Class Update: Hepatitis C Direct-acting Antivirals

Date of Review: September 2017

End Date of Literature Search: Week 1, July 2017

Current Status of PDL Class:
See Appendix 1.

Purpose for Class Update:
To evaluate new comparative evidence that of the benefits and harms of direct-acting antivirals (DAAs) for the treatment of chronic hepatitis C (CHC).

Research Questions:
1. Is there new comparative evidence for differences in efficacy/effectiveness or harms between available DAAs for the treatment of CHC?
2. Are there specific subpopulations based on severity of disease, extrahepatic manifestations, comorbidities, or level of fibrosis that may benefit from one particular DAA over another DAA or benefit from immediate treatment?
3. Is there new evidence to support an optimal time to initiate treatment for CHC based on improved effectiveness or less harms?

Conclusions:
- There is low quality evidence from a Cochrane systematic review that DAAs reduce the risk of no sustained virologic response (SVR) (higher likelihood of achieving SVR) compared to control (54.1% vs. 23.8%; RR 0.44; 95% CI 0.37 to 0.52; p<0.000001, ARR 30.3%; NNT 4). This is consistent with previous literature. There did not seem to be a difference between the different DAAs based on subgroup analysis and all subclasses of DAAs showed evidence of a significant effect on SVR. There was no difference in SVR between treatment-experienced (RR 0.50; 95% CI 0.36 to 0.69) and treatment-naïve (RR 0.48; 95% CI 0.41 to 0.56) participants.
- Low-quality evidence from a Cochrane systematic review showed no difference in serious adverse events with DAAs (2.77%) compared to control (5.6%) (OR 0.93; 95% CI 0.75 to 1.15; p=0.52).
- Low quality evidence from a Cochrane systematic review found no difference in CHC morbidity or all-cause mortality from the DAAs compared to placebo or no intervention (OR 3.72; 95% CI 0.53 to 26.18). There were very few data on mortality with DAAs (15/2377; 0.63%) compared to control (1/617; 0.16%) from 11 trials. There was no data on hepatitis C-related morbidity.
- There is insufficient evidence that treatment of CHC with DAA-containing regimens improves quality of life or other clinically important outcomes including ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy or hepatocellular carcinoma (HCC).
- Due to poor quality and limited data, definitive conclusions on the efficacy of re-treatment in patients with NS5A resistance associated variants (RAVs) who have failed treatment with a NS5A inhibitor cannot be made. Current guidelines recommend deferral of treatment in this population, pending additional evidence.
data, or if retreatment is urgent, tailoring the regimen based on resistance testing, using a treatment duration of 24 weeks and adding ribavirin (RBV). Additionally, for genotype 3 (GT3) sofosbuvir (SOF) treatment-experienced patients, deferral of treatment is also recommended unless urgent retreatment is required. A recent study evaluating sofosbuvir/velpatasvir (SOF/VEL) with a new NS3/NS4A protease inhibitor (voxilaprevir [VOX]) demonstrated an SVR of 96% (253/263) in patients previously treated with an NS5A inhibitor. A full review of this medication and supporting data is pending.

- Limited data are available according to severity of fibrosis. Studies define patients by cirrhosis status. There is insufficient evidence from clinical trials that patients with early stages of disease (F0-F2) achieve higher SVR rates than those with more advanced disease, or whether delayed treatment leads to poorer long-term clinical outcomes. However, an assessment of the patient’s readiness to treat and education on the importance of compliance and follow-up are vital for successful treatment. Factors to consider before deciding to treat early fibrosis stages (F0-F1) include: 1) the slow progression of disease to cirrhosis, 2) limited treatment options for the re-treatment of HCV in cases of relapse or reinfection, and 3) possibility of superior DAA regimens in the pipeline.

