	62,534	62,282	9	5	15	16	16
Crook	22,623	20,896	20,662	20,729	20,815	1	3	2	2	4
Curry	21,165	22,364	22,462	22,248	22,339	2	5	3	2	6
Deschutes	158,532	157,895	160,083	162,277	165,954	9	9	12	9	26
Douglas	103,065	107,696	107,400	107,164	106,940	22	25	28	25	26
Gilliam	1,637	1,871	1,953	1,953	1,947	0	0	1	0	0
Grant	6,817	7,452	7,410	7,317	7,283	1	0	0	2	2
Harney	6,691	7,409	7,368	7,212	7,146	1	0	1	0	0
Hood River	21,916	22,435	22,414	22,584	22,675	1	1	0	0	2
Jackson	201,248	203,474	204,718	206,412	208,545	23	25	22	27	45
Jefferson	19,996	21,680	21,686	21,749	21,145	4	3	2	1	3
Josephine	80,982	82,865	82,680	82,930	83,306	24	9	23	15	23
Klamath	66,227	66,349	66,296	65,912	65,910	9	9	7	8	8
Lake	7,043	7,875	7,920	7,771	7,820	2	1	0	1	1
Lane	350,209	351,921	353,481	354,542	356,212	40	43	53	57	72
Lincoln	46,227	46,022	45,885	46,151	46,350	8	6	12	7	17
Linn	116,392	116,894	118,135	118,360	118,765	16	16	13	20	11
Malheur	30,721	31,322	30,757	30,630	30,479	2	4	5	3	0
Marion	317,192	316,025	317,826	319,985	323,614	38	36	38	44	37
Morrow	11,480	11,202	11,181	11,244	11,336	0	0	2	1	1
Multnomah	727,990	737,492	748,091	759,256	766,135	91	94	95	92	115
Polk	77,846	75,612	75,996	76,353	76,794	5	6	8	3	9
Sherman	1,709	1,770	1,734	1,732	1,731	0	1	0	0	2
Tillamook	24,899	25,265	25,389	25,287	25,317	5	0	3	1	5
Umatilla	73,525	76,054	76,668	76,820	76,720	6	6	8	6	8
Union	25,285	25,761	25,775	25,759	25,652	2	1	3	3	4
Wallowa	6,848	7,025	6,995	6,821	6,814	0	2	1	0	0
Wasco	24,098	25,254	25,228	25,487	25,477	4	2	6	9	3
Washington	536,920	531,440	539,464	547,672	554,996	21	29	15	26	31
Wheeler	1,375	1,447	1,419	1,424	1,381	0	0	0	1	0
Yamhill	99,235	99,355	99,800	100,255	100,725	9	8	7	7	5

Table 60 continued on next page

Table 60, continued

	HCV rates/100,000 population					NCHS	County	HCV rate/100,000
County	2009	2010	2011	2012	2013	5-year average	5-year average	5-year average
Baker	12.42	6.21	0.00	6.29	18.73	16,031	1.4	8.73
Benton	10.87	8.18	5.81	3.47	1.15	85,473	5.0	5.85
Clackamas	7.02	7.96	6.84	8.60	10.56	382,791	31.4	8.20
Clatsop	13.45	18.88	10.76	18.77	24.16	37,192	6.4	17.21
Columbia	14.13	12.16	10.13	4.06	14.19	49,377	5.4	10.94
Coos	14.36	7.93	23.89	25.59	25.69	62,669	12.2	19.47
Crook	4.42	14.36	9.68	9.65	19.22	21,145	2.4	11.35
Curry	9.45	22.36	13.36	8.99	26.86	22,116	3.6	16.28
Deschutes	5.68	5.70	7.50	5.55	15.67	160,948	13.0	8.08
Douglas	21.35	23.21	26.07	23.33	24.31	106,453	25.2	23.67
Gilliam	0.00	0.00	51.20	0.00	0.00	1,872	0.2	10.68
Grant	14.67	0.00	0.00	27.33	27.46	7,256	1.0	13.78
Harney	14.95	0.00	13.57	0.00	0.00	7,165	0.4	5.58
Hood River	4.56	4.46	0.00	0.00	8.82	22,405	0.8	3.57
Jackson	11.43	12.29	10.75	13.08	21.58	204,879	28.4	13.86
Jefferson	20.00	13.84	9.22	4.60	14.19	21,251	2.6	12.23
Josephine	29.64	10.86	27.82	18.09	27.61	82,553	18.8	22.77
Klamath	13.59	13.56	10.56	12.14	12.14	66,139	8.2	12.40
Lake	28.40	12.70	0.00	12.87	12.79	7,686	1.0	13.01
Lane	11.42	12.22	14.99	16.08	20.21	353,273	53.0	15.00
Lincoln	17.31	13.04	26.15	15.17	36.68	46,127	10.0	21.68
Linn	13.75	13.69	11.00	16.90	9.26	117,709	15.2	12.91
Malheur	6.51	12.77	16.26	9.79	0.00	30,782	2.8	9.10
Marion	11.98	11.39	11.96	13.75	11.43	318,928	38.6	12.10
Morrow	0.00	0.00	17.89	8.89	8.82	11,289	0.8	7.09
Multnomah	12.50	12.75	12.70	12.12	15.01	747,793	97.4	13.02
Polk	6.42	7.94	10.53	3.93	11.72	76,520	6.2	8.10
Sherman	0.00	56.50	0.00	0.00	115.54	1,735	0.6	34.58
Tillamook	20.08	0.00	11.82	3.95	19.75	25,231	2.8	11.10
Umatilla	8.16	7.89	10.43	7.81	10.43	75,957	6.8	8.95
Union	7.91	3.88	11.64	11.65	15.59	25,646	2.6	10.14
Wallowa	0.00	28.47	14.30	0.00	0.00	6,901	0.6	8.69
Wasco	16.60	7.92	23.78	35.31	11.78	25,109	4.8	19.12
Washington	3.91	5.46	2.78	4.75	5.59	542,098	24.4	4.50
Wheeler	0.00	0.00	0.00	70.22	0.00	1,409	0.2	14.19
Yamhill	9.07	8.05	7.01	6.98	4.96	99,874	7.2	7.21

Table 61. Leading underlying causes of death among deaths with HBV as multiple cause of death, Oregon 2009–2013

ICD10	Count	Percent	Name
C220	36	22.6%	Liver cell carcinoma
B169	27	17.0%	Acute hepatitis B without delta agent and without hepatic coma
B181	12	7.5%	Chronic viral hepatitis B without delta agent
C229	5	3.1%	Malignant neoplasm of liver, not specified as primary or secondary
C349	4	2.5%	Malignant neoplasm of unspecified part of bronchus or lung
F102	4	2.5%	Alcohol dependence
K703	4	2.5%	Alcoholic cirrhosis of liver
K709	4	2.5%	Alcoholic liver disease, unspecified
X42	4	2.5%	Accidental poisoning by and exposure to narcotics and psychodysleptics
B182	3	1.9%	Chronic viral hepatitis C
J449	3	1.9%	Chronic obstructive pulmonary disease, unspecified
K746	3	1.9%	Other and unspecified cirrhosis of liver
X44	3	1.9%	Accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances
Other	47	29.6%	Misc.
Total	**159**	**100.0%**	

Table 62. Leading underlying causes of death among deaths with HCV as multiple cause of death, Oregon 2009–2013

ICD10	Count	Percent	Name
B182	885	40.1%	Chronic viral hepatitis C
C220	293	13.3%	Liver cell carcinoma
K703	140	6.3%	Alcoholic cirrhosis of liver
C229	96	4.3%	Malignant neoplasm of liver, not specified as primary or secondary
J449	40	1.8%	Chronic obstructive pulmonary disease unspecified
X42	39	1.8%	Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified
K746	34	1.5%	Other and unspecified cirrhosis of liver
K709	33	1.5%	Alcoholic liver disease, unspecified
K704	32	1.4%	Alcoholic hepatic failure
C349	31	1.4%	Malignant neoplasm of unspecified part of bronchus or lung
I251	29	1.3%	Atherosclerotic cardiovascular disease
C80	20	0.9%	Malignant neoplasm without specification of site
Other	535	24.2%	Misc.
Total	**2,207**	**100.0%**	

Table 63. High Risk Adult Screening Project, 2007–2013

Source: Oregon High Risk Adult Screening Project, July 2014

HCV screening results by age, Oregon High Risk Adult Screening Project, 2007–2013					
	HCV test result				
Age group	**Negative**	**Positive**	**Total**	**Total (%)**	**Positive (%)**
0–12	2	0	2	0%	0%
13–19	202	12	214	5%	6%
20–24	753	67	820	21%	8%
25–29	754	69	823	21%	8%
30–34	547	94	641	16%	15%
35–39	376	100	476	12%	21%
40–44	267	102	369	9%	28%
45–49	218	88	306	8%	29%
50–54	109	70	179	4%	39%
55–59	68	36	104	3%	35%
60–64	34	5	39	1%	13%
65+	18	1	19	0%	5%
Total	**3,348**	**644**	**3,992**	**100%**	**16%**

Note: 3,992/4,027 (99.1%) data available

HCV screening results by sex, Oregon High Risk Adult Screening Project, 2007–2013					
	HCV test result				
Sex	**Negative**	**Positive**	**Total**	**Total (%)**	**Positive (%)**
Female	1,415	279	1,694	42%	16%
Male	1,965	368	2,333	58%	16%
Total	**3,380**	**647**	**4,027**	**100%**	**16%**

Note: 4,027/4,027 (100%) data available

HCV screening results by race, Oregon High Risk Adult Screening Project, 2007–2013					
	HCV test result				
Race	**Negative**	**Positive**	**Total**	**Total (%)**	**Positive (%)**
AI/AN	91	18	109	3%	17%
Asian	18	3	21	1%	14%
Black	46	10	56	1%	18%
Mixed	37	6	43	1%	14%
NH/PI	20	3	23	1%	13%
Other	40	7	47	1%	15%
Refused	6	0	6	0%	0%
White	2,985	570	3,555	92%	16%
Multiracial	1	1	2	0%	50%
Total	**3,244**	**618**	**3,862**	**100%**	**16%**

Note: 3,862/4,027 (95.9%) data available

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Table 63, continued

HCV screening results by ethnicity, Oregon High Risk Adult Screening Project, 2007–2013					
HCV Test Result					
Hispanic	**Negative**	**Positive**	**Total**	**Total (%)**	**Positive (%)**
Yes	254	43	297	8%	14%
No	2,820	542	3,362	92%	16%
Total	**3,074**	**585**	**3,659**	**100%**	**16%**

Note: 3,659/4,027 (90.9%) data available

Table 64. High Risk Adult Screening Project, 2007–2013

Source: Oregon High Risk Adult Screening Project, July 2014/missing and unknown values removed

		HCV test result				
Risk questions		**Negative**	**Positive**	**Total**	**Total (%)**	**Positive (%)**
Transfusion	No	3,135	581	3,716	97%	16%
	Yes	87	34	121	3%	28%
	Subtotal	**3,222**	**615**	**3,837**	**100%**	**16%**
	Note: 3,837/4,027 (95.3%) data available					
Inject drugs not prescribed (ever)	No	1,068	34	1,102	28%	3%
	Yes	2,263	610	2,873	72%	21%
	Subtotal	**3,331**	**644**	**3,975**	**100%**	**16%**
	Note: 3,975/4,027 (98.7%) data available					
	If yes, primary drug injected					
	Miscellaneous	1	0	1	0%	0%
	Cocaine	38	24	62	2%	39%
	Heroin	454	129	583	21%	22%
	Methamphetamine/speed	1,631	430	2,061	74%	21%
	Other	58	13	71	3%	18%
	Prefer to not disclose	1	0	1	0%	0%
	Speedball	15	4	19	1%	21%
	Subtotal	**2,198**	**600**	**2,798**	**100%**	**21%**
	Note: 2,798/2,873 (97.4%) data available					
Incarcerated	No	1,110	87	1,197	32%	7%
	Yes	2,070	532	2,602	68%	20%
	Subtotal	**3,180**	**619**	**3,799**	**100%**	**16%**
	Note: 3,799/4,027 (94.3%) data available					
Medical employment	No	2,749	547	3,296	90%	17%
	Yes	331	49	380	10%	13%
	Subtotal	**3,080**	**596**	**3,676**	**100%**	**16%**

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Table 64, continued

Risk questions		HCV test result				
		Negative	Positive	Total	Total (%)	Positive (%)
	Note: 3,676/4,027 (91.3%) data available					
Ever an STD	No	2,056	381	2,437	66%	16%
	Yes	1,051	217	1,268	34%	17%
	Subtotal	**3,107**	**598**	**3,705**	**100%**	**16%**
	Note: 3,705/4,027 (76.5%) data available					
Current IDU	Current IDU (injected ≤ 3 yrs)	1,662	438	2,100	85%	21%
	Previous IDU (injected > 3 yrs)	275	92	367	15%	25%
	Subtotal	**1,937**	**530**	**2,467**	**100%**	**21%**
	Note: 3,551/4,027 (88.2%) data available; "Not IDU" was not shown n= 1,084					
Sex contact with hepatitis	No	580	125	705	43%	18%
	Yes	720	230	950	57%	24%
	Subtotal	**1,300**	**355**	**1,655**	**100%**	**21%**
	Note: 1,655/2,195 (75.4%) data available					
Household contact with hepatitis	No	436	129	565	33%	23%
	Yes	931	215	1,146	67%	19%
	Subtotal	**1,367**	**344**	**1,711**	**100%**	**20%**
	Note: 1,711/2,195 (77.9%) data available					
Needle contact with hepatitis	No	524	80	604	50%	13%
	Yes	424	175	599	50%	29%
	Subtotal	**948**	**255**	**1,203**	**100%**	**21%**
	Note: 1,203/2,195 (54.8%) data available					
Tested in jail (asked 2012–2013 only)	No	950	127	1,077	81%	12%
	Yes	227	28	255	19%	11%
	Subtotal	**1,177**	**155**	**1,332**	**100%**	**12%**

Table 65. Current injection drug users in the High Risk Adult Screening Project, 2007–2013

Source: Oregon High Risk Adult Screening Project, July 2014; current use is defined as having injected in the three years prior to the HCV test.

Not IDU, previous IDU and other (internally inconsistent or missing/unknown values) were excluded below; n = 2,100

Age	Negative	Positive	Total	Total (%)	HCV positive (%)
0–12	1	0	1	0%	0%
13–19	116	10	126	6%	8%
20–24	440	54	494	24%	11%
25–29	406	54	460	22%	12%
30–34	293	76	369	18%	21%
35–39	188	77	265	13%	29%
40–44	112	66	178	9%	37%
45–49	49	47	96	5%	49%
50–54	24	33	57	3%	58%
55–59	18	17	35	2%	49%
60–64	0	3	3	0%	100%
65+	0	0	0	0%	0%
Total	**1,647**	**437**	**2,084**	**100%**	**21%**

Note: 2,084/2,100 (99.2%) data available

Birth cohort (born 1945–1965)	Negative	Positive	Total	Total (%)	HCV positive (%)
Birth cohort	94	107	201	10%	53%
Before/after birth cohort	1,553	330	1,883	90%	18%
Total	**1,647**	**437**	**2,084**	**100%**	**21%**

*2,084/2,100 (99.2%) data available

Sex	Negative	Positive	Total	Total (%)	HCV positive (%)
Female	727	197	924	44%	21%
Male	935	241	1,176	56%	20%
Total	**1,662**	**438**	**2,100**	**100%**	**21%**

Note: 2,100/2,100 (100%) data available

Race	Negative	Positive	Total	Total (%)	HCV positive (%)
AI/AN	41	11	52	2%	21%
Asian	4	3	7	0%	43%
Black	15	6	21	1%	29%
NH/PI	9	3	12	1%	25%
White	1,500	383	1,883	90%	20%
Other	37	11	48	2%	23%
Total	**1,662**	**438**	**2,100**	**100%**	**21%**

Note: 2,100/2,100 (100%) data available

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Table 65, continued

Hispanic	Negative	Positive	Total	Total (%)	HCV positive (%)
No	1,415	374	1,789	94%	21%
Yes	93	27	120	6%	23%
Total	**1,508**	**401**	**1,909**	**100%**	**21%**

Note: 1,909/2,100 (90.9%) data available

Testing setting (2012–2013)	Negative	Positive	Total	Total (%)	HCV positive (%)
Health department or other setting	290	47	337	61%	14%
Jail	114	20	134	24%	15%
Needle exchange site	64	13	77	14%	17%
Total	**468**	**80**	**548**	**100%**	**15%**

Note: 548/662 (82.8%) data available

Drug of choice	Negative	Positive	Total	Total (%)	HCV positive (%)
Cocaine	15	6	21	1%	29%
Heroin	357	104	461	22%	23%
Methamphetamine/ speed	1,212	317	1,529	74%	21%
Speedball	12	3	15	1%	20%
Other	35	4	39	2%	10%
Total	**1,631**	**434**	**2,065**	**100%**	**21%**

Note: 2,065/2,100 (98.3%) data available

County	Negative	Positive	Total	Total (%)	HCV positive (%)
Baker	6	2	8	0%	25%
Benton	59	17	76	4%	22%
Clackamas	4	0	4	0%	0%
Clatsop	16	4	20	1%	20%
Coos	7	3	10	0%	30%
Crook	1	1	2	0%	50%
Deschutes	288	55	343	16%	16%
Douglas	172	51	223	11%	23%
Hood River	1	0	1	0%	0%
Jackson	181	38	219	10%	17%
Josephine	5	1	6	0%	17%
Klamath	49	9	58	3%	16%
Lake	0	1	1	0%	100%
Lane	325	145	470	22%	31%

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Table 65, continued

County	Negative	Positive	Total	Total (%)	HCV positive (%)
Lincoln	10	3	13	1%	23%
Linn	129	27	156	7%	17%
Malheur	1	0	1	0%	0%
Marion	300	59	359	17%	16%
Multnomah	1	0	1	0%	0%
Tillamook	2	0	2	0%	0%
Umatilla	72	17	89	4%	19%
Wasco	31	5	36	2%	14%
Total	**1,660**	**438**	**2,098**	**100%**	**21%**

Note: 2,098/2,100 (99.9%) data available

Sex contact	Negative	Positive	Total	Total (%)	HCV positive (%)
No	533	119	652	54%	18%
Yes	393	166	559	46%	30%
Total	**926**	**285**	**1,211**	**100%**	**24%**

Note: 1,211/2,100 (57.7%) data available

Household contact	Negative	Positive	Total	Total (%)	HCV positive (%)
No	474	109	583	46%	19%
Yes	498	174	672	54%	26%
Total	**972**	**283**	**1,255**	**100%**	**23%**

Note: 1,255/2,100 (59.8%) data available

Needle contact	Negative	Positive	Total	Total (%)	HCV positive (%)
No	428	70	498	50%	14%
Yes	348	142	490	50%	29%
Total	**776**	**212**	**988**	**100%**	**21%**

Note: 988/2,100 (47.0%) data available

Table 66. Oregon Department of Corrections screening data, 2009–2012

	2009				2010			
Test	**Total tests**	**Negatives**	**Positives**	**% positive**	**Total tests**	**Negatives**	**Positives**	**% positive**
HBsAg *	2,244	2,209	35	1.6%	1,967	1,937	30	1.5%
HBsAb **	2,211	982	1,229	55.6%	1,940	906	1,034	53.3%
Anti-HCV	2,260	1,730	530	23.5%	2,001	1,501	500	25.0%

	2011				2012			
Test	**Total tests**	**Negatives**	**Positives**	**% positive**	**Total tests**	**Negatives**	**Positives**	**% positive**
HBsAg *	2,085	2,052	33	1.6%	2,523	2,490	33	1.3%
HBsAb **	2,055	1,029	1,026	49.9%	2,673	1,273	1,400	52.4%
Anti-HCV	2,335	1,909	426	18.2%	2,706	2,207	499	18.4%

* Presence of hepatitis B surface antigen indicates presence of chronic infection with HBV

** Presence of hepatitis B surface antibody indicates either past history of infection or immunization with HBV vaccine

Table 67. Deschutes County Jail Screening Program, 2011–2012

Ever Screened for HCV — yes			
Number of times detained	**Count**	**Percent**	**Total count**
1st time	2	25	8
2–5 times	15	42	36
6 or more times	36	54	67
Total	**53**	**48**	**111**

Note: 111/137=81% data available

Ever Screened for HCV — yes			
Ever incerated at ODOC facility	**Count**	**Percent**	**Total count**
Yes	31	69	45
No	21	32	65
Total	**52**	**47**	**110**

Note: 110/137=81% data available

Ever Screened for HCV — yes			
Age group	**Count**	**Percent**	**Total count**
<20	1	50	2
20–29	24	39	61
30–39	21	75	28
40–49	6	33	18
50–59	2	40	5
60 plus	1	50	2
Total	**55**	**47**	**116**

Note: 116/137=85% data available

Glossary

ACDP: Acute and Communicable Disease Prevention

ACIP: Advisory Committee on Immunization Practices

AI/AN: American Indians and Alaska Natives

ALT: Alanine aminotransferase levels

AMH: Addictions and Mental Health Division

CBOs: Community-based organizations

CDC: Centers for Disease Control and Prevention

DAAs: Direct-acting antivirals

DCC: Decompensated cirrhosis

ESLD: End-stage liver disease

HAV: Hepatitis A virus

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HCC: Hepatocellular carcinoma

HIV: Human immunodeficiency virus

IDU: Injection drug use

MAP: Medical Assistance Programs

MSM: Men who have sex with men

NNDS: National Notifiable Diseases Surveillance System

ODOC: Oregon Department of Corrections

OHA: Oregon Health Authority

OHSU: Oregon Health & Science University

PIs: Pacific Islanders

PIFN: Pegylated interferon

PWIDs: Persons who inject drugs

QALY: Quality-adjusted life year

RNA: Ribonucleic acid

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Viral Hepatitis in Oregon

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OHA 8598 (06/2015)

Abstract ID: 93 **Day / Time:** Sunday, Nov 15, 5:15 PM – 5:30 PM

Effectiveness of Ledipasvir/Sofosbuvir in Treatment Naïve Genotype 1 Patients Treated in Routine Medical Practice

Category: Hepatitis C

Descriptor: FO5. Therapeutics: Approved Agents

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Aim: Assess the effectiveness of ledipasvir/sofosbuvir±ribavirin (LDV/SOF±RBV) in treatment naïve genotype 1 (GT1) hepatitis C virus (HCV)-infected veterans treated in routine medical practice.

Methods: This observational, intent-to-treat cohort analysis used the Veterans Affairs' Clinical Case Registry to identify all treatment naïve GT1 HCV-infected veterans initiating 8 or 12 weeks of LDV/SOF±RBV by 31 December 2014. Patients were excluded for liver transplantation or baseline HCV RNA<1000 IU/mL. Undetectable (UD) rates at the end of treatment (EOT) were determined from the HCV RNA results on or after the EOT with data available through 3 May 2015. Veterans without an EOT test who were UD on the most recent test prior to the EOT were considered EOT UD. EOT UD rates of those on LDV/SOF and LDV/SOF+RBV were compared with Chi-Square. Multivariate models of EOT UD included age, sex, race/ethnicity, cirrhosis by ICD-9, diabetes, HIV, baseline HCV RNA, genotype subtype and regimen.

Results: In total, 569 treatment naïve GT1 veterans initiated LDV/SOF±RBV; 524 LDV/SOF and 45 LDV/SOF+RBV. The mean age was 61.2 years, 95% were male, 32% were black, 32% had cirrhosis. Patients receiving LDV/SOF+RBV were more likely to have cirrhosis than patients receiving LDV/SOF (73.3% vs 28.4%, p<0.001). At the time of this abstract, 93.3% (531/569) of all patients were EOT UD; the remaining 38 patients were considered treatment failures with HCV RNA detectable after EOT (n=17), no EOT test and HCV RNA detectable on their last on treatment test (n=17) or died <12 weeks after EOT (n=4). Among patients who received LDV/SOF, cirrhotics had lower EOT UD rates than non-cirrhotics (88.6% (132/149) vs. 94.7% (355/375), p=0.02); EOT UD rates were 97.0% (32/33) in cirrhotic patients receiving LDV/SOF+RBV. Among non-cirrhotics with baseline HCV RNA<6,000,000 IU/ml receiving LDV/SOF±RBV, EOT UD rates were 93.2% (110/118) for those who completed 8 weeks of therapy and 96.6% (172/178) for those who completed 12 weeks of therapy (p=0.28). In multivariate models, patients were less likely to achieve EOT UD with cirrhosis (OR 0.48, 95%CI 0.23-0.99, p=0.04).

Conclusions: In this large real-world cohort, treatment naïve GT1 HCV-infected patients had very high EOT UD rates with LDV/SOF±RBV. Non-cirrhotics with HCV RNA<6,000,000 IU/mL were as likely to achieve EOT UD with 8 weeks as 12 weeks of therapy. Patients with cirrhosis were significantly less likely to achieve EOT UD. SVR data for the cohort will be presented.

Disclosures: Lisa Backus: No conflict of interest; Pamela Belperio: No conflict of interest; Troy Shahoumian: No Answer.; Timothy Loomis: No conflict of interest; Larry Mole: No conflict of interest

Abstract ID: 94 **Day / Time:** Sunday, Nov 15, 5:30 PM – 5:45 PM

Treatment Outcomes With 8, 12 and 24 Week Regimens of Ledipasvir/Sofosbuvir for the Treatment of Hepatitis C Infection: Analysis of a Multicenter Prospective, Observational Study

Category: Hepatitis C

Descriptor: FO5. Therapeutics: Approved Agents

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Background and Aims: The real-world safety and efficacy of ledipasvir/sofosbuvir (LDV/SOF) in clinical clinical practice has not been reported. The aim of this study is to evaluate the safety and efficacy of LDV/SOF containing regimens for the treatment of patients (pts) in HCV-TARGET, a multicenter, prospective, observational cohort study.

Methods: Patients who initiated HCV treatment in clinical practice were enrolled and treated according to the local standards of care at academic (n=38) and community medical centers (n=13) in North America (n=47) and Europe (n=4). Information was collected from the medical records and abstracted into a unique centralized data core. Independent data monitors systematically review data entries for completeness and accuracy. Demographic, clinical, adverse events (AEs) and virological data are collected throughout treatment and post-treatment follow-up.

Results: To date, 1628 pts have initiated LDV/SOF-based therapy in HCV-TARGET; 181 patients have an intended regimen LDV/SOF for 8 wks, 799 for 12 wks, and 433 for 24 wks. Demographics include 61% male, mean age of 60 yrs (age >65, 25%), 20% Black, 96% G1 (67% G1a, 26% 1b, 7% G1nos), 42% had evidence of cirrhosis (18% prior or current decompensation), 3% had HIV co-infection, and 11% had received a liver transplant. 53% of pts had received prior HCV therapy, with 15% of these having failed a prior DAA-based regimen. 42% of patients were receiving acid suppression medication during therapy. Treatment regimen: 87% of G1, naïve, noncirrhotic patients had a baseline HCV RNA <6 million IU/mL; 35% of these received an 8-wk regimen. 215 patients are receiving RBV plus LDV/SOF and were more likely to be treatment experienced (68%), have cirrhosis (57%, with half having history of decompensation), or a liver transplant (40%). Efficacy: 466 have completed treatment in the 8 and 12 weeks groups. The SVR4 for the combined 8 and 12 week regimens was 96% (148/154); 8-wk regimen 97.8% (43/44) for 12-wk regimen 95.5% (105/110). Safety: Adverse events

were reported in 56% of pts (headache in 20%, fatigue 18%, nausea 8%, diarrhea 6%, and insomnia 6%), 27 SAEs were reported, 0.9% had premature d/c of therapy (none in 8 wk regimen), and 5 patient deaths were reported (4 in 12-wk and 1 in 24-wk regimens). Complete safety data for the cohort and updated SVR data for the 8, 12 and 24 regimens will be presented.

Conclusions: Preliminary safety and efficacy data from HCV-TARGET suggests that LDV/SOF-containing 8 and 12-wk treatment regimens are generally safe, well tolerated, and highly effective across a broad spectrum of patients and clinical practices.

Sponsored by: HCV-TARGET is funded in part by AbbVie, BristolMyers Squibb, Gilead, Janssen, Kadmon, and Merck.

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Effectiveness of 12 or 24 week LDV/SOF and 12 week LDV/SOF + RBV in treatment-experienced patients with cirrhotic, genotype 1 Hepatitis C: Real-world experience from the TRIO Network.

Category: Hepatitis C

Descriptor: FO5. Therapeutics: Approved Agents

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Background: The current recommendations for treatment of cirrhosis in HCV genotype 1 patients are dependent on prior treatment. 12 week ledipasvir/sofosbuvir (LDV/SOF) is recommended in treatment-naïve patients whereas 24 week LDV/SOF is recommended for prior treatment failures. In addition, 12 week LDV/SOF + RBV has been suggested as an alternative to 24 week LDV/SOF for treatment failures (Bourlière M, et al. Abs #82, AASLD 2014). No data is really available comparing these regimens in real-world patients that previously failed treatment. AIM: To evaluate real-world SVR12 in treatment failure patients with HCV genotype 1 and cirrhosis treated with 12 or 24 weeks of LDV/SOF or 12 weeks of LDV/SOF + RBV.

Methods: Data were obtained through Trio Health's Innervation Platform, a cloud-based disease management platform, and directly from specialty pharmacies for 250 treatment-experienced, genotype 1 patients with cirrhosis that initiated LDV/SOF ± RBV between Oct 2014 and Mar 2015. 20% (50/250) of the patients were treated in community practices with the remainder from academic centers.

Results: Patient demographics for 3 groups are shown in the table. Intended treatments were: 21% (52/250 patients) 12 week LDV/SOF, 72% (180/250) 24 week LDV/SOF and 7% (18/250) 12 week LDV/SOF + RBV. SUMMARY: An examination of a real-world heterogeneous Hepatitis C population revealed a preference for 24 week LDV/SOF in this sample of treatment-experienced patients with cirrhotic genotype 1 HCV. The use of 12 week LDV/SOF + RBV is minimal, suggesting that RBV was viewed as an unnecessary addition to the shorter duration course, though subsequent analyses may find a shift in preferences. SVR data on this population will be available at the meeting.

Baseline Characteristics	12 wk LDV/SOF	24 wk LDV/SOF	12 wk LDV/SOF + RBV	Total
Patient no.	52	180	18	250
Age – mean (range)	62 (42-82)	60 (27-87)	57 (40-67)	60 (27-87)
Age >=65 - no. (%)	14 (27%)	38 (21%)	1 (6%)	53 (21%)
Male - no. (%)	28 (54%)	124 (69%)	11 (61%)	163 (65%)

Black - no. (%)	11 (21%)	20 (11%)	0	31 (12%)
ALT - mean (s.d.)	82 (83)	84 (58)	77 (39)	83 (63)
AST - mean (s.d.)	83 (72)	83 (50)	79 (34)	83 (54)
HCV RNA >=6MM IU/ml - no. (%)	9 (17%)	26 (14%)	3 (17%)	38 (15%)
Genotype 1A - no. (%)	40 (77%)	132 (73%)	14 (78%)	186 (74%)
Prior Null Responder	24 (46%)	76 (42%)	5 (28%)	105 (42%)
Prior Responder/Relapse	14 (27%)	82 (46%)	12 (67%)	108 (43%)
Prior BOC or TVR	12 (23%)	60 (33%)	5 (28%)	77 (31%)
Prior SOF	8 (15%)	23 (13%)	6 (33%)	37 (15%)

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Annals of Internal Medicine

MEDICINE AND PUBLIC ISSUES

Restrictions for Medicaid Reimbursement of Sofosbuvir for the Treatment of Hepatitis C Virus Infection in the United States

Soumitri Barua; Robert Greenwald, JD; Jason Grebely, PhD; Gregory J. Dore, MBBS, PhD; Tracy Swan; and Lynn E. Taylor, MD

The aim of this study was to systematically evaluate state Medicaid policies for the treatment of hepatitis C virus (HCV) infection with sofosbuvir in the United States. Medicaid reimbursement criteria for sofosbuvir were evaluated in all 50 states and the District of Columbia. The authors searched state Medicaid Web sites between 23 June and 7 December 2014 and extracted data in duplicate. Any differences were resolved by consensus. Data extracted were whether sofosbuvir was covered and criteria for coverage based on the following categories: liver disease stage, HIV co-infection, prescriber type, and drug or alcohol use. Of the 42 states with known Medicaid reimbursement criteria for sofosbuvir, 74% limit sofosbuvir access to persons with advanced fibrosis (Meta-Analysis of Histologic Data in Viral Hepatitis [METAVIR] fibrosis stage F3) or cirrhosis (F4). One quarter of states require persons co-infected with HCV and HIV to be receiving antiretroviral therapy or to have suppressed HIV RNA levels. Two thirds of states have restrictions based on prescriber type, and 88% include drug or alcohol use in their sofosbuvir eligibility criteria, with 50% requiring a period of abstinence and 64% requiring urine drug screening. Heterogeneity is present in Medicaid reimbursement criteria for sofosbuvir with respect to liver disease staging, HIV co-infection, prescriber type, and drug or alcohol use across the United States. Restrictions do not seem to conform with recommendations from professional organizations, such as the Infectious Diseases Society of America and the American Association for the Study of Liver Diseases. Current restrictions seem to violate federal Medicaid law, which requires states to cover drugs consistent with their U.S. Food and Drug Administration labels.

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Highly effective (cure rate >90%), once-daily, oral interferon-free treatments with minimal adverse effects are now available for hepatitis C virus (HCV) infection. Worldwide, an estimated 80 to 150 million persons have chronic HCV (1, 2). If left untreated, chronic HCV can lead to cirrhosis, liver failure, and hepatocellular carcinoma (HCC) (3, 4). Rates of advanced liver disease complications, associated health care costs, and liver disease–related mortality are rising worldwide (3, 4). Regimens for treating HCV seem to be curative and reduce liver-related and all-cause mortality (5). Uptake of HCV treatment has been low in many settings (6–8) in part because of the poor tolerability of interferon-based regimens. Widespread access to interferon-free regimens has the potential to greatly affect HCV morbidity and mortality.

Sofosbuvir, a pan-genotypic nucleotide analogue NS5B polymerase inhibitor indicated for treatment of chronic HCV in combination with other direct-acting antivirals (DAAs), was approved by the U.S. Food and Drug Administration (FDA) on 6 December 2013. Sofosbuvir is the first DAA indicated for use as part of an interferon-free regimen. Compared with interferon-based therapy, sofosbuvir-based interferon-free regimens show response rates greater than 90%, shortened treatment duration (8 to 12 weeks), and improved tolerability and safety (although with some combinations, lower responses are seen in persons with more advanced disease and certain HCV genotypes) (9–14).

The wholesale acquisition cost of sofosbuvir is $1000 per day (equating to $84 000 for a 12-week course) and must be used with 1 or more medications at additional cost. A fixed-dose, single-tablet combination of sofosbuvir and ledipasvir (an NS5A inhibitor) is now available at a wholesale acquisition cost of $1125 per day ($63 000, $94 500, and $189 000 for an 8-, 12-, and 24-week course, respectively). The high price of these regimens and high demand (actual or anticipated) for them has led payers to institute restrictions on their access, although by law, Medicaid programs are entitled to a rebate of at least 23% (15, 16). Although some payers have negotiated ample rebates, they have not altered their reimbursement restrictions.

Further complicating matters is the fact that different federal standards apply depending on whether a beneficiary is eligible under "traditional" Medicaid or is "newly eligible" for Medicaid in 1 of the 28 states that have implemented the Patient Protection and Affordable Care Act Medicaid expansion provision (16). Within the 51 fee-for-service Medicaid programs, there are also different programs and requirements for different populations and different models of care financing and delivery (for example, fee-for-service and managed care organizations). For the purposes of this article, we have focused on state fee-for-service programs and not managed care. Because our focus here is on clinical factors, detailed legal analysis of the many complex Medicaid program rules is beyond the scope of this article.

In the United States, a disproportionate number of persons living with HCV have low income (17). For purposes of this article, "low income" means having income at or below the highest state Medicaid eligibility limit for parents of dependent children. Currently, the state with the highest Medicaid income eligibility limit is Connecticut at 201% of the federal poverty level. Further, the 2015 federal poverty level for a single person in all states except Alaska and Hawaii is $11 770; 201% equals $23 658 (18). Most persons are eligible for reimbursement of HCV therapy through Medicaid, which is the jointly funded federal and state partnership that

provides health insurance for low-income persons meeting the program's eligibility criteria. Each state has wide discretion in administering its own Medicaid program. Although this creates unique Medicaid programs in each state, states must follow some federal standards (16). These include covering all FDA-approved drugs, consistent with FDA labeling, whose manufacturers participate in Medicaid's prescription drug rebate program (19), and not discriminating in drug coverage—thus a state "may not arbitrarily deny or reduce the amount, duration, or scope of a required service . . . to an otherwise eligible beneficiary solely because of the diagnosis, type of illness, or condition" (20).

In 2014, the American Association for the Study of Liver Disease and the Infectious Diseases Society of America (AASLD/IDSA) issued recommendations (21) for testing, managing, and treating HCV (which are updated regularly). Little is known about the consistency in applying these guidelines by state Medicaid committees to reimbursement criteria for sofosbuvir. The aim of this study was to systematically evaluate state Medicaid policies for the reimbursement of sofosbuvir for HCV treatment in the United States.

METHODS

We evaluated Medicaid reimbursement criteria for sofosbuvir for all 50 states and the District of Columbia. We searched state Medicaid Web sites between 23 June and 7 December 2014. Locating criteria for coverage was difficult. Each state has different means of organizing Medicaid information online, no consistent word search was able to locate each policy, and each state required a different process to find the appropriate policies or forms. As such, this search was confined to online information. When state policy was unclear, and when states did not operate a fee-for-service pharmacy program, we indicated that the state criteria and policies were unknown. Only states with fee-for-service programs were included.

Data were extracted by 2 coauthors in duplicate and entered into a standardized spreadsheet; 2 different coauthors crosschecked the extracted data. Any differences were resolved by consensus. Each entry was double-checked by another coauthor to ascertain accuracy. For each state, the following data were extracted from Medicaid reimbursement criteria: whether sofosbuvir was covered (paid for by Medicaid) and the criteria for coverage. Most Medicaid programs require preapproval of certain medications before a patient may receive them, and providers must complete this prior authorization. For each state, Medicaid prior authorization criteria for sofosbuvir were also extracted, where available. The date of the state Medicaid reimbursement publication and uniform resource locators of the prior authorization and the preferred drug list were recorded and entered into a database (Microsoft Excel, version 14.4.4 [Microsoft]).

Criteria for sofosbuvir coverage based on the following categories were recorded: liver disease stage, HIV co-infection, prescriber type, and drug or alcohol use. For criteria about liver disease staging, data were collected on the level of fibrosis required for reimbursement (either none indicated, Meta-Analysis of Histologic Data in Viral Hepatitis [METAVIR] fibrosis stage F2 or higher, or F3 or F4), eligibility for persons with decompensated cirrhosis, and whether a liver biopsy was mandatory to provide evidence of advanced fibrosis. For criteria about HIV co-infection, data were collected on whether HIV status needed to be documented, and if positive, whether the patient had to be receiving antiretroviral therapy (ART) or have suppressed HIV RNA levels. For prescriber type, data were collected on whether the prescriber had to be a specialist (gastroenterology, hepatology, infectious diseases, or liver transplantation) or whether treatment decisions needed to be made in consultation with a specialist. For criteria about drug or alcohol use, data were collected on whether there were any substance-related access criteria, and if so, whether drug or alcohol counseling was required, whether patients had to be evaluated for drug and/or alcohol dependence, whether a period of abstinence was required (1, 3, 6, or 12 months) before sofosbuvir therapy, and whether drug or alcohol testing and/or treatment was required before sofosbuvir therapy.

RESULTS

Overall, 42 states (82%), including the District of Columbia, had publicly available information about Medicaid reimbursement criteria for sofosbuvir (**Tables 1** and **2** and **Figures 1** and **2**). Nevada is the only state that does not require prior authorization for sofosbuvir. Nine states have unknown criteria, with neither the prior authorization nor eligibility information publicly available.