- There are still several limitations in the current evidence for the treatment of CHC:
  - There is still insufficient evidence for the optimal treatment of patients who have had a virologic failure to a previous NS5A or NS5B inhibitor. Risk of DAA resistance is a major concern in this population.
  - There is still a lack of head-to-head trials for most DAA regimens. In some populations, data on DAs are limited to open-label, uncontrolled, or historically controlled trials.
  - Trials often exclude patients with chronic hepatitis B virus (HBV), HIV, cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and severe alcohol or substance abuse. When decompensated cirrhosis is included, there are very little data in patients with Child-Pugh class C.
  - There is no direct evidence that treatment with antiviral therapy for CHC leads to improved long-term clinical outcomes in incidence of HCC, liver transplantation, or mortality.
  - Clinical trials do not analyze results based on Medicaid or other insurance type. However, based on age of participants, comorbidities, and nature of CHC, applicability to Medicaid patients is high.

Recommendations:
- In accordance with the Memorandum of Understanding (MOU) between the Oregon Health Authority and Oregon Law Center:
  - Expand coverage for HCV treatment with HCV stage F-2 with no requirement to be prescribed by a specialist.
  - Expand coverage for HCV treatment for all individuals with HCV co-infected with HIV.
  - Include additional extrahepatic manifestations into coverage criteria.
- Due to recent FDA safety alert, include baseline HBV monitoring into PA criteria (Appendix 5).

Previous Conclusions:
- There is low quality evidence that the DAA regimens are effective in achieving a SVR rate of ≥ 85-90%. SVR rates differ between patients based on disease severity, genotype, and baseline NS5a resistant amino acid variants (RAVs). Relapse may be reduced with baseline NS5A polymorphism screening.
- The regimens that have been studied in patients with cirrhosis include mostly Child-Pugh A and B. There are very limited data in Child-Pugh C.
- From the only comparative data available, there is low quality evidence that 12 weeks SOF/VEL may be modestly superior to 12 weeks SOF + RBV in patients with GT2 (SVR 99% vs. 95%, respectively; absolute difference 5.2%; 95% CI, 0.2-10.3%; p=0.02). Treatment with 24 weeks of SOF/VEL may also be superior to 24 weeks of SOF + RBV in patients with GT3 (SVR 95% vs. 80%; respectively; absolute difference 14.8%; 95% CI 9.6-20%; p<0.001). There are no other

alternative treatment regimens approved for GT2 and there is insufficient comparative data for other treatments available for GT3 (LDV/SOF + RBV or DCV/SOF).

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  - There is still insufficient evidence for the optimal treatment of patients who have had a virologic failure to a previous NS5A or NS5B inhibitor. Risk of DAA resistance is a major concern in this population.
  - There is still a lack of head-to-head trials for most DAA regimens. In some populations, data on DAAs are limited to open-label, uncontrolled, or historically controlled trials.
  - Trials often exclude patients with chronic hepatitis B virus (HBV), HIV, cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and severe alcohol or substance abuse. When decompensated cirrhosis is included, there are very little data in patients with Child-Pugh class C.
  - There is no direct evidence that treatment with antiviral therapy for CHC leads to improved long-term clinical outcomes in incidence of HCC, liver transplantation, or mortality.

- Given the high sensitivity and specificity of image tests to stage fibrosis (specifically, transient elastography [FibroScan], acoustic radiation force impulse imaging [ARFI], shear wave elastography [SWE]) and potential harms of liver biopsy, these less invasive options are favored for prescribers considering CHC treatment with a DAA.

**Previous Recommendations:**

- Continue to prioritize treatment for persons with advanced liver disease (METAVIR stage F3 or F4), as well as those at greatest risk of developing complications of liver disease, including:
  - All patients awaiting a liver transplantation
  - All patients post solid organ transplant
  - HIV coinfection with METAVIR stage F2 or greater
  - Patients with extrahepatic manifestations
- Make DCV preferred and replace LDV/SOF with DCV with SOF and RBV in current prior authorization (PA) for patients with GT3 CHC with cirrhosis.
- Due to extensive drug-drug interactions and safety concerns, make OMB/PTV-R + RBV and OMB/PTV-R + DAS non-preferred.
- For those with METAVIR stage F2 or lower, DAA regimens do not need to be prescribed by or in consultation with a specialist.