Of the 42 states, including the District of Columbia, with known Medicaid reimbursement criteria for sofosbuvir, 81% (n = 34) restrict sofosbuvir reimbursement on the basis of liver disease stage (**Table 1**). In 4 states (10%), reimbursement is restricted to only persons with cirrhosis (F4). In two thirds of states (n = 27), sofosbuvir reimbursement is restricted to persons with advanced fibrosis (F3) or cirrhosis (F4). In 2 states (5%) and 1 state (2%), reimbursement is also provided for those with moderate (F2) and mild (F1) fibrosis, respectively. In the remaining states, no reimbursement criteria are based on disease stage (n = 8 [19%]). Sofosbuvir use is restricted in persons with decompensated cirrhosis in 7 states (17%). Colorado is the only state that explicitly includes persons with decompensated cirrhosis. Liver biopsy staging is required for demonstrating cirrhosis in 5 states (12%), although Arkansas also requires a liver biopsy for evidence of bridging fibrosis (F3). In Tennessee, a liver biopsy or transient elastography are the only options allowed to demonstrate cirrhosis.

Nineteen states (45%) require information about HIV status. Ten (24%) require that patients be receiving ART or have evidence of HIV virologic suppression.

Twenty-nine states (69%) have restrictions based on prescriber type. In 14 states (33%), the prescriber

Table 1. U.S. State Eligibility/Ineligibility Criteria for Sofosbuvir Approval*

Requirement	States, *n*	States
Fibrosis†		
None indicated	8	Alabama, Massachusetts, Minnesota, Mississippi, North Carolina, Nevada, Utah, and Wyoming
Minimum stage F2	3	Maryland, Maine‡, and Oklahoma
Minimum stage F3–F4	31	Alaska; Arkansas; Arizona; California; Colorado; Connecticut§; Washington, DC; Delaware§; Florida; Iowa; Idaho; Illinois§; Indiana; Kentucky; Louisiana; Missouri; Montana; Nebraska; New Hampshire; New York; Ohio; Oregon§; Pennsylvania; Rhode Island; South Dakota; Tennessee; Virginia; Vermont; Washington; Wisconsin; and West Virginia
Decompensated cirrhosis‖		
Ineligible	7	Alaska; Washington, DC¶; Idaho; Kentucky; Oklahoma; Tennessee; and Washington
Eligible	1	Colorado
Mandatory liver biopsy to prove cirrhosis		
Liver biopsy	5	Alaska**, Arkansas, Iowa, Louisiana††, and Nebraska
Liver biopsy or elastography	1	Tennessee‡‡
HIV co-infection		
Requests documentation of HIV status	19	Alaska; Alabama; Arizona; California; Washington, DC; Delaware; Florida; Louisiana; Massachusetts; Maryland; Nebraska; New Hampshire; New York; Ohio; Oregon; South Carolina; Vermont; Wisconsin; and West Virginia
If HIV co-infection, the patient must be receiving ART or have a controlled viral load	10	Alaska§§; Alabama§§; Arizona§§; California§§; Washington, DC; Delaware§§; Florida§§; Maryland§§; New York; and West Virginia§§
Prescriber limitations		
Must be a hepatologist, gastroenterologist, or infectious diseases or liver transplantation physician	14	Florida, Iowa, Indiana, Louisiana, Maryland, Maine, New Hampshire, New York, Ohio, Pennsylvania, Rhode Island‖‖, Tennessee¶¶, Wisconsin, and Washington***
By or in consultation with one of these physicians	15	Arizona; California; Colorado; Connecticut; Washington, DC; Idaho; Illinois†††; Kentucky; Mississippi; Montana; Oklahoma; Oregon; South Dakota; Virginia; and West Virginia
None indicated	13	Alabama, Alaska, Arkansas, Delaware, Iowa, Massachusetts, Missouri, Nebraska, Nevada, North Carolina, Minnesota, Utah, and Wyoming
Prior authorization		
Unknown information on prior authorization	9	Georgia, Hawaii, Kansas, Michigan, New Jersey, North Dakota, New Mexico, South Carolina, and Texas
State without this requirement	1	Nevada

ART = antiretroviral therapy.
* When states are not included in a category, it is not certain whether they are providing or denying access to sofosbuvir on the basis of that limitation, only that there is not a written rule in their publicly reported policy.
† Meta-analysis of Histologic Data in Viral Hepatitis (METAVIR) fibrosis stage (F0–F4).
‡ F1.
§ Must be F4.
‖ Defined as a Child-Pugh score >6 (class B or C).
¶ If HIV co-infection.
** For F3.
†† For genotypes 2 and 3.
‡‡ Only 2 options given for proving cirrhosis.
§§ Requires either HIV viral load (copies/mL) or $CD4^+$ cell count ($\times 10^9$ cells/L).
‖‖ Other prescribers may request designation as an approved prescriber upon submission of a written request supporting this capability.
¶¶ Must have state Medicaid provider identification.
*** State Medicaid provider identification or prescriber is participating in and/or consults with Project Extension for Community Healthcare Outcomes (22).
††† Only first prescription needs consultation.

has to be a specialist (gastroenterology, hepatology, infectious diseases, or liver transplantation), whereas in 15 states (36%), treatment decisions can be made by a nonspecialist after consultation with a specialist.

Of the 42 states, including the District of Columbia, with known Medicaid reimbursement criteria for sofosbuvir, 88% of states (*n* = 37) include drug or alcohol use in their eligibility criteria for sofosbuvir reimbursement. Eight states (19%) require that all patients be evaluated for substance use disorder or alcohol dependence, and 50% of states (*n* = 21) require a period of abstinence from drugs or alcohol use or abuse for all patients (**Table 2**). An additional 9 states (21%) require abstinence only for patients with a history of substance abuse. Most states require that all patients, regardless of history, abstain from drug and alcohol use for 6 months (*n* = 11), whereas others require abstinence periods of 1 month (*n* = 2), 3 months (*n* = 5), or 12 months (*n* = 2). Most states (*n* = 27 [64%]) require urine drug screening before treatment to assess drug or alcohol use, with

Table 2. U.S. State Substance Use–Related Requirements for Sofosbuvir Approval*

Requirements Related to Substance Use	States, *n*	States
Unknown†	9	Georgia, Hawaii, Kansas, Michigan, New Jersey, North Dakota, New Mexico, South Carolina, and Texas
Inquires or has criteria related to substance use or abuse‡	37	All except Connecticut, Indiana, Nevada, Minnesota, and Utah
Requires counseling about abstention or effects of alcohol or drugs	6	Colorado; Maine; Mississippi; West Virginia; Washington, DC; and Montana
Requires all patients to be evaluated for a substance use disorder and/or alcohol dependence	8	California, Nebraska, Tennessee, Kentucky, New York, Vermont, Virginia, and Ohio
Requires a period of abstinence from drugs and/or alcohol use or abuse before treatment for all patients, regardless of history		
Time unknown	1	Ohio§
1 mo	2	Florida and Wyoming
3 mo	5	Alaska; Washington, DC; Delaware; Iowa; and Missouri
6 mo	11	Kentucky, Mississippi, Pennsylvania, South Dakota, West Virginia, Oregon, Alabama, Colorado, Wisconsin, Montana, and Oklahoma
12 mo	2	Louisiana‖ and Illinois
Requires a period of abstinence from drug and/or alcohol use or abuse only for persons with any history of abuse (past or recent) before HCV treatment		
3 mo	1	Washington¶
6 mo	8	Arizona**, California, Idaho, Washington**, Maryland, Nebraska, Tennessee, and Rhode Island
"Commitment to abstinence"	1	North Carolina††
Asks about or requires substance or alcohol use disorder treatment for persons with a history of abuse	17	Arkansas, California, Florida, Kentucky, Maryland, New Hampshire, Nebraska, North Carolina††, Pennsylvania, Rhode Island, Tennessee, Virginia, Washington, Montana, Wisconsin, Massachusetts, and Vermont
Allows persons to bypass abstinence or recent abuse if in treatment	6	California, Florida, Maryland, Nebraska, Rhode Island, and Washington‡‡
Requires persons with a history to be in, or have completed, treatment	3	Tennessee, Kentucky, and Virginia
Requires drug or alcohol testing before treatment		
For everyone	21	Alaska; California; Colorado; Washington, DC; Delaware; Florida; Hawaii; Illinois; Iowa; Kentucky; Louisiana; Missouri§§; Nebraska; New Hampshire; New York; Tennessee; Virginia; West Virginia; Wyoming; Oklahoma; and Vermont
Only for those with a history of abuse	6	Pennsylvania, Mississippi‖‖, Arizona¶¶, Idaho***, Louisiana***, and Colorado†††
Prior authorization form inquires about alcohol or substance use or abuse, but no particular requirements are apparent	4	Massachusetts, New York, New Hampshire, and Arkansas

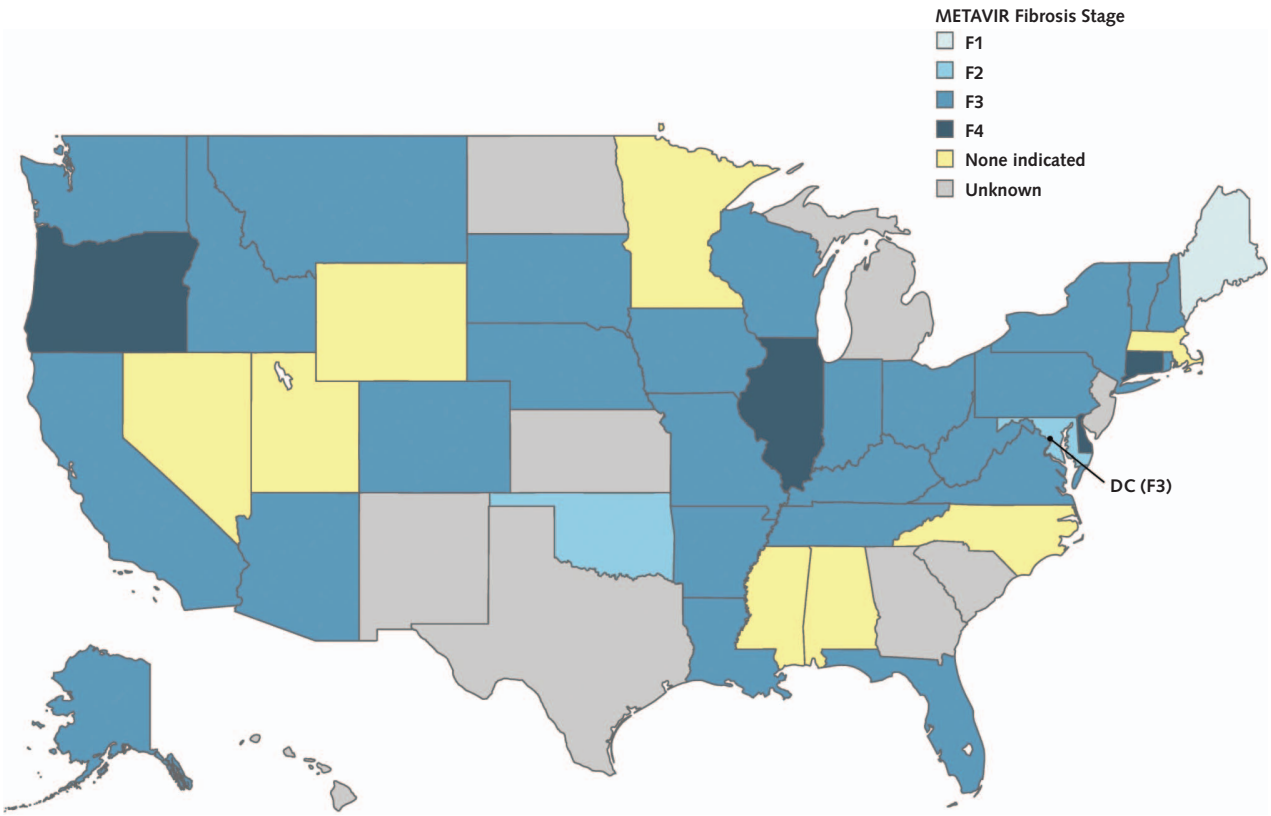
HCV = hepatitis C virus.
* When states are not included in a category, it is not certain whether they are providing or denying access to sofosbuvir on the basis of that limitation, only that there is not a written rule in their publicly reported policy.
† No prior authorization or criteria available.
‡ Some states in their abstention policies (either generally or for persons with past or current substance use) explicitly state that persons must refrain from alcohol or drug *abuse*, whereas others are more broad in requiring that persons abstain from alcohol or drug *use*.
§ Requires screening for and maintenance of sobriety before and during treatment.
‖ Illinois does not specifically reference a period of abstinence but instead broadly requires that a person "not have evidence of substance abuse diagnosis or treatment" in the past 12 mo. It is also the only state to include a long list of data sources that will be used for verification, including but not limited to medical record entries, the state's narcotic prescription registry database, reports from a hospital, and/or records of an emergency department visit.
¶ If in treatment, must have been in remission for 3 mo.
** Must have been in remission for 6 mo.
†† Alcohol only.
‡‡ If participating in treatment, abstinence requirement decreases to 3 mo.
§§ Within each of 3 previous mo.
‖‖ Injection drug use only.
¶¶ Random drug screens during treatment.
*** Monthly during treatment.
††† Routine during treatment.

only 6 (14%) requiring testing specifically for persons with previous drug or alcohol abuse. Six states permit persons enrolled in addiction treatment to bypass abstinence requirements. Further, 6 states require drug and alcohol counseling. Overall, 69% of states (*n* = 29) had restrictions based on advanced liver disease and drug or alcohol use criteria, 5% (*n* = 2) had restrictions based only on advanced liver disease, 19% (*n* = 8) had restrictions based only on drug or alcohol use criteria, and 7% (*n* = 3) had no restrictions on advanced liver disease nor drug or alcohol use criteria.

DISCUSSION

Considerable heterogeneity is present in Medicaid reimbursement criteria for sofosbuvir across the United States. Restrictions based on liver disease severity are common, with three quarters of states restricting sofos-

Figure 1. Medicaid reimbursement criteria for sofosbuvir based on documented level of liver fibrosis stage required for reimbursement.



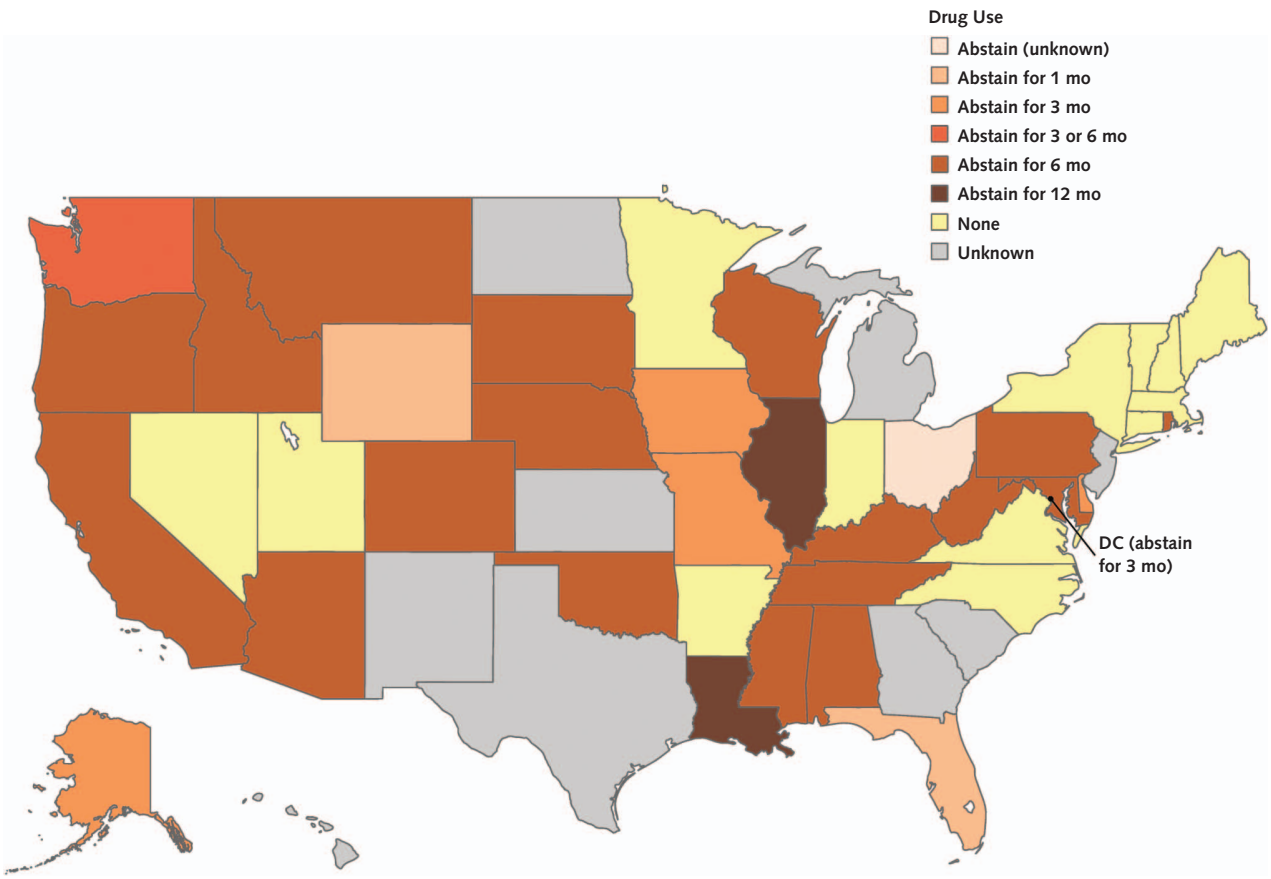
METAVIR = Meta-Analysis of Histologic Data in Viral Hepatitis.

buvir to persons with advanced fibrosis (F3) or cirrhosis (F4). One quarter of states require that persons living with HIV be receiving ART or have suppressed HIV RNA levels, whereas two thirds restrict sofosbuvir on the basis of prescriber type. Drug or alcohol use is included in the eligibility criteria of 88% of state Medicaid committees, with half requiring a period of abstinence and two thirds requiring urine drug screening. The restrictions are not consistent with the FDA-approved labeling for sofosbuvir or evidence-based recommendations and should be reconsidered (23).

Most states restrict sofosbuvir reimbursement to persons with advanced fibrosis (F3) or cirrhosis (F4), which is inconsistent with recent AASLD/IDSA recommendations (20). These recommendations state that HCV treatment is indicated for all patients with chronic HCV (regardless of disease stage) because HCV therapy is curative; improves quality of life; slows liver disease progression; and reduces the risk for cirrhosis, end-stage liver disease, HCC, and all-cause mortality (21). The recommendations state that patients at highest priority for immediate treatment include those with advanced fibrosis (F3) or compensated cirrhosis (F4) because of the higher risk for severe complications (for example, hepatic decompensation or HCC). Patients with fibrosis (F2) are listed in the next priority group for treatment because of their high risk for complications (21). However, most states do not include persons with fibrosis (F2) in their Medicaid reimbursement criteria. Note that persons with advanced fibrosis remain at risk for HCC even after achieving sustained virologic response (SVR) and must have long-term surveillance (24). In contrast, once HCV is cured in persons with mild to moderate liver disease, liver disease progression is rare. Requiring liver biopsy may pose the highest risk for death in HCV care with all-oral regimens.

The requirement that HIV-infected persons be receiving ART or have suppressed HIV RNA levels is also inconsistent with AASLD/IDSA recommendations indicating that persons co-infected with HIV and HCV are also at high priority for treatment because of their high risk for complications (21). HIV accelerates the HCV disease course, with faster progression to cirrhosis, liver failure, and increased HCV-related mortality (25–27). The safety and efficacy of sofosbuvir-based, interferon-free combination therapy for co-infected persons is similar to results among those with HCV monoinfection (21, 28, 29). Reasons are varied about why co-infected persons may not be receiving ART (for example, normal $CD4^+$ T-cell counts and low HIV RNA levels) or have suppressed HIV RNA levels (for example, drug-resistant HIV). Physicians who treat such co-infected persons

Figure 2. Medicaid reimbursement criteria for sofosbuvir based on the required period of abstinence from drug and alcohol use.



may prefer to commence and complete HCV treatment first, before ART initiation, because HCV therapy is brief; further, DAA therapy often limits what antiretrovirals can be used concomitantly because of drug–drug interactions.

Two thirds of states have restrictions based on physician type, which is inconsistent with current practice whereby internists, other primary care physicians, HIV physicians not trained as infectious diseases specialists, nurse practitioners, and physician assistants treat HCV with pegylated interferon and ribavirin. The availability of sofosbuvir-based, interferon-free regimens simplifies therapy and reduces treatment-associated toxicities, which offers an opportunity for an expanded provider base for HCV treatment in patients without advanced cirrhosis (30).

The overwhelming majority of states restrict access to sofosbuvir for persons who inject drugs (PWID), those receiving treatment for drug dependency (for example, opioid substitution therapy), and those drinking alcohol. Most new and existing cases of HCV in the United States exist among current or former PWID (31). Since 2002, the National Institutes of Health HCV guidelines support HCV treatment regardless of injection drug use (32), and the AASLD/IDSA, European Association for the Study of the Liver, International Network on Hepatitis in Substance Users, and World Health Organization all advocate for inclusion of persons who use drugs in HCV treatment (21, 33–35). A growing body of evidence shows that there is no justification for systematically withholding HCV treatment from PWID (21, 33, 36). The SVR rates are similar in PWID with or without opiate replacement therapy (21, 33, 36–39). Drug use in the 6 months preceding HCV therapy initiation is not necessarily associated with poorer response to HCV therapy (40–42). Reported rates of reinfection after SVR among PWID are low—generally a 1% to 5% risk per year, although concerns about reinfection rates in other subpopulations, such as surgeons, do not garner similar attention (33, 43). Rather than recommending the exclusion of PWID, AASLD/IDSA guidelines include PWID with earlier liver disease stages among a second-order priority group because of the prevention benefit of potential treatment; HCV treatment among PWID may decrease HCV transmission (21). In addition, evidence shows that HCV treatment of current and former PWID is cost-effective, particularly when the prevention benefits are consid-

ered (44). Further, Medicaid does not similarly deny medications for other diseases to persons who use or have used drugs or alcohol.

Alcohol misuse and HCV infection frequently coexist (45–48). Hepatitis C virus and alcohol act synergistically in causing more severe liver injury than seen with either disease alone (4, 48, 49). Persons with coexisting alcohol disorders are at a higher risk for HCV-related complications (4, 48, 49). Curing HCV is easier than curing alcohol disorders because pharmacotherapy for alcohol misuse is limited, and behavioral interventions are not always successful. The SVR rates are similar in drinkers and nondrinkers (49, 50).Further, the AASLD/IDSA recommendations have no HCV treatment restrictions regarding alcohol use.

This study examined criteria in Medicaid fee-for-service programs only—not in Medicaid managed care organizations. Results therefore reflect a subset of overall state Medicaid reimbursement criteria for sofosbuvir rather than a comprehensive catalog of all restrictions in state Medicaid programs. Future research on reimbursement criteria in Medicaid managed care organizations will be important to develop a more thorough understanding of Medicaid enrollees' access to sofosbuvir.

Current restrictions may violate federal Medicaid law, which requires states to cover drugs consistent with their FDA labels. Under the federal Medicaid statute, virtually all drugs from pharmaceutical manufacturers that have rebate agreements with the Secretary of Health and Human Services (which includes the manufacturer of sofosbuvir) must be available under state Medicaid programs, with only limited methods of restricting coverage (19). None of the restrictions on sofosbuvir coverage detailed here seem to meet the criteria for permissible restrictions. Although the price of new therapies creates financial challenges for federal and state Medicaid budgets, decisions for prioritizing patients for more immediate therapy should be based on clinical criteria and medical evidence. It is recommended that the restrictions be removed; apart from potentially being a human rights violation, they do not make (economic) sense in terms of clinical, public, and long-term health. In setting restrictions as a concession to economic constraints, the significant longer-term public health and economic benefits of curing HCV should be considered and weighed against the upfront treatment costs.

Concerns include that full coverage for HCV treatment could, in the short term, mean less coverage for other conditions. It is unrealistic, however, to expect that all potential candidates will immediately seek HCV treatment. One example of this is Massachusetts. Despite relatively unrestricted sofosbuvir access in its Medicaid fee-for-service program, recent data indicate that only 14% of Massachusetts Medicaid enrollees known to be diagnosed with HCV are engaged in treatment (22, 51).

Transparent, easily accessible, consistent, and evidence-based Medicaid criteria will permit greater and more equitable access to DAAs. As the HCV standard of care changes over time, it will be inefficient and costly to have differing treatment access protocols in the 51 fee-for-service programs and many more Medicaid managed care plans, with all of them being revised over time. More consistency is needed across the system so that where a Medicaid patient lives does not dictate what treatment she or he receives. Although this study examined sofosbuvir in particular, the first FDA-approved DAA as part of an interferon-free regimen, Medicaid may be setting a precedent as new DAAs are approved. Medicaid policies should be responsive to changes in standards of care and new treatment developments. State Medicaid pharmacy and therapeutics committees (or their equivalent) are generally responsible for implementing these policy changes and should be expected to act as expeditiously as possible to ensure that significant clinical changes are addressed in state Medicaid programs. These data suggest that state Medicaid policies for access to new DAAs should be reviewed and revised in line with national clinical recommendations.

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Note: Dr. Taylor and Mr. Greenwald had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Taylor affirms that she has listed everyone who contributed significantly to the work. There was no involvement of any pharmaceutical company or commercial entity in the preparation of this work.

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Annals of Internal Medicine

IDEAS AND OPINIONS

Limited Access to New Hepatitis C Virus Treatment Under State Medicaid Programs

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The burden of fatal liver disease is increasing in the estimated 3.2 million adults chronically infected with hepatitis C virus (HCV) in the United States (1–3). Sofosbuvir (Sovaldi, Gilead Sciences), which was approved by the U.S. Food and Drug Administration in December 2013, is a new oral HCV treatment that, when combined with other therapies, has a therapeutic efficacy (cure) greater than 90% across the 4 major HCV genotypes, limited adverse effects, and a shorter treatment window (usually 12 weeks) than its interferon-based predecessors (4). However, this drug currently retails at $84 000 per patient, forcing many payers to ration this lifesaving treatment. As such, Medicaid programs, which cover approximately 25% of patients with HCV infection who are hospitalized but have limited budgets, face the challenge of deciding who should receive new, costly treatments (4, 5).

To understand policies that might affect patient access to new HCV therapies, we obtained preferred drug lists and prior authorization criteria from state Medicaid fee-for-service program Web sites and, when these were unavailable, elicited feedback from Medicaid programs through direct communication. We compared the guidelines used by state Medicaid programs with those published by the Infectious Diseases Society of America (IDSA) and the American Association for the Study of Liver Diseases (AASLD) (www.hcvguidelines.org). On the basis of data collected from May through November 2014, Medicaid programs in 31 states had designated sofosbuvir a "nonpreferred" drug, the prescription of which requires that clinicians provide evidence of medical necessity as defined by state-specific laws. Seventeen states applied a "preferred" designation, and although demonstrated medical necessity is not necessarily required in these states, all but 2 required clinicians to seek "prior authorization" for sofosbuvir prescription (**Table**).

Approval criteria vary widely by state, but most programs require scoring of liver fibrosis for sofosbuvir approval. Per IDSA/AASLD guidelines, treatment is of "highest priority" for persons with METAVIR fibrosis scores of F3 or F4 and "high priority" for those with a score of F2. In 33 state Medicaid programs, patients must have a score of F3 or F4, indicative of severe liver disease, to receive treatment with sofosbuvir. Of note, 4 states require liver biopsy to prove the level of fibrosis rather than allowing for the use of less invasive blood or imaging tests. Many state Medicaid programs limit treatment to patients at the most immediate risk for death from liver disease.

Newer HCV therapies have been hailed by the IDSA and the AASLD for their improved simplicity and safety compared with older, interferon-based treatments; thus, nonspecialist physicians, rather than a limited number of specialists, may be able to manage treatment for most HCV-infected persons (that is, nonrelapsing patients without serious comorbid conditions). However, 30 states require that sofosbuvir be prescribed by, or in consultation with, a specialist—usually a hepatologist, gastroenterologist, or infectious disease physician. The extent to which finding a specialist who accepts Medicaid may pose a barrier to HCV treatment remains unclear, although some Medicaid directors reported concern for patients living in rural areas. The IDSA/AASLD guidelines recommend collaboration with specialists (through the use of telemedicine, if needed) for treatment management when primary care physicians have limited experience.

Many prior authorization criteria require abstinence from the use of alcohol, illicit drugs, or both in the months leading up to treatment approval (ranging from 1 to 12 months before treatment for both). Thirty-five states require that patients abstain from alcohol use or abuse, and 30 states require abstinence from any illicit drug use before treatment approval. An additional 4 states require abstinence only from injection drug use.

Drug screens may further stigmatize a key population at risk for HCV infection that already faces substantial barriers to care despite its demonstrably similar adherence to HCV treatment compared with that of the general population (6). The IDSA/AASLD guidelines recommend that patients abstain from alcohol and drug use but do not suggest that treatment be withheld. Rather, they recommend that patients be provided with counseling and education and simpler and less toxic regimens, such as the newer sofosbuvir-based therapies, and receive referrals for psychiatric and opioid substitution therapies. In fact, the guidelines highlight the public health benefit of treating persons likely to transmit infection to others, such as those who inject drugs.

Additional hurdles not outlined here include denial of prescription based on parameters of HIV co-infection (such as a minimum $CD4^+$ cell count and maximum viral load and demonstrated stable HIV treatment), requirements of weekly refills, the investigation of prior pharmacy refill records to estimate patient adherence, and the use of nonvalidated standardized tests to assess "patient readiness." Some states also allow prescribing physicians to subjectively rate patients' likelihood of completing treatment.

A major limitation is that this review did not include criteria for Medicaid managed care organizations,

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Table. Prior Authorization Criteria for Sofosbuvir Prescription Under State Medicaid Fee-for-Service Programs

State	Status	Abstain From Alcohol Use Before Treatment	Abstain From Alcohol Abuse Before Treatment	Abstain From Drug Use Before Treatment	Abstain From Injection Drug Use Before Treatment	Minimum METAVIR Fibrosis Score	Specialist Prescriber
Alabama	NP	✓	✓	✓	✓	F2	–
Alaska	NP	✓	✓	✓	✓	F3*	–
Arizona	NP	–	✓	✓	✓	F3	✓
Arkansas	NP	–	✓	–	✓	F3*	–
California	NP	–	–	–	–	F3	–
Colorado	NP	–	✓	✓	✓	F3	✓
Connecticut	P†	–	–	–	–	–	–
Delaware	NP	✓	✓	✓	✓	F4	–
District of Columbia	NP	✓	✓	✓	✓	F2	✓
Florida	NP	✓	✓	✓	✓	F3	✓
Georgia	NP	–	–	–	–	F3	–
Hawaii	P	–	✓	✓	✓	F3	✓
Idaho	NP	–	✓	–	✓	F3	✓
Illinois	NP	✓	✓	✓	✓	F4	✓
Indiana	NP	–	–	–	–	F4	✓
Iowa	NP	✓	✓	✓	✓	F3*	✓
Kansas	NP	–	✓	✓	✓	F3	✓
Kentucky	P	–	✓	✓	✓	F3	✓
Louisiana	NP	–	✓	✓	✓	F3*	✓
Maine	P	–	–	–	–	F1	✓
Maryland	P	✓	✓	✓	✓	F2	✓
Massachusetts	P	–	–	–	–	NA	–
Michigan‡	NA	–	–	–	–	–	–
Minnesota	P	–	–	–	–	–	–
Mississippi	P	✓	✓	✓	✓	–	✓
Missouri	NP	✓	✓	✓	✓	F3	–
Montana	P	✓	✓	✓	✓	F3	✓
Nebraska	NP	✓	✓	✓	✓	F3	–
Nevada	P†	–	–	–	–	–	–
New Hampshire	NP	–	✓	✓	✓	F3	✓
New Jersey‡	P	–	–	–	–	–	–
New Mexico	NA	–	–	–	–	F3	–
New York	NP	–	–	–	–	F3	✓
North Carolina	NP	–	✓	–	–	–	–
North Dakota	NP	✓	✓	✓	✓	F2	✓
Ohio	NP	✓	✓	✓	✓	F3	✓
Oklahoma	NP	–	✓	–	✓	F2	✓
Oregon	P	–	✓	✓	✓	F4	✓
Pennsylvania	P	✓	✓	✓	✓	F3	✓
Rhode Island	NP	–	–	–	–	F3	–
South Carolina‡	NP	–	–	–	–	–	–
South Dakota	NP	✓	✓	✓	✓	F3	✓
Tennessee	NP	–	✓	✓	✓	F3	✓
Texas‡	NA	–	–	–	–	–	–
Utah‡	P	–	–	–	–	–	–
Vermont	P	✓	✓	✓	✓	F3	✓
Virginia	NP	✓	✓	✓	✓	F3	✓
Washington	NP	✓	✓	–	✓	F3	✓
West Virginia	NP	✓	✓	✓	✓	F3	✓
Wisconsin	P	–	✓	✓	✓	F3	✓
Wyoming	P	–	✓	✓	✓	–	–

METAVIR = Meta-analysis of Histologic Data in Viral Hepatitis; NA = not available; NP = nonpreferred; P = preferred.
* Biopsy required.
† No prior authorization required.
‡ No published criteria.

which cover most Medicaid recipients in some states. Prior authorization criteria used by such programs often, but do not necessarily, align with fee-for-service criteria in those states.

This listing of prior approval criteria by state Medicaid offices provides insight into the pressure that approval of new, costly HCV treatments places on state Medicaid programs and the resultant warehousing policies that limit access to lifesaving treatment. It also reveals the decision-making processes being used by drug utilization review boards that are reportedly choosing approval criteria on the basis of a mix of medical evidence, cost considerations, and perhaps-unmeasured preferences. The financial burden necessitating warehousing strategies for HCV treatment is not unique to Medicaid programs, and investigation of prior authorization strategies used by other public and private payers is warranted.

Treatment of patients with HCV infection is cost-effective from a societal point of view (7), but the combination of the high cost of treatment and insufficient Medicaid budgets precludes programs from providing widespread access to treatment. Under any financial context, when payers make decisions about HCV treatment, it will be important to consider the ethics and public health implications of prioritizing patients for treatment. The effects of prior approval policies for new HCV treatments on patient outcomes warrant continued investigation.

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

A Technology Assessment

Final Report

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About ICER

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

About CTAF

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

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

Table of Contents

Abbreviations used in this report

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

Abstract

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

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

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

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

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

Executive Summary

Background

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

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

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

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

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

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

Evidence Review

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

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

Table ES1: Clinical Subgroups

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

Table ES2: Therapies Considered in this Assessment

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

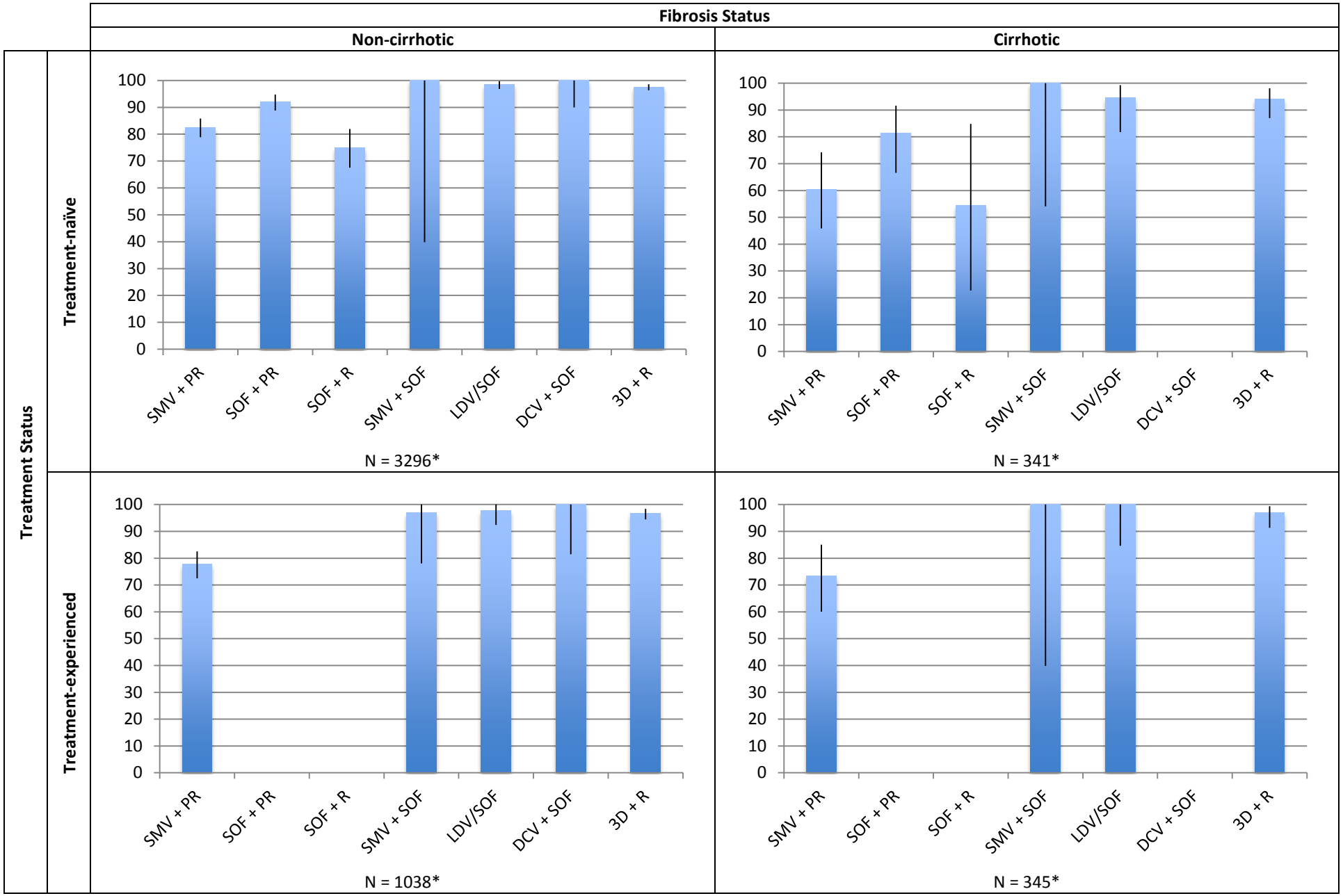
We included all prospective randomized trials and cohorts that reported SVR12 or SVR24 in HCV genotype 1 infected populations. The SVR results for each of the regimens by clinical subgroup are shown in Figure ES1 on page ES4. The evidence on the clinical effectiveness of the all-oral DAA combination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