**Background:**

Chronic hepatitis C (CHC) infection is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma (HCC). It is also the leading indication for liver transplantation in the Western world. The global prevalence is 1.6%, and in the United States (U.S.) approximately 50% of affected individuals remain unaware of their diagnosis. The goal of treatment for CHC is to reduce the occurrence of end-stage liver disease and its related complications. However, results from clinical trials designed to evaluate long-term health outcomes or health related quality of life are not available. In addition, only about 10-20% of people with CHC go on to develop cirrhosis (8-16% of all people infected with HCV) and the time to progress to cirrhosis varies at an average of 40 years. Approximately 20% of individuals infected with HCV will clear the virus. HCV is divided into seven major genotypes with variable geographical distribution and prevalence. In the U.S., GT1 infection is found in about 75% of patients with CHC; GT2 and GT3 represent about 20% of CHC patients. Subgenotypes 1a and 1b are the most common subgenotypes of GT1. Cure rates for GT 1a and 1b infection may differ depending on the treatment

**Direct Acting Antiviral Abbreviations:**
regimen. Data suggests that fibrosis progression occurs most rapidly in patients with GT3; DAA regimens have also been less effective in patients with this genotype.\(^3\)

The SVR rate is defined as the proportion of patients who experience a decline in HCV-RNA to undetectable levels following completion of antiviral treatment, as measured by a sensitive polymerase chain reaction assay. It is the standard marker of successful treatment in clinical trials. There is some evidence based on only on observational data of an association of SVR and reductions in mortality, liver failure, and cancer.\(^5\) However, the results of these observational studies should be interpreted with great caution. SVR is still a non-validated, surrogate outcome and it is not clear that SVR is a ‘cure’ for HCV. Many of the observational studies compared two groups that were both treated making it difficult to attribute different outcomes to treatment.\(^1\) SVR has previously been shown as an invalid surrogate for clinical outcomes for the efficacy of interferons.\(^4\) Trials have historically used SVR at week 24 of follow-up (SVR24) as a primary endpoint. More recent studies use SVR rate at 12 weeks (SVR12) as the primary endpoint based on evidence that the majority of patients with SVR12 maintain SVR at 24 weeks.\(^6\)

The two major predictors of SVR are viral genotype and pre-treatment viral load.\(^7\) Other factors associated with an increased likelihood of SVR include female sex, age less than 40 years, non-Black race, lower body weight, absence of insulin resistance, and absence of bridging fibrosis or cirrhosis on liver biopsy. Studies that include patients with decompensated cirrhosis, renal failure or other comorbidities, and minority racial or ethnic groups are lacking though these patients remain the most difficult to successfully treat.\(^8\)

Patients at greatest risk for progression to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis (METAVIR stage 2 or higher). Patients with compensated cirrhosis are at risk of progressing to decompensation, developing hepatocellular carcinoma, and are at higher risk for death. Urgency to treat patients with CHC is higher when risk of decompensated cirrhosis or death from liver-related diseases is higher; treatment urgency is also higher in liver transplant recipients with CHC in order to prolong graft survival. Disease progression varies greatly among patients with compensated liver disease and the number needed to treat to prevent adverse long-term outcomes is dependent on several factors. The newer DAAAs will be most beneficial in patients at highest risk for cirrhosis-related events.\(^9\) However, treatment of CHC with DAAs at earlier stages of fibrosis incur substantial upfront costs but can be cost-effective long-term if adverse events are avoided from cure.\(^10\) Patients with decompensated liver disease are a challenging population to treat because of symptomatic complications related to cirrhosis (i.e., jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy). Clinical trials define decompensated cirrhosis as Child-Turcotte-Pugh (CTP) class B or C cirrhosis; the majority of decompensated cirrhosis patients included in trials have CTP class B cirrhosis. Those with stage 3 to 4 disease develop end stage liver disease at a rate of 1 to 2% per year after achieving SVR.\(^1\)