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

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

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

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



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

Care Value Analysis: Cost-Effectiveness Model

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

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

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

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

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

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

Health System Value Analysis

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

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

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

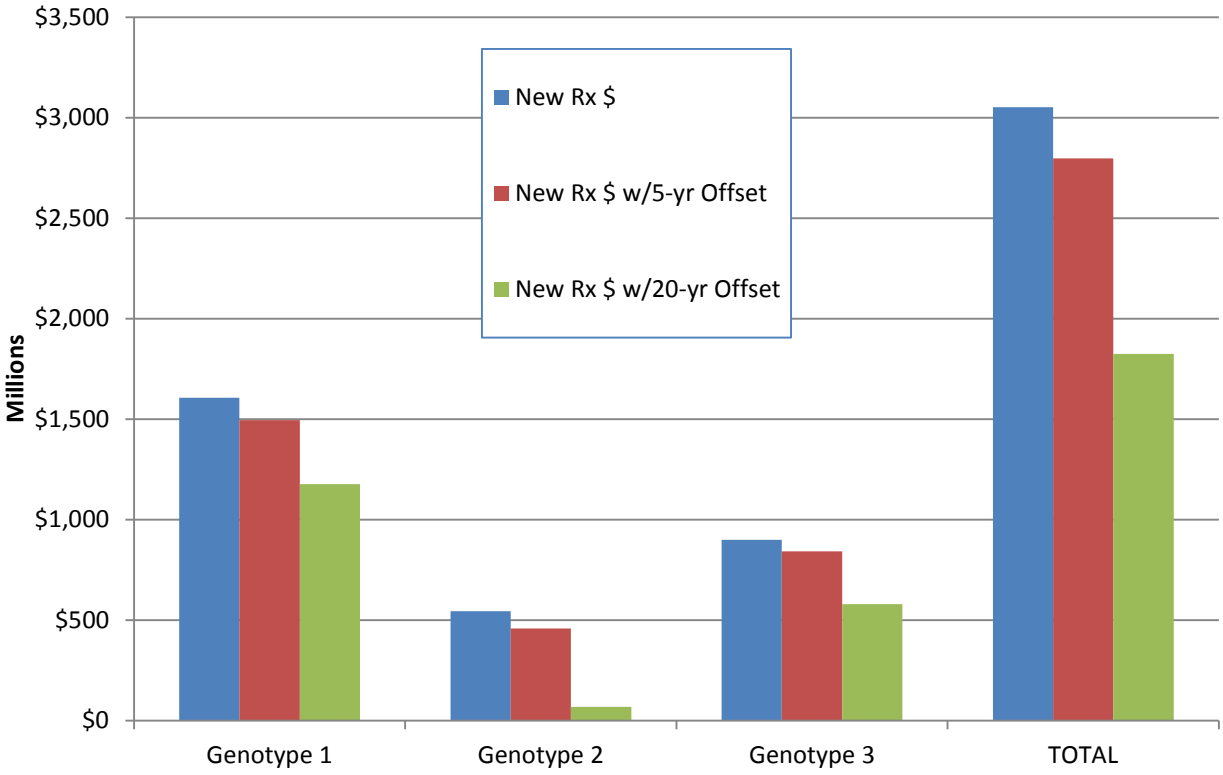
Our model suggests that full uptake of new HCV treatments among known-infected patients would increase costs by approximately $1.6 billion, $545 million, and $901 million for genotypes 1, 2, and 3 respectively (see Figure ES2 on page ES8), resulting in a total increase of $3 billion, or $33 PMPM. This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

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

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

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

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



Drug Pricing to Meet Per-Member Per-Month Benchmarks

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

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

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

Summary

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

CTAF Votes on Comparative Clinical Effectiveness and Value

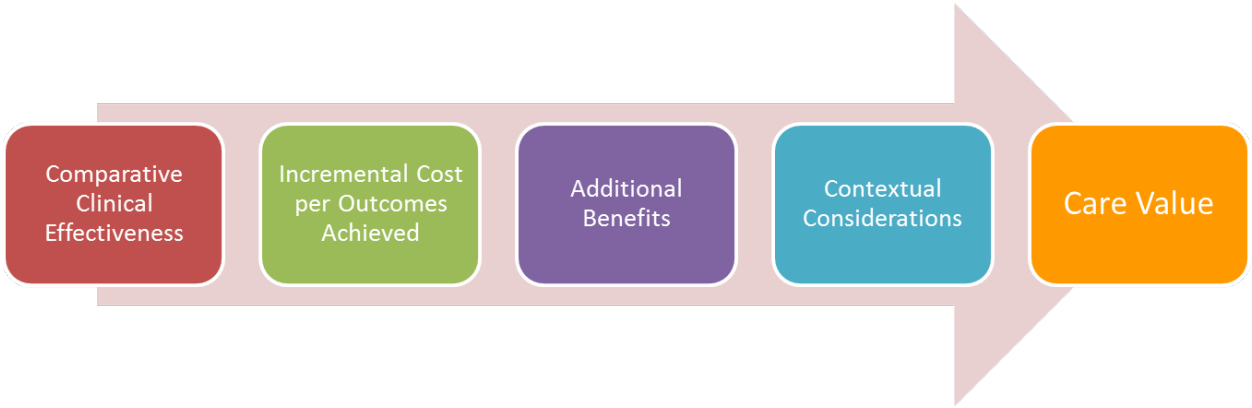
During CTAF public meetings, the CTAF Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, a cost analysis of the applications of the medical technologies or treatments under examination, and the supplementary information presented. Because any judgment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

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

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

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

Figure ES3. Care Value Framework



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

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

Figure ES4. Health System Value Framework

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

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

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

Comparative Clinical Effectiveness

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

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

Value

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

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

Policy Roundtable Discussion and Key Policy Recommendations

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

Clinical Considerations Policy Roundtable

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

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

[d] See footnote c on the previous page

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

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

Specialty Drug Pricing and Payment Policy Roundtable

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

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

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

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

Introduction

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

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

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

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

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

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

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

1. Background

1.1 Hepatitis C

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

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

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

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

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

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

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

1.2 Definitions

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

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

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

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

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

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

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

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

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

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

1.3 Treatment of Chronic Hepatitis C Infection

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

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

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

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

Treatment of Genotype 1

Pegylated interferon plus ribavirin

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

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

Boceprevir and Telaprevir

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

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

Simeprevir and Sofosbuvir

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

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

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

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

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

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

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

Table 2: Therapies for Hepatitis C by Class

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

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

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

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

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

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

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

2. Clinical Guidelines

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

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

http://www.hcvguidelines.org

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

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

The Department of Veterans Affairs (VA)

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

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

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

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

European Association for the Study of the Liver (EASL)

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

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

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

National Institute for Health and Care Excellence (NICE)

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

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

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

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

3. Coverage Policies

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

3.1 Ledipasvir/sofosbuvir (Harvoni)

Medicare & Medicaid

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

Regional Private Payers

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

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

National Private Payers/Pharmacy Benefit Managers

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

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

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

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

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

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

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

3.2 Sofosbuvir

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

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

3.3 Simeprevir

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

3.4 Coverage Policies across Payers

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

Coverage for several patient characteristics is summarized below:

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

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

Several other coverage requirements are summarized below:

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

4. Previous Systematic Reviews and Technology Assessments

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

4.1 Formal Health Technology Assessments

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

4.2 Systematic Reviews

No published systematic reviews of the newest DAAs were identified.

5. Ongoing Studies

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

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

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

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

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

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

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

6. Evidence Review (Methods & Results)

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

Table 4: Therapies Considered in this Assessment

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

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

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

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

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

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

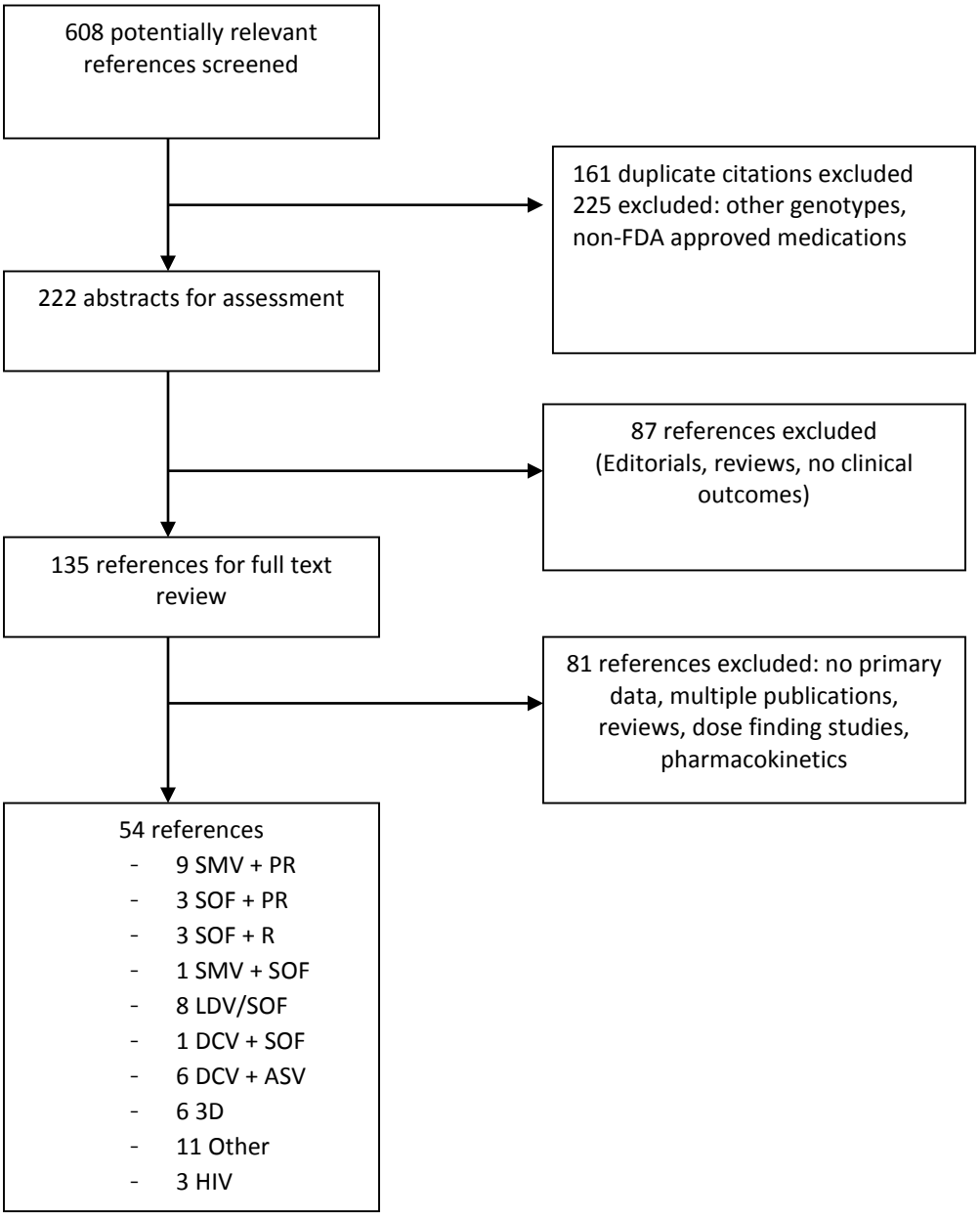
considering the domains listed below, which are adapted from the methods guide of the Agency for Healthcare Research & Quality (AHRQ):

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

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

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

Figure 1. Selection of Studies for Inclusion in Review



Key Patient Outcomes

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

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

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

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

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

6.1 Overview of the Key Studies by Treatment Regimen

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

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

Simeprevir + PR

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

Sofosbuvir + PR

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

Sofosbuvir + R

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

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

Simeprevir + sofosbuvir

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

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

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

Ledipasvir/sofosbuvir

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

Daclatasvir + sofosbuvir

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

Daclatasvir + asunaprevir

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

3D

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

Important Subgroups

HIV co-infection

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

Pre- or post-transplant

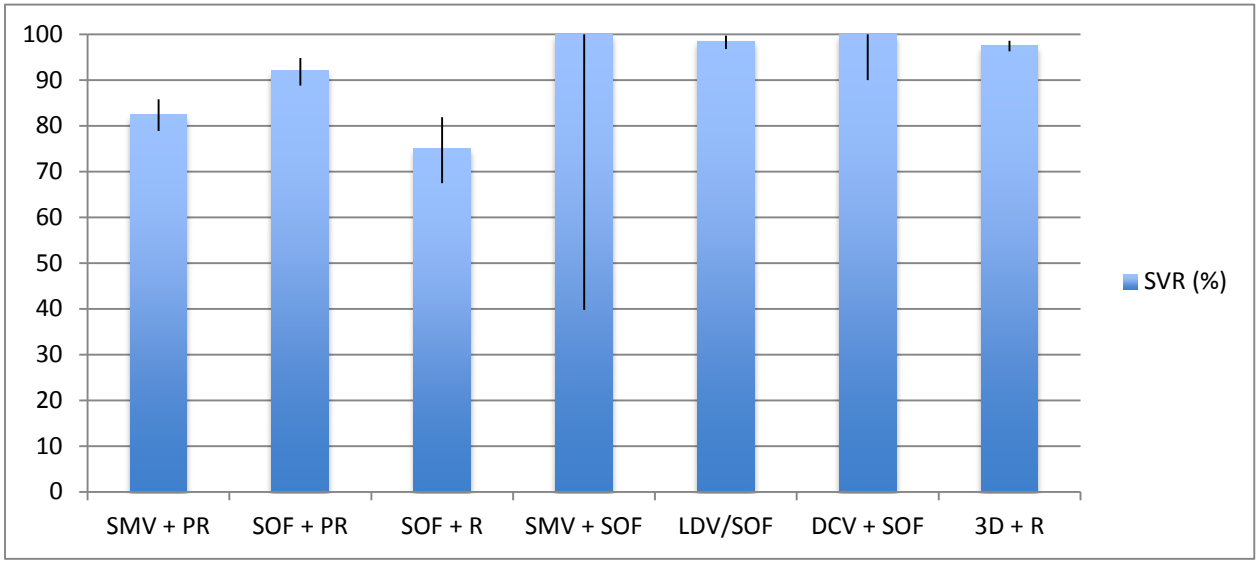
Similarly, data on the outcomes of treatments for patients on the liver transplant waiting list or post-transplant are rapidly emerging. There are four published trials: one in patients awaiting transplant and three in patients with recurrent infections after liver transplant (see Appendix Tables C19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

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

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

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

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



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

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

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

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

Tx Treatment
SVR Sustained virologic response
DR Discontinuation rate

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

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

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

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

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

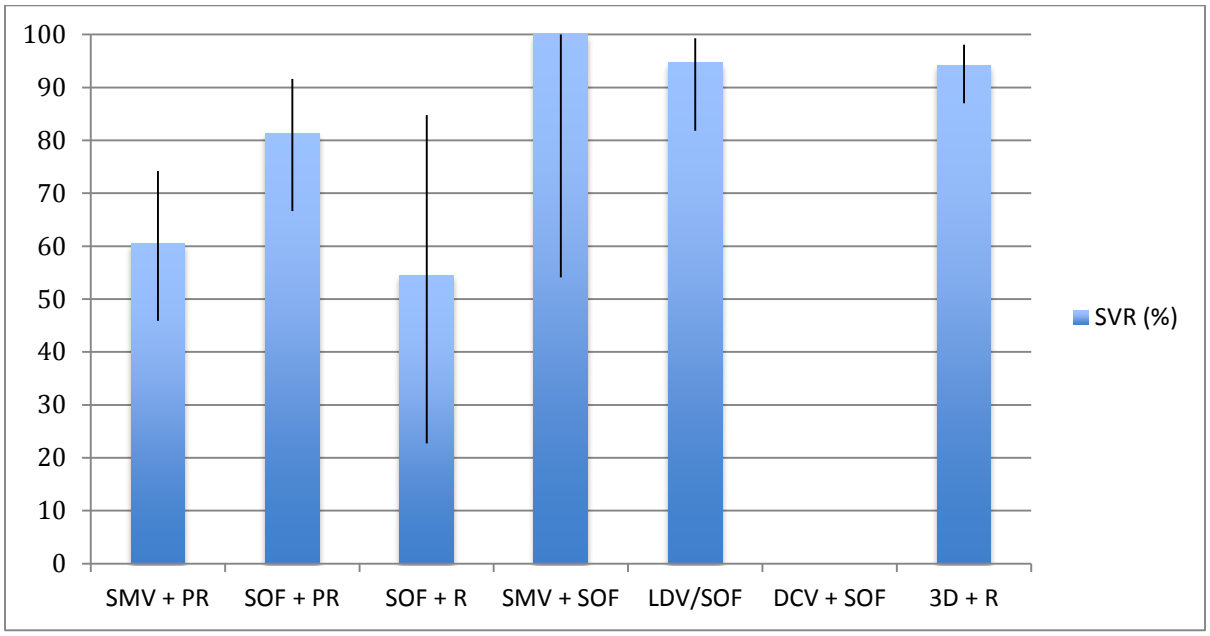


Table 6 gives more detail on each combination therapy as well as additional treatment combinations, primarily varying by length of treatment. The discontinuation rates are generally lower for the new combination therapies, but the confidence intervals are very wide, reflecting the small number of patients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

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

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

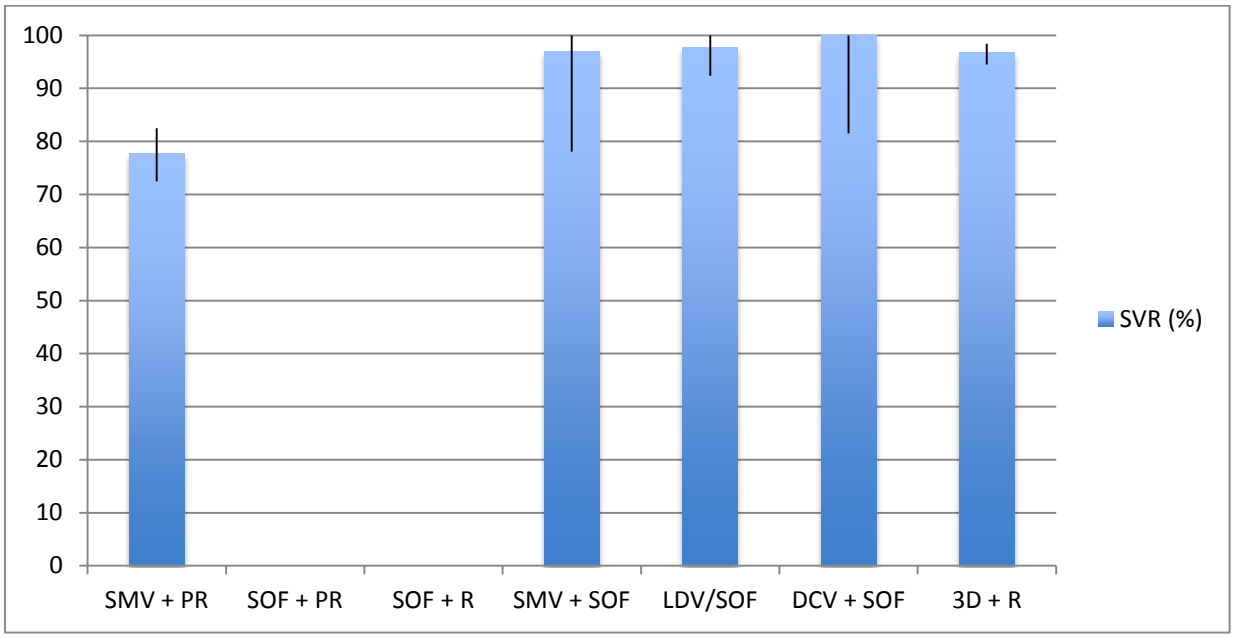
Tx Treatment
SVR Sustained virologic response
- No data
DR Discontinuation rate

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

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

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

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



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

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

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

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

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

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

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

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

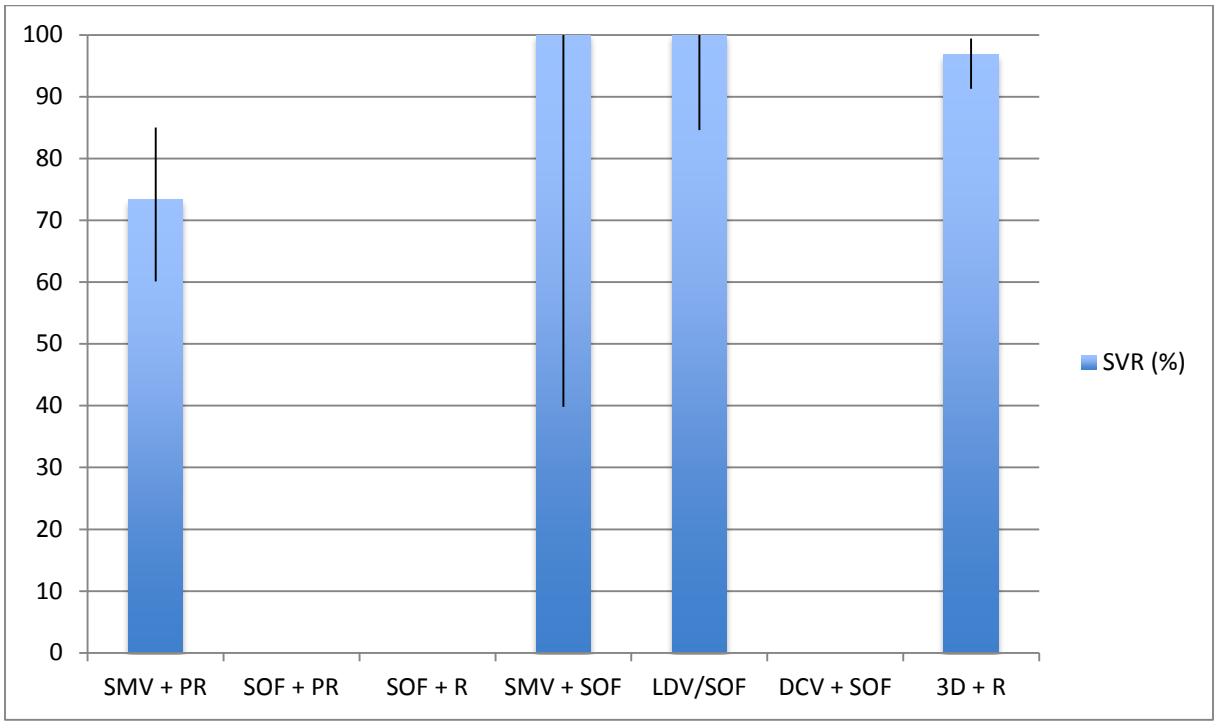


Table 8: Summary Estimates of SVR and Discontinuation Rates for Treatment-experienced Patients with Cirrhosis

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

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

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

6.6 Harms of Treatment

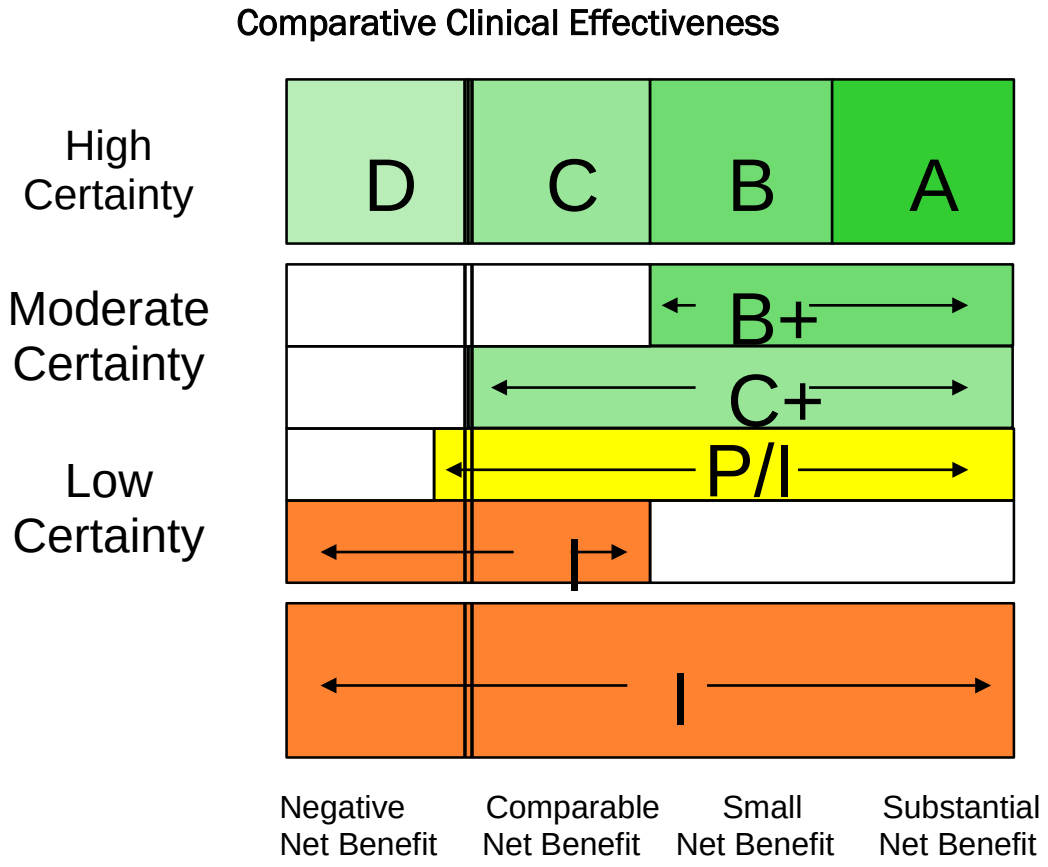
The adverse events reported in the clinical trials are summarized in Table 9 on the next page. The combinations that include ribavirin have an increased incidence of anemia, particularly when taken for 24 weeks or when combined with interferon. The combinations that include simeprevir are associated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

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

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

6.7 ICER Staff Evidence Rating

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



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

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

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

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

6.8 Summary

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

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

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

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

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

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

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

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

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

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

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

7.1 Prior Published Evidence on Costs and Cost-effectiveness

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

Sofosbuvir vs. Simeprevir

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

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

Sofosbuvir vs. Older Regimens

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

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

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

Cost-Effectiveness of All-Oral Hepatitis C Regimens

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

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

7.2 Model of Care Value: Overview and Methods

Overview

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Perspective

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

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

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

Patient Population

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

Natural History of Progression and Treatment Effects

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

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

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

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

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

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

Costs

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

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

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

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

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

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

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

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

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

Quality-of-life / Health State Utilities

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

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

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

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

Calculating Results

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

Scenario and Sensitivity Analyses

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

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

7.3 Model of Care Value: Results

The cost-effectiveness results are presented in three parts:

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

7.3.1 Base-case Results

Treatment-naïve cohort and "treat all" strategy

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

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

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

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

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

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

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

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

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

Treatment-experienced cohort and "treat all" strategy

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

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

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

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

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

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

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

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

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

Comparisons with PR only

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

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

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

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

Eff —Effectiveness

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

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

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

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

Eff — Effectiveness

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

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

Combined treatment-experienced and treatment-naive cohort

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

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

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

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

† — Regimen for treatment-naïve patients

‡ — Regimen for treatment-experienced patients

Incr Eff — Incremental Effectiveness

7.3.2 Scenario Analyses

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

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

Distribution among fibrosis stages

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

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

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

Discontinuation rates

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

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

Age of cohort is 50 years

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

7.3.3 Sensitivity Analyses

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

One-way sensitivity analyses

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

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

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

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

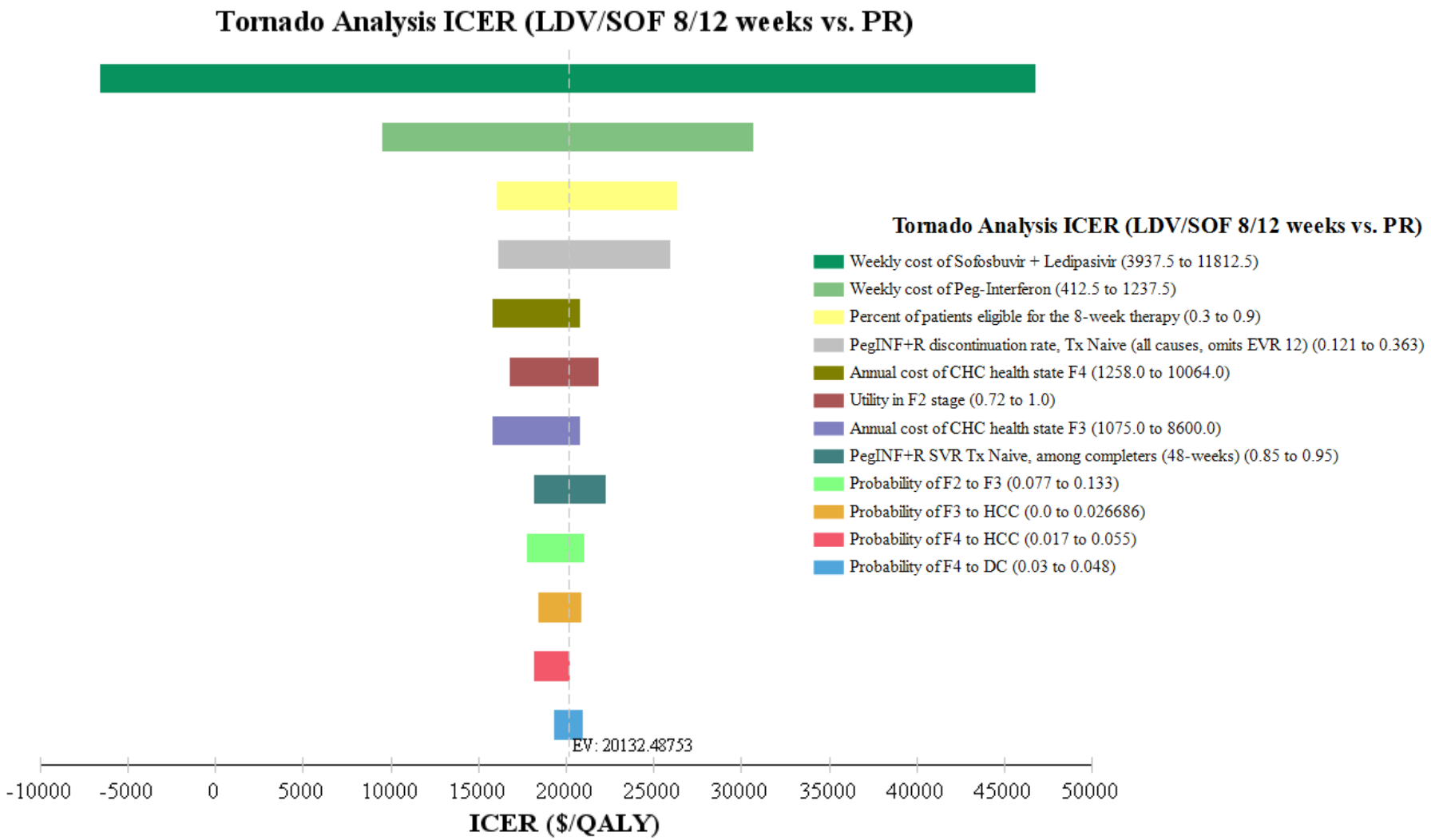
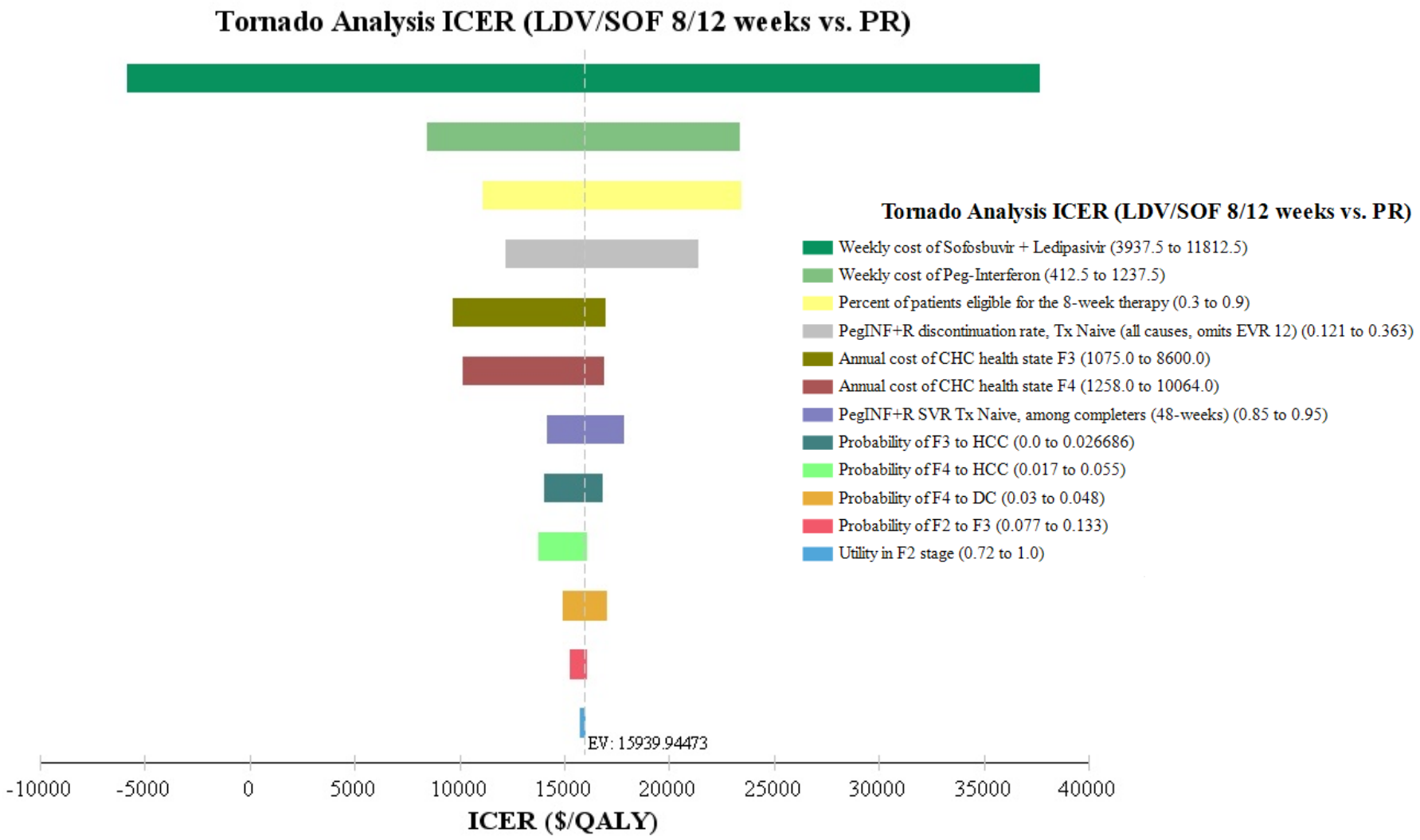


Figure 7: One-way Sensitivity Analyses for Treatment-naïve Patients and "Treat at F3, F4" Strategy



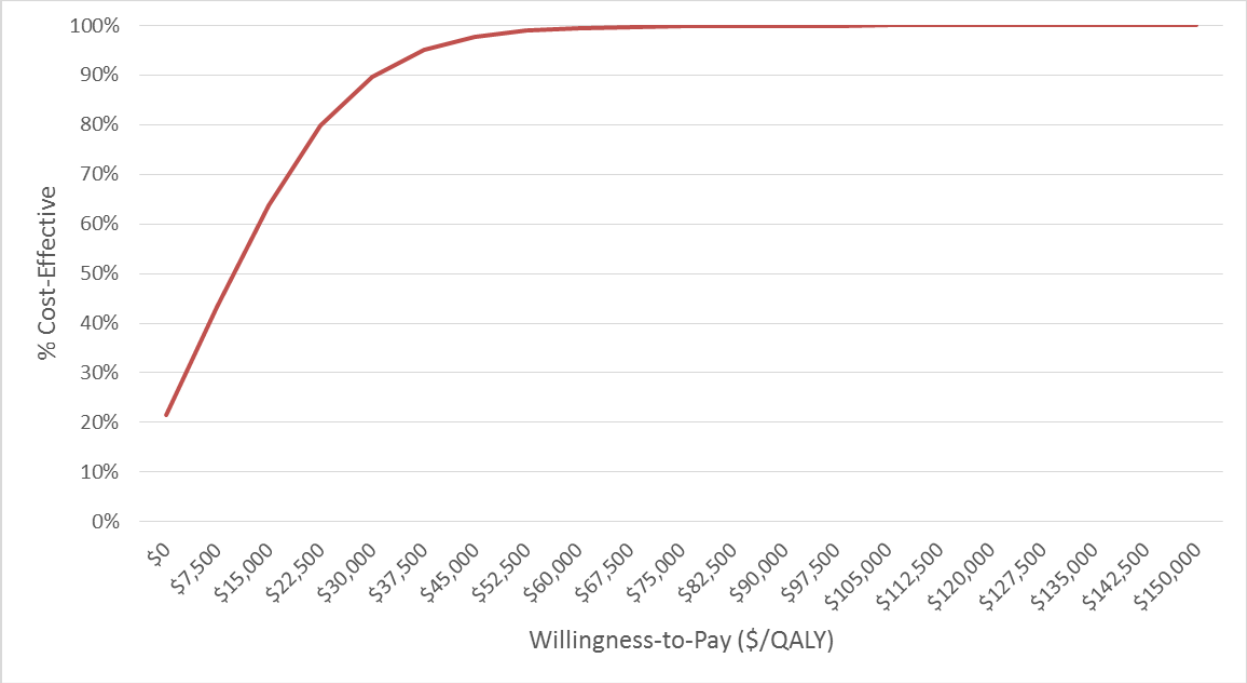
Multi-way probabilistic sensitivity analyses

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

Treat all

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

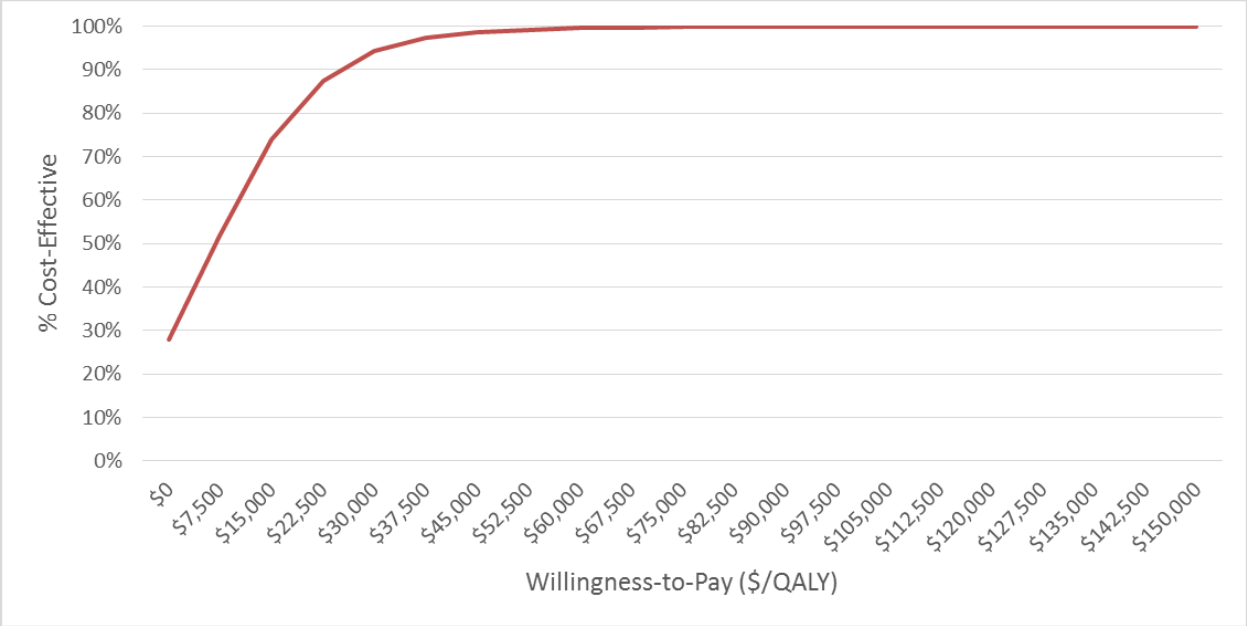
Figure 8: Cost-effectiveness Acceptability Curve for LDV/SOF 8/12 weeks, Treatment-naive, "Treat All" (Compared to PR Alone)