Virologic failure is defined as confirmed HCV RNA level at or above the lower limit of quantification (LLOQ) during treatment after previously being below the LLOQ; relapse is defined as confirmed HCV RNA level at or above the LLOQ after treatment after previously achieving an SVR.\(^11\) Virologic failure is typically associated with the emergence of resistance-associated variants (RAVs) that can cause cross resistance to other DAAs in the same class.\(^12\) Baseline RAVs exist in a minority of patients and are found in most patients who fail to achieve SVR with DAA treatment. Sofosbuvir (SOF), an NS5B inhibitor, appears to have the highest genetic barrier to resistance.\(^12\) Genetic polymorphisms that reduce drug susceptibility have been reported for the NS5A and NS3/4A (protease inhibitor) drug classes. The presence of baseline NS5A RAVs has been reported in the range from 1% to 23% and can significantly reduce SVR12 rates in patients with GT3 treated with daclatasvir (DCV) plus SOF compared to patients without the NS5A RAV (SVR rates of 54% vs. 92%, respectively).\(^13\) Another review of 35 clinical trials in patients with HCV GT1 found that pretreatment NS5A RAVs were detected in 13% of GT 1a and 18% with GT 1b and had an impact on SVR in some

patients, particularly treatment-experienced patients with GT 1a HCV.\textsuperscript{14} There remains debate on which patients should be screened for the presence of RAVs at baseline.

Therapies to treat CHC have advanced significantly over the past several years. Prior to 2011, the combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) was the standard of care and approximately only 55-60% of patients achieved a SVR with this regimen. In 2011, the FDA approved the first generation DAAs boceprevir and telaprevir.\textsuperscript{15} The DAAs target specific proteins of the virus, causing disruption of viral replication. There are currently four classes of DAAs, defined by their mechanism of action and therapeutic target (NS3/4A inhibitors, protease inhibitors [PIs], NS5B inhibitors and NS5A inhibitors). Due to adverse events, high rates of resistance and long duration of treatments, telaprevir was removed from the market and boceprevir is no longer a recommended therapy. Since then, a variety of second generation DAAs have been approved by the FDA resulting in many interferon-free options, fewer adverse events, and SVR12 rates that exceed 90% (Table 1). However, newer DAAs are associated with substantial cost and unknown effects on long-term clinical outcomes. A significant challenge is to identify patients who will most benefit from treatment since only 5-20% of CHC patients will develop cirrhosis over 20 years.\textsuperscript{16} Additionally, the lack of head-to-head trials, and the use of single-arm cohort studies make it difficult to compare the relative efficacy of the different DAA regimens available. Studies do not measure long-term morbidity or mortality. A major gap in the evidence remains the optimal treatment of patients who have had a virologic failure to a previous NS5A or NS5B inhibitor. Risk of DAA resistance is a major concern in this population. Two additional pangenotypic medications have been studied in those who have failed an NS5A inhibitor. One is a triple drug combination including SOF, VEL and a new NS3/4A inhibitor, voxilaprevir (VOX). The second is a combination of a NS3/4A inhibitor, glecaprevir (GLE) and a NS5A inhibitor, pibrentasvir (PIB). These agents will be reviewed at a future meeting.

The Oregon Drug Use Review/Pharmacy & Therapeutics (P&T) Committee initially prioritized treatment for the fee-for-service population to patients in greatest need of treatment. Limited real-world experience and data, consideration for the number of patients waiting for treatment, limited provider expertise, and the limited number of alternative treatment options in cases of treatment resistance and patient comorbidities all played a role in prioritizing treatment. As more treatment options become available, real world experience increases, and the community standard evolves, the P&T Committee has expanded treatment in a step-wise fashion to patients with less severe disease. Current drug policies in place approve treatment for patients with fibrosis Metavir stage 3 or 4, or patients with extrahepatic manifestations at any stage of fibrosis, patients in the setting of solid organ transplant, and in patients with fibrosis Metavir stage 2 or greater coinfected with HIV.

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<thead>
<tr>
<th>Table 1. Direct-acting Antiviral Regimens for Chronic Hepatitis C.</th>
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<tr>
<td><strong>Drug Brand Name</strong></td>
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<tr>
<td>Daklinza® and Solvaldi®</td>
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<tr>
<td>Epclusa®</td>
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<td>Harvoni®</td>
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<td>Olysio®</td>
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**Direct Acting Antiviral Abbreviations:**

- **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®
- **EBR/GZR** (elbasvir/grazoprevir): Zepatier®
- **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®
- **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®
- **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®
- **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®
- **SOF** (sofosbuvir): Sovaldi®

**Abbreviations:**

- **CHC** = chronic hepatitis C
- **GT** = genotype

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**Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted through week 1, July 2017. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. Randomized controlled trials and abstracts are in Appendix 3 and 4.

**Systematic Reviews:**

**Cochrane Collaboration**

A systematic review and meta-analysis was conducted by the Cochrane Collaboration to assess the benefits and harms of all DAAs in the treatment of CHC.¹ The three pre-specified primary outcomes were a composite of hepatitis C-related morbidity (cirrhosis, ascites, variceal bleeding, hepatorenal syndrome, hepatic encephalopathy or HCC) or all-cause mortality, serious adverse events, and health-related quality of life. The proportion of participants without SVR 12 or 24 weeks after completion of treatment was a secondary outcome. A comprehensive search for RCTs comparing DAAs versus no intervention or placebo or any medication intervention except for a DAA (pegylated interferon) through October 2016 identified 138 trials including 51 different DAAs, including both discontinued DAAs and those still under development. Many trials used for FDA approval of currently available DAAs were excluded from this analysis due to wrong control or study design. 85 of the 138 trials assessed DAAs on the market or currently under development. All trials had a high risk of bias due to inadequate allocation concealment, unclear or unblinding, incomplete outcome data or unclear selective reporting. Trials included treatment-naïve participants (95 trials), treatment-experienced (17), or both (24 trials). The majority of trials were in GT1 (119 trials); trials with genotypes 2-6 were extremely limited. In addition to traditional meta-analysis, Trial Sequential Analysis was performed to better control for random errors due to sparse data. HIV was an exclusion criterion for the analysis.

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criteria in 102 trials. In all but 1 trial, funding source was either not reported in sufficient detail or the trial was financially supported by an organization with a financial interest in the trial results.¹

Overall, the review found very low quality evidence of no difference in CHC morbidity or all-cause mortality from the DAAs compared to placebo or no intervention (OR 3.72; 95% CI 0.53 to 26.18).¹ There were very few data on mortality with DAAs (15/2377; 0.63%) compared to control (1/617; 0.16%) from 11 trials. There was no data on hepatitis C-related morbidity. Very low-quality evidence showed no difference in serious adverse events with DAAs (2.77%) compared to control (5.6%) (OR 0.93; 95% CI 0.75 to 1.15; p=0.52). Simeprevir was the only DAA showing a significantly lower risk of serious adverse events (OR 0.62; 95% CI 0.45 to 0.86). However, when one trial with an extreme result was excluded, the meta-analysis showed no difference. There was very low quality evidence from 32 trials that DAAs reduce the risk of no SVR compared to control (17.6% vs. 69.7%, respectively; RR 0.44; 95% CI 0.37 to 0.52; p<0.000001, ARR 52.1%; NNT 2). This was confirmed by Trial Sequential Analysis and the tests for statistical heterogeneity indicated significant heterogeneity, with a high risk of bias. There did not seem to be a difference between the different DAAs based on subgroup analysis and all subclasses of DAAs showed evidence of a significant effect on no SVR. The subgroup analysis comparing the DAAs in different genotypes did show evidence of a difference between the subgroups (p=0.002; I² = 73.6%). There was no difference in SVR between treatment-experienced (RR 0.50; 95% CI 0.36 to 0.69) and treatment-naïve (RR 0.48; 95% CI 0.41 to 0.56) participants. There is insufficient evidence to make conclusions on quality of life. Only one trial assessed quality of life and found no difference.