Treat at F3 and F4 only

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

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



7.4 Health-System Value Analysis: Methods

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

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

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

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

7.5 Health-System Value Analysis: Results

Budgetary Impact: Per 1,000 Patients Treated

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

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

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

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

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

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

Budgetary Impact: Medi-Cal/Department of Corrections Population

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

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

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

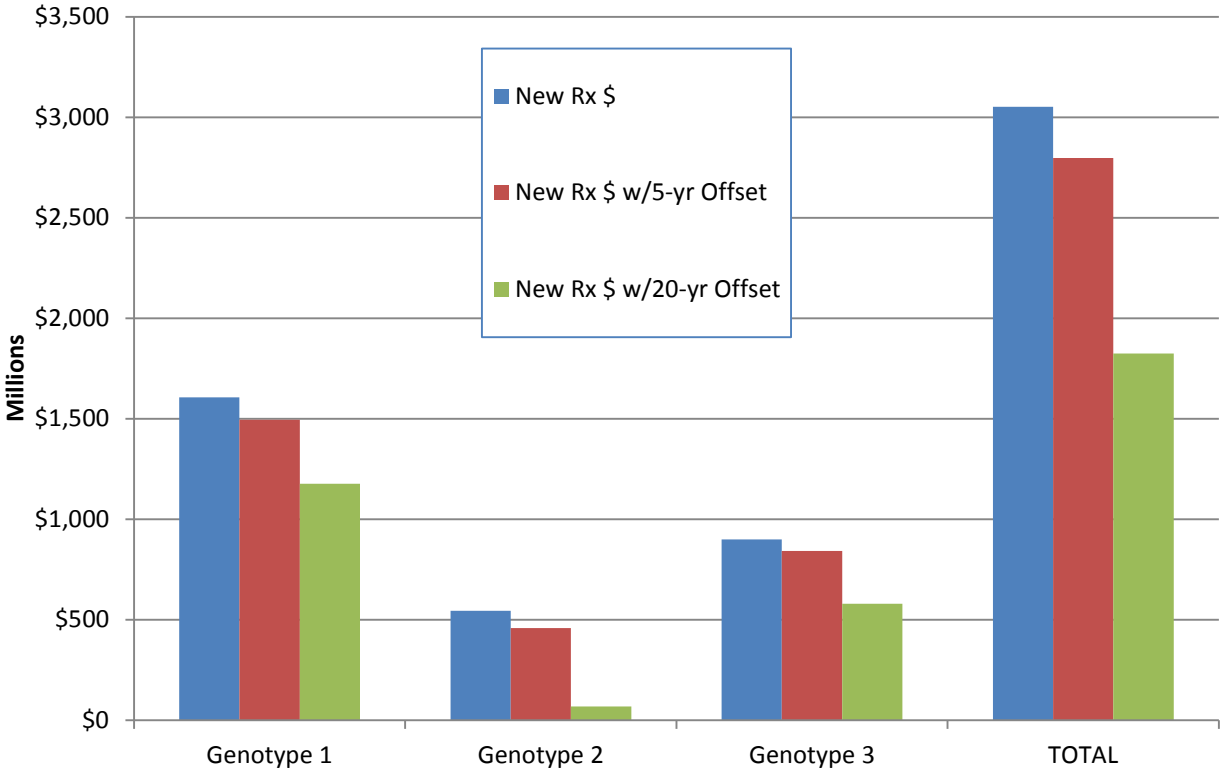
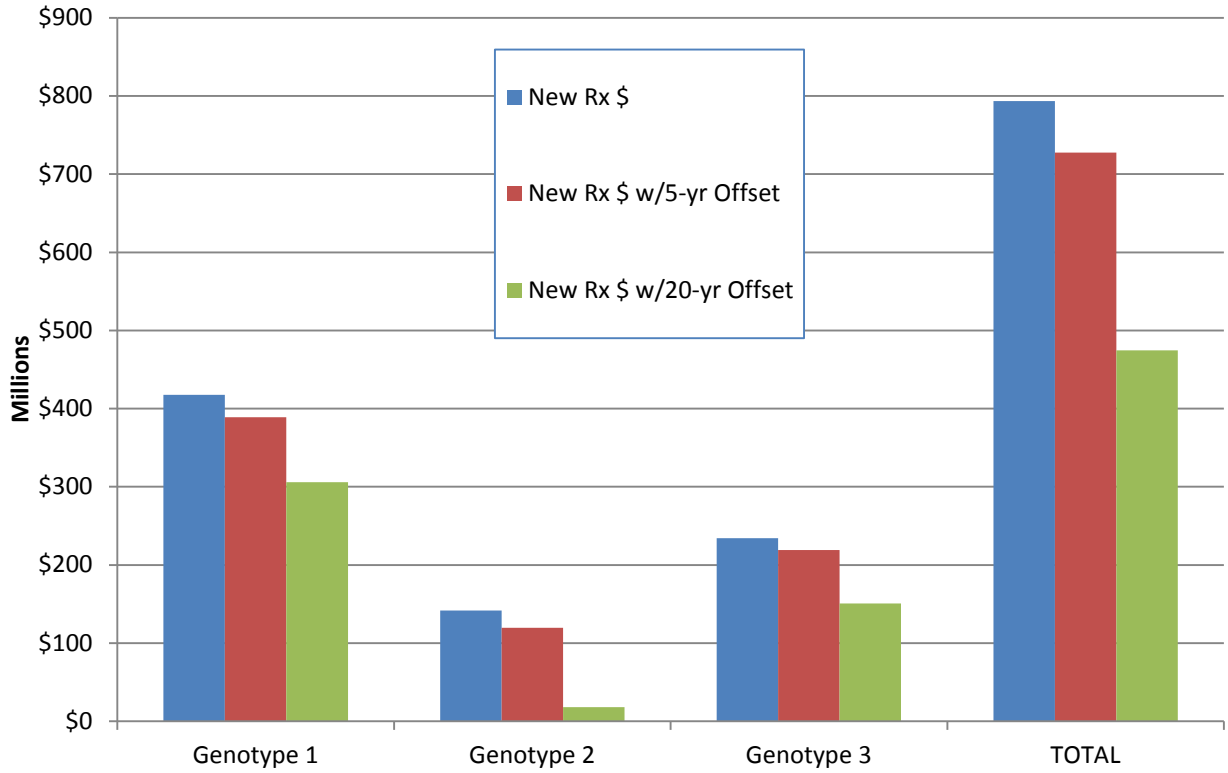


Figure 11 on the following page illustrates the budgetary impact with treatment commenced only for patients at fibrosis levels of F3 and F4 (approximately one-quarter of the potential patient pool). The initial expenditures for new therapies are reduced to approximately $800 million (~$9 PMPM, a 1.4%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

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



Additional Analyses Following the 12/18/14 CTAF Meeting

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

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

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

Drug Pricing to Meet Per-Member Per-Month Benchmarks

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

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

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

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

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

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

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

7.6 Summary

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

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

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

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

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

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

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

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

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

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

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

8. Questions and Discussion

8.1 About the CTAF Process

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

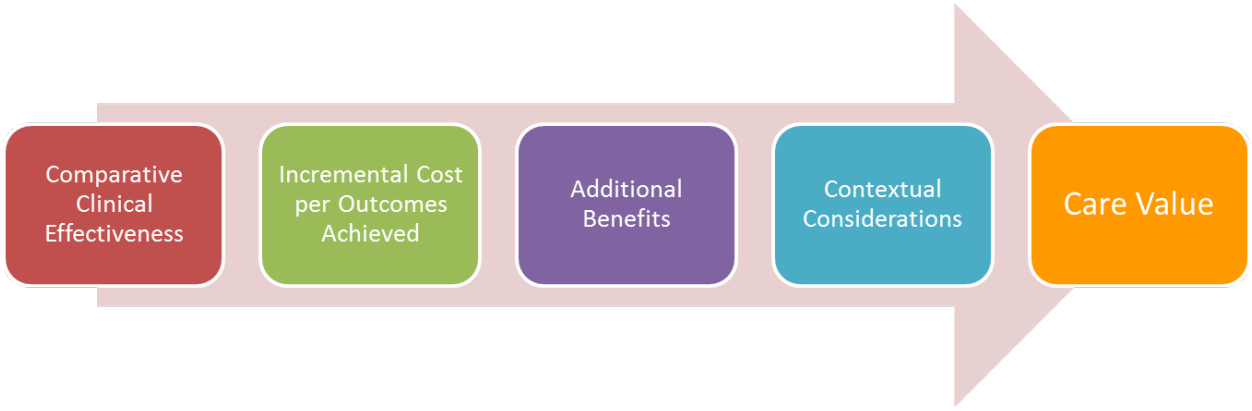
At each meeting, after the CTAF Panel vote, a policy roundtable discussion is held with the CTAF Panel, clinical experts, and representatives from provider groups, payers, and patient groups. This is intended to bring stakeholders into the discussion on how best to apply the evidence to guide patient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

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

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

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

Figure 12. Care Value Framework



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

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

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

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

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

Figure 13. Health System Value Framework

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

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

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

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

8.2 Summary of the Votes and Considerations for Policy

Clinical Effectiveness (based on the evidence presented)

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

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

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

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

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

Value

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

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

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

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

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

[h] See footnote g on the previous page.

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

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

Roundtable Discussions and Key Policy Implications

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

Table 22. Clinical Considerations Policy Roundtable Participants

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

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

Table 23. Specialty Drug Pricing and Payment Policy Roundtable Participants

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

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

Clinical Considerations Policy Roundtable

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

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

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

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

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

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

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

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

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

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

Specialty Drug Pricing and Payment Policy Roundtable

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

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

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

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

Payment

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

Policy

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

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

Care Redesign

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

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

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

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APPENDICES

Appendix A: Coverage Policies

Appendix Table A1: Coverage Policies for LDV/SOF

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

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

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

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

Appendix Table A2: Coverage Policies for Sofosbuvir + PR

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

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

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

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

Appendix Table A3: Coverage Policies for Sofosbuvir + R

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

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

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

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

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

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

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

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

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

Appendix Table A5: Coverage Policies for Simeprevir + PR

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

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

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

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

Appendix B: Search Strategies

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

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

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

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

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

Appendix C: Supplemental Tables from Chapter 6

Simeprevir + PR

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

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

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

FDA approved or probable treatment dose/duration only

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

Sofosbuvir + PR

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

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

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

FDA approved or probable treatment dose/duration only

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

Sofosbuvir + R

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

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

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

FDA approved or probable treatment dose/duration only

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

Simeprevir + Sofosbuvir

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

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

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

FDA approved or probable treatment dose/duration only

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

Ledipasvir/Sofosbuvir

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

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

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

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

FDA approved or probable treatment dose/duration only

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

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

Daclatasvir + Sofosbuvir

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

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

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

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

FDA approved or probable treatment dose/duration only

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

Daclatasvir + Asunaprevir

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

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

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

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

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

FDA approved or probable treatment dose/duration only

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

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

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

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

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

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

FDA approved or probable treatment dose/duration only

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

HIV Co-infection

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

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

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

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

FDA approved or probable treatment dose/duration only

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

Pre- or post-liver transplant

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

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

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

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

FDA approved or probable treatment dose/duration only

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

Appendix D: Supplementary Tables for Chapter 7

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

‡ – Upper limit selected by authors.

EVR = Early Virologic Response

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

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

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

***** – Treatment-naïve.

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

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

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

Table D6: Utility Loss with CHC Treatment

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

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

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

Appendix E: Explanation of Disease Progression and Markov Model Details

Figure E1: Hepatitis C Natural History Markov Representation

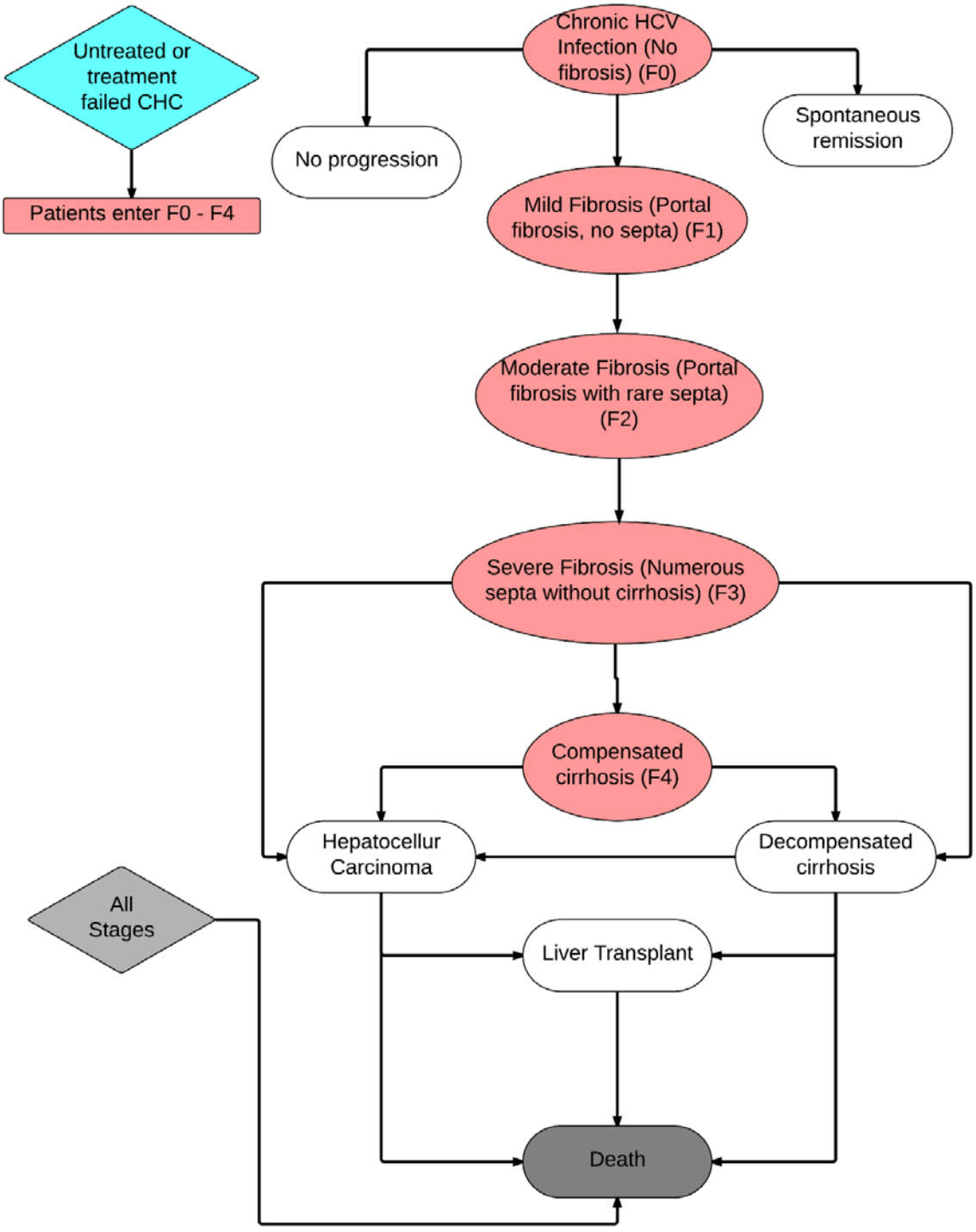

Figure E1 description: Patients enter the Markov model either when they receive no treatment, after unsuccessful therapy, or treatment discontinuation, in stages F0 through F4. The black arrows indicate annual progression of liver damage. The one time "no-progression" proportion from F0 fibrosis state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

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

Post-SVR progression and regression model

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

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

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

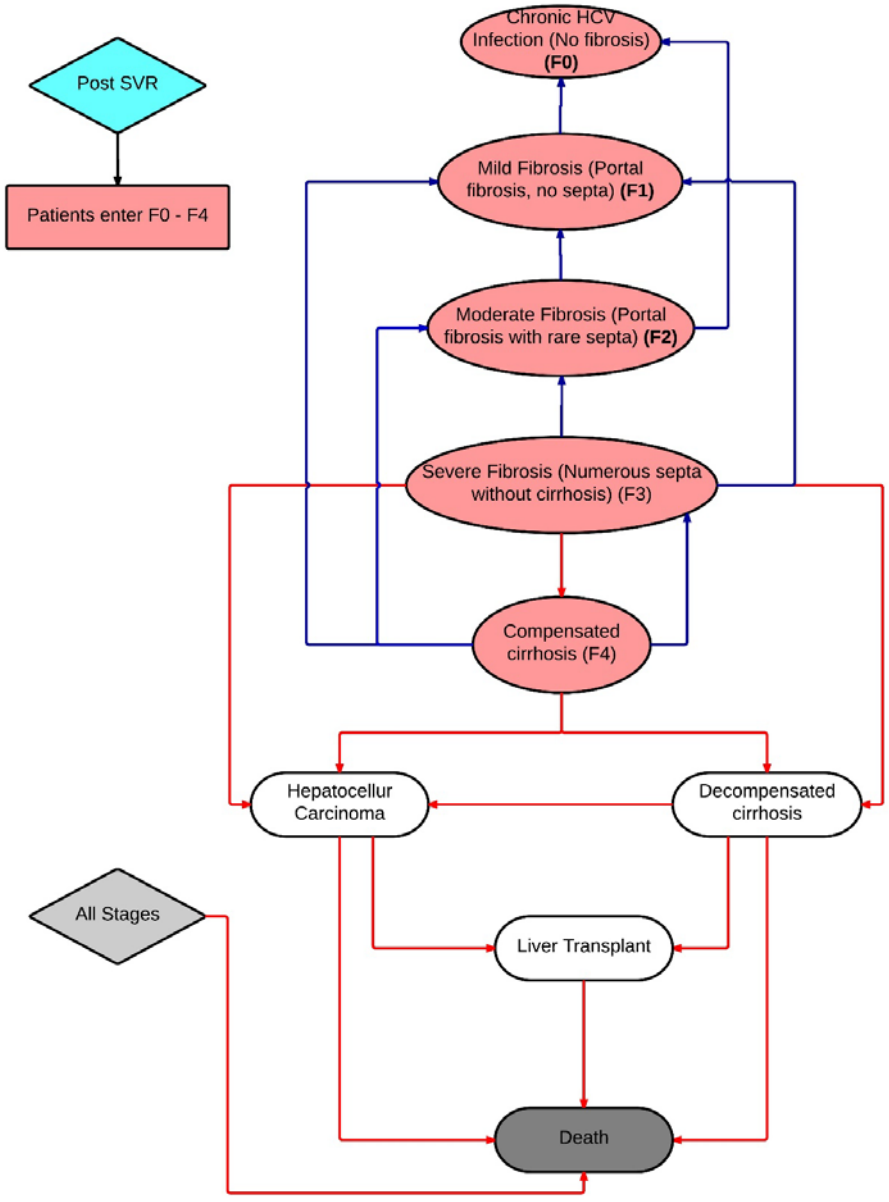

Figure E2 description: Patients enter the Markov model after successful therapy in stages F0 through F4. Blue arrows indicate proportional regression from source state to a lower fibrosis state. The regression data covers a wide time range, between 1 and 10 years post regression. In this model, the regression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