None of the trials measured the effects of DAAs on clinically important outcomes including ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy or HCC.

The authors concluded that there was insufficient evidence to confirm or reject that DAAs have any clinical effects, but they do seem to reduce the risk of no SVR, which is a non-validated surrogate outcome and the clinical significance of these effects on a non-validated surrogate outcome is unclear.

Criticism from experts in this field have argued that many clinical trials on DAA therapy were excluded from this review since they did not have an untreated control group but instead used the historical control response rates. Additionally, it is unlikely to have data supporting a benefit on HCV-related morbidity and all-cause mortality because of the natural history of HCV infection; clinical outcomes may take years to become apparent.¹⁷ Furthermore, experts cite data that SVR is associated with health benefits including a decrease in liver inflammation, rate of progression of liver fibrosis, HCC, and liver transplantation.¹⁷

**CADTH:**
Three CADTH reports addressing resistance-associated variants (RAVs) in HCV treatment were identified. However, they were all Rapid Response Reports with little detail or synthesis of included studies.

1) A CADTH Rapid Response Report reviewed the comparative clinical effectiveness of NS3 or NS5B inhibitors in DAA-naïve and DAA-experienced patients with RAVs of HCV.¹⁸ Thirteen publications met inclusion criteria and were included in the report. Many of the studies were post-hoc analyses of previously conducted studies and included only patients for whom sequencing data was available. The prevalence of baseline polymorphisms were often low and impact on outcomes is hard to determine based on this data. The included studies were limited due to small sample sizes, industry funding, and inclusion of four pooled analyses with unknown quality assessment of the included trials. The report concluded the following:

- In GT1 HCV treatment-naïve patients, the SVR rates (92% - 100%) with SOF (n=38) and PTV +/- DAS (n=7) containing treatment regimens were comparable between patients with and without NS5B RAVs.

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b. In GT1 treatment-experienced patients (prior SOF or SOF/LDV), SVR rates with SOF containing regimens (n=23) were comparable with and without NS5B RAVs (78%).

c. In HCV GT1 treatment-naive patients, SVR rates with GZR-containing regimens were comparable between patients with and without NS3 RAVs.

d. In HCV GT1 treatment-naïve patients, SVR rates with PTV or simeprevir containing regimens varied depending on the other drugs used in combination.

2) Another CADTH Rapid Response Report reviewed the clinical effectiveness of re-treatment in patients with NS5A RAVs who have failed on treatment with NS5A inhibitors. Only three publications met the inclusion criteria and were included in the report. All of these were non-randomized, open-label, and non-comparative studies. One was a ‘real world’ study, another study reported outcomes of one single arm from an eight-arm phase 2a study, and the third study was a sub-study of ION-4. They all had a high risk of bias and were low quality. Therefore, a literature search through June 2016 did not identify data to determine if patients who fail other NS5A inhibitors could be successfully retreated using the same intervention strategies. Retreatment strategies included SOF plus SIM after failure with a DCV-based regimen, retreatment with LDV/SOF after failure with LDV/SOF, and LDV/SOF for 24 weeks after failure with 12 weeks. SVR12 was 87.5%, 91% and 89%, respectively suggesting that these regimens are effective. However, the small sample sizes and low quality preclude a definitive conclusion.