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

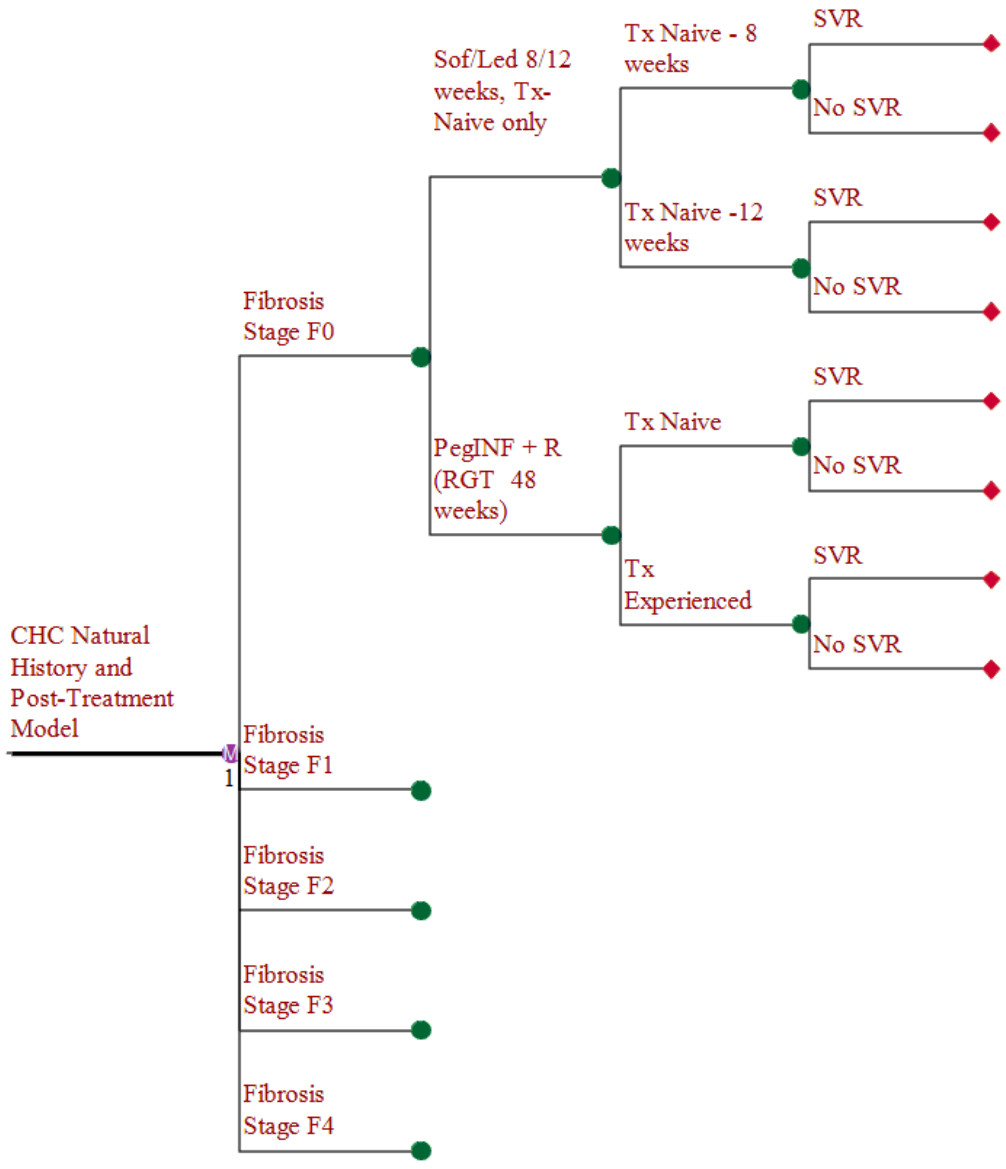

Figure E3 depicts a simplified tree of the model for illustrative purposes. This structure shows only five of 26 Markov states representing 15 health states. See Appendix Figures E1 and E2 for details of the Markov model. The Markov model is the same for all treatment policies. The policy analysis starts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

Appendix F: Scenario Analyses

Table F1: Scenario 1: Increased Discontinuation Rates

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

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

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

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

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

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

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

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

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

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

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

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

Table F3: Scenario 3: Modified F0-F3 Costs

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

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

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

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

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

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

Table F4: Scenario 4: Age Set to 50

Scenario Analysis
Age

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

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

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

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

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

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

Appendix G: Budgetary Impact Tables

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

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

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

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

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

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

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

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

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

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

Caring Ambassadors Program
Lorren Sandt, Executive Director
P.O. Box 1748
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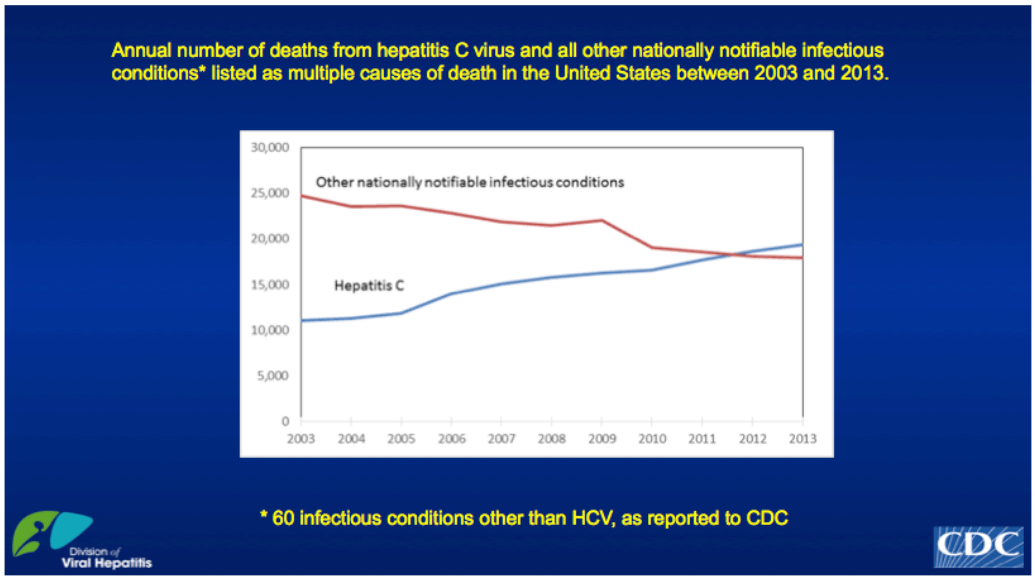
Public Comment
HCV Antivirals Class Update and Treatment Guidelines

OSU Drug Use Research and Management Program
Oregon Drug Use Review / Pharmacy & Therapeutics Committee
January 28, 2016

The Caring Ambassadors Program is a national, nonprofit, advocacy organization based in Oregon City, Oregon. We respectfully submit our written comment on the current criteria and suggested update to the current Hepatitis C PDL class on Daklinza® **and** Technivie® for treatment of Chronic Hepatitis C Virus (HCV). **We ask that Oregon's Medicaid program allow full access to all FDA approved hepatitis C direct acting agents by placing all these medications on the Preferred Drug List (PDL). This will allow medical decisions to be made between provider and patient, and will remove the current restrictions in place limiting patient access to these medications in accordance with the Center for Medicaid and CHIP Services' November 5, 2015 guidance sent to all state Medicaid programs.**[1]

Hepatitis C is the **most common**, chronic, blood-borne viral infection in the United States, yet it remains an unrecognized threat in the minds of many Americans. At least 3.8 to 4.5 million Americans have been infected with the hepatitis C virus including an estimated 95,000 Oregonians. [2] A recent study from the Centers of Disease Control (CDC) shows that the annual number of deaths from hepatitis C have now surpassed all other notifiable infectious diseases combined. [3]



Unfortunately, Oregon has a significantly higher hepatitis C mortality rate than the rest of the country.[2] We can and should do better than this for the health of all Oregonians.

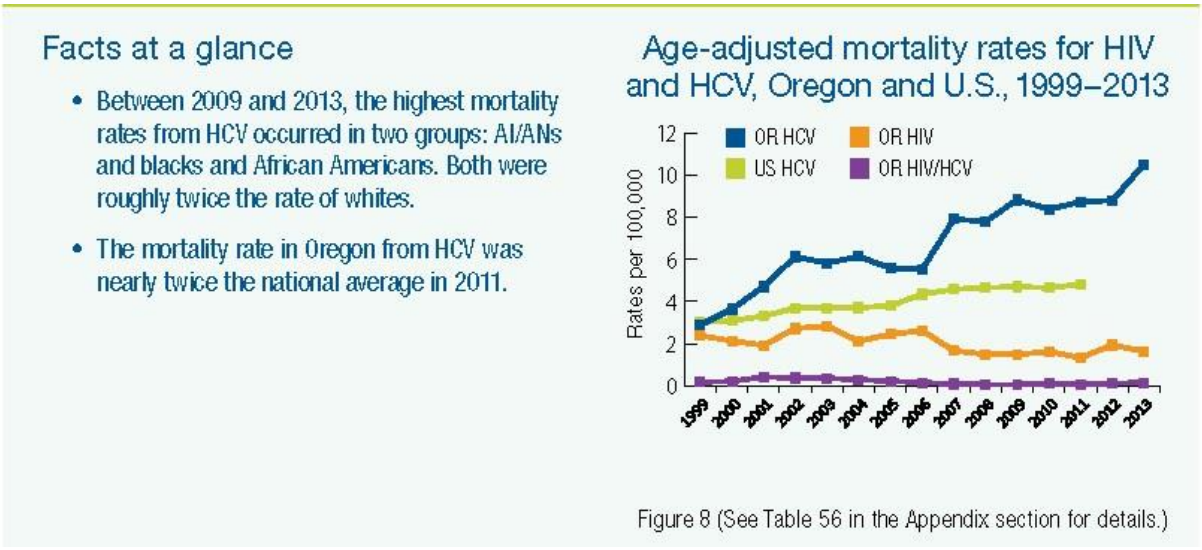


Figure 8 (See Table 56 in the Appendix section for details.)

Direct Acting Antivirals for HCV

New hepatitis C direct acting agents provide a cure for nearly all patients after an 8 to 12 week course of treatment. These new hepatitis C medications provide individuals with a cure to their once life-long inhibiting disease. However, it is critical that individuals receive access to these treatments in order to receive the benefits the medications offer. It should be noted that only those individuals who are diagnosed are aware of their infection and would be currently eligible to access treatment. In Oregon, approximately 50% of people living with hepatitis C are unaware of their infection.[2] Diagnosing people with hepatitis C will take several years, so those eligible to receive treatment will be spread out over many years. At the current rate of hepatitis C treatment, as estimated by the experts in our state, it may take as long as 40 years to cure everyone in Oregon from hepatitis C.

CMS Guidance

On November 5, 2015, CMS issued guidance to remind state Medicaid programs of their obligation to cover all FDA approved medications manufactured by companies participating in Medicaid rebate program, and any limitations must be based on clinical outcomes.

In the letter, CMS wrote:

> "When establishing formularies, states must ensure compliance with the requirements in section 1927(d)(4), including the requirements of section 1927(d)(4)(C) of the Act. Under this provision, a covered outpatient drug may only be excluded with respect to the treatment of a specific disease or condition for an identified population if, based on the drug's labeling, or in the case of a drug the prescribed use of which is not approved under the FFDCA, but is a medically accepted indication based on information from the appropriate compendia described

in section 1927(k)(6), the excluded drug does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome of such treatment for such population over other drugs included in the formulary and there is a written explanation (available to the public) of the basis for the exclusion.

Accordingly, to the extent that states provide coverage of prescription drugs, they are required to provide coverage for those covered outpatient drugs of manufacturers that have entered into, and have in effect, rebate agreements described in section 1927(b) of the Act, when such drugs are prescribed for medically accepted indications, including the new DAA HCV drugs."

CMS stated they are concerned:

> "that some states are restricting access to DAA HCV drugs contrary to the statutory requirements in section 1927 of the Act by imposing conditions for coverage that may unreasonably restrict access to these drugs. For example, several state Medicaid programs are limiting treatment to those beneficiaries whose extent of liver damage has progressed to metavir fibrosis score F3, while a number of states are requiring metavir fibrosis scores of F4. Certain states are also requiring a period of abstinence from drug and alcohol abuse as a condition for payment for DAA HCV drugs. In addition, several states are requiring that prescriptions for DAA HCV drugs must be prescribed by, or in consultation with specific provider types… As such, the effect of such limitations should not result in the denial of access to effective, clinically appropriate, and medically necessary treatments using DAA drugs for beneficiaries with chronic HCV infections. States should, therefore, examine their drug benefits to ensure that limitations do not unreasonably restrict coverage of effective treatment using the new DAA HCV drugs."

They are specifically referring to OREGON in this letter. CMS has asked states to comply with the Patient Protection and Affordable Care Act or be in jeopardy of **violating the law**. Other states that previously implemented these restrictions are either changing them or may be facing legal action from their citizens.

Pennsylvania

- Voted to amend treatment criteria to open up access to F0 for patients with HIV, HBV and extrahepatic manifestations. For everyone else F2 or above.
- Disease severity can now be established by physical exam, imaging or any non-invasive markers.
- They completely **eliminated the sobriety requirement**.

District of Columbia

- They **no longer have a drug or alcohol restriction**, so no urine tox. They are putting wording in the PA that providers and patients will work together to assure adherence.
- HIV and/or HBV coinfection with HCV patients can be treated at any fibrosis score (including F0).

- Anyone who was a stage F1-F2 on fibrosure or other, thus in-between, will be considered an F2 and treated.
- They will not require a letter of medical necessity IF using their preferred drug (currently Viekira).

New York

- **No restrictions** when using Viekira

The CMS guidance also discusses the importance of following the most appropriate clinical guidelines in making treatment decisions. Two leading expert organizations, the American Association for the Study for Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA), have recently updated their treatment guidelines, *"Recommendations for Testing, Managing, and Treating Hepatitis C."* They concluded that the treatment for hepatitis C would benefit nearly all of those who are chronically infected and the goal should be to treat all patients as promptly as feasible to improve their health and to reduce hepatitis C transmission. The professional guidance for treating hepatitis C is clear—**treatment is recommended and beneficial for all patients with hepatitis C, unless they have a short life expectancy.**

By limiting the use of potent HCV treatments to those who have already developed significant liver damage, you are exposing Oregonians with cirrhosis to an individual risk of developing HCC at 1-6% per year.[4] This means that ~ 8400+ patients will require costly liver cancer imaging tests every 6 months for the rest of their lives. Treatment time can be shortened in patients without cirrhosis to 8 weeks saving even more money. Treatment in cirrhotic patients may be 40% more expensive than treating earlier stage disease. You must not be shortsighted and consider all of the downstream fiscal and societal costs when looking at this disease and how to treat it.

Current Oregon Medicaid guidelines requires that medication be prescribed by or in consultation with a hepatologist or gastroenterologist—this is an unnecessary additional hurdle for patients seeking treatment, and further discriminates against those who cannot access this type of specialist. Further, this strict requirement is not in line with the community standard. Infectious disease specialists have successfully treated viral hepatitis for years with therapies that were more complex and had much harsher side effects. It is already a long wait list to see a hepatologist or a gastroenterologist, how can a handful of these doctors also handle consulting on all HCV cases?

Current Oregon Medicaid guidelines disallows treatment for patients who use drugs and alcohol—there is no substantiated reason for this exclusion and adopting it will bar many of the patients most in need of treatment from being cured of their virus. This exclusion is not in line with the guidelines of AASLD. The State of Oregon is currently guilty of discriminating against its own most marginalized citizens.

Coverage under Medicaid Managed Care Plans

> "CMS is also concerned that in many states, Medicaid managed care organizations (MCOs) or other managed care arrangements' conditions for payment for DAA HCV drugs appear to be more restrictive than coverage under the states' fee-for-service (FFS) programs. Furthermore,

in states with multiple MCOs or arrangements, the conditions for payment for DAA HCV drugs often differ between various plans.

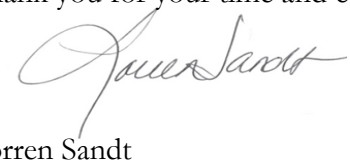
CMS reminds states that the drugs under the approved state plan must be available to individuals enrolled in Medicaid managed care arrangements. As with their FFS program, states are urged to carefully monitor the DAA HCV drug coverage policies of their MCOs to ensure enrollees have appropriate access. States have the option to include these drugs in the managed care contracts and capitation rates or to "carve out" the drugs used in the treatment of chronic HCV infections from managed care contracts and capitation rates and instead provide access to these drugs through FFS or other arrangements.

Consistent with the regulation at 42 CFR §438.210, **services covered under Medicaid managed care contracts (with MCOs, prepaid inpatient health plans, and prepaid ambulatory health plans) must be furnished in an amount, duration, and scope that is no less than the amount, duration, and scope for the same services for beneficiaries under FFS Medicaid.** While managed care plans may place appropriate limits on DAA HCV drugs using criteria applied under the state plan, such as medical necessity, the managed care plan may not use a standard for determining medical necessity that is more restrictive than is used in the state plan.

CMS recognizes the challenges of defining policies in the face of new and innovative drug treatments**. It will monitor the policies and conditions states impose for the coverage of DAA HCV drugs to ensure compliance with the requirements of the Act and access to effective, clinically appropriate, and medically necessary treatments for beneficiaries. CMS will monitor state compliance with their approved state plans, the statue, and regulations to assure that access to these medications is maintained.**"

With many new treatments now available, and more soon to come, we have a chance to halt this disease in its tracks; but not if we to discriminate against people accessing the Oregon Health Plan. **We are requesting that you remove the current access restrictions and allow doctors and their patients to decide the right course of therapy so that the Oregon Health Plan will be in accordance with the CMS guidance, and all Oregon Medicaid beneficiaries with hepatitis C can gain access to the hepatitis C cure medications in a timely fashion.** Denying treatment to Oregonians who can be cured of their virus and creating a new population of patients with cirrhosis is both a costly and a deadly path for all concerned.

Thank you for your time and consideration.



Lorren Sandt
Executive Director
Caring Ambassadors Program

1. State Release #172 ASSURING MEDICAID BENEFICIARIES ACCESS TO HEPATITIS C (HCV) DRUGS, CMS 11/5/2015

2. Viral Hepatitis in Oregon https://public.health.oregon.gov/DiseasesConditions/HIVSTDViralHepatitis/AdultViralHepatitis/Documents/Viral_Hepatitis_Epi_Profile.pdf [last accessed 1/27/16]
3. Continued Rising Mortality from Hepatitis C Virus in the United States, 2003-2013, Holmberg et al, IDSA 2015
4. Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance. Sangiovanni A1, et al Gastroenterology. 2004 Apr;126(4):1005-

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one in four
chronic health

a voice for patients
1in4.org

January 28, 2016

Roger Citron and Members of the
Oregon Pharmacy & Therapeutics Committee
OSU College of Pharmacy - Drug Use Research & Management @
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35
Salem, OR 97301-1079

Re: Hepatitis C Prior Authorization Criteria

Good Afternoon. For the record, my name is BJ Cavnor and I serve as Executive Director for One in Four Chronic Health, the chronic health care collaborative in Oregon.

We appreciate the opportunity to share our concerns and help craft the best possible policy solution to provide care, and cures to people living with viral hepatitis C (HCV).

It would be disingenuous to speak about the treatments (cure) for HCV without acknowledging the cost of the drugs. However, it borders on the hypocritical to ignore the scientific facts these new direct acting antiviral (DAA) treatments cure more than 98% of patients who use them. In brief, CMS states that the high cost of these DAA cannot be a barrier or impediment to treatment.

In their letter to November 2015 State Technical Contacts, "Assuring Medicaid Beneficiaries Access To Hepatitis C (HCV) Drugs"[i] the agency stated their concern that some states are restricting or denying coverage of DAA drugs contrary to the statutory requirements in section 1927 of the Social Security Act.

State who participate in Medicaid and Medicaid Managed Care Agreements are required to provide access and coverage of FDA approved drugs:

> *Coverage of prescription drugs is an optional benefit in state Medicaid programs, though all fifty (50) states and the District of Columbia currently provide this benefit. States that provide assistance for covered outpatient drugs of manufacturers that have entered into, and have in effect, rebate agreements described in section 1927(b) of the Social Security Act (the Act) under their Medicaid fee-for-service (FFS) programs or Medicaid managed care plans are required to comply with the requirements of section 1927(d)(1) and (2) of the Act.*
>
> *Section 1927(d)(1) of the Act provides that a state may subject a covered outpatient drug to prior authorization, or exclude or otherwise restrict coverage of a covered outpatient drug if the prescribed use is not for a medically accepted indication as defined by section 1927(k)(6) of the Act, or the drug is included in the list of drugs or drug classes (or their medical uses), that may be excluded or otherwise restricted under section 1927(d)(2) of the Act.*

Section 1927(k)(6) of the Act defines the term "medically accepted indication" as any use of a covered outpatient drug which is approved under the Food Drug And Cosmetic Act (FFDCA), 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).

We come before you today with the request that we continue working together to expand treatment to Oregonians living with HCV. We request that in keeping with the CMS recommendations, the Pharmacy and Therapeutics Board take the following immediate actions to expand access and be in compliance. These actions are:

- Denying patients treatment if metavir fibrosis scores under F4, regardless of comorbidities;
- Abstinence from alcohol, drugs and cigarettes;
- The requirement that treatment can only be prescribed/provided by gastroenterologists and hepatologists;
- The removal of homelessness or lack of mailing address as a barrier to treatment.

Thank you for the opportunity to provide this testimony to you today, should you have any questions, please feel free to contact me at 206/601-8453.

Respectfully,

BJ Cavnor
Executive Director

[1] DeBoy, A.M. Acting Director, Disabled and Elderly Health Programs Group, Centers for Medicaid and Medicare Services, Assuring Medicaid Beneficiaries Access To Hepatitis C (HCV) Drugs 11/05/2015 https://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Downloads/Rx-Releases/State-Releases/state-rel-172.pdf