3) A third CADTH Rapid Response Report reviewed the clinical effectiveness of HCV therapies containing NS5A inhibitors in DAA-naive patients with HCV GT1 and with NS5A RAVs at baseline. Current NS5A inhibitors include daclatasvir (DCV), velpatasvir (VEL), ledipasvir (LDV), elbasvir (EBR), and ombitasvir (OMB). A total of 16 publications were included in the report (eight secondary analyses of RCTs, five observational, one review article and two guidelines). However, the majority of studies were with DCV + asunaprevir, which the manufacturer is no longer seeking FDA approval for. The proportion of patients with NS5A RAVs at baseline with GT 1b HCV achieved a lower SVR (38-42%) than those without (88-99%). There were limited studies identified on other treatment regimens in patients with NS5A RAVs at baseline. One study found that in patients with HCV1b treated with DCV+SMV, the proportion of patients who achieved SVR12 was 50% for patients with NS5A RAVs and 91% for those without. One study evaluated treatment with LDV/SOF and found that SVR12 was not different for those with GT1 and baseline NS5A RAVs compared to those without (99% for both groups). Lastly, a study showed a decreased SVR12 for treatment with EBR/GZR in those with RAVs (58%) compared to without (96%). There were no studies on the cost-effectiveness of screening for NS5A RAVs at baseline. There is variability in the guidelines regarding recommendations for baseline testing, and recommendations are based on low quality evidence. Due to the poor quality and limited data, definitive conclusions cannot be made.

Clinical Practice Guidelines:
The World Health Organization (WHO) updated their guidelines for the screening care and treatment of persons with CHC in April 2016. The Veterans Affairs (VA) National Hepatitis C Resource Center updated treatment guidelines in March 2016, and the Guidelines from the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) updated their recommendations for testing, managing, and treating CHC in April 2017. The AASLD/IDSA guidelines are routinely updated to reflect rapidly changing evidence with the DAAs. The AASLD/IDSA guideline has many limitations with poor methodological quality. The panel lacks non-specialist members and there is no assessment of risk of bias for individual studies. In addition, the authors and sponsors of the guideline have multiple conflicts of interest.

The AASLD/IDSA guidelines were updated in April 2017 with the following changes:

1. Initial Treatment of CHC:

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a. Modified the duration of LDV/SOF in patients without cirrhosis to 8 weeks for non-black, HIV-uninfected, and whose HCV RNA is less than 6 million IU/ml. Previous recommendation was 8 weeks for those without cirrhosis and whose HCV RNA is less than 6 million IU/ml. The analysis on duration was not randomized and baseline characteristics may have varied between 8- and 12-week groups so the guidelines no longer recommend shortening treatment duration to less than 12 weeks for HIV-infected patients and African-American patients.
b. Updated grading of SOF/VEL for GT5 and 6
c. Language added related to recent data regarding 8 weeks of OMB/PTV-R + DAS for GT 1b with early stage fibrosis. A single phase b, single-arm study (n=163) showed a 98% SVR with 8 weeks of OMB/PTV-R + DAS.

2. Retreatment:
   a. For GT3, PEG/RBV treatment-experienced patients without cirrhosis, DCV/SOF or SOF/VEL for 12 weeks is recommended. For those with cirrhosis, EBR/GZR plus SOF or SOF/VEL plus RBV for 12 weeks is recommended. EBR/GZR plus SOF is recommended based on an unpublished study (n=100) with 53 patients who failed treatment with PEG/RBV. SVR12 was 100% with this regimen. This data is only available as a poster presentation.\(^2\)

3. Decompensated:
   a. Recommendations (SOF/VEL or LDV/SOF) for those with decompensated cirrhosis and GT 5 or 6 were made based on an extrapolation of data from trials in patients with compensated cirrhosis and GT 5 or 6. It is unclear if these results can be generalized to those with decompensated cirrhosis and there remains very limited data with DAAs in patients with CHC GT 5 and 6 with decompensated cirrhosis. \(^2\)

A further update from the AASLD/IDSA guidelines on treatment of adolescents with CHC is in progress.\(^2\)

Publication of both the WHO and VA guidelines preceded the approval of SOF/VEL and this agent is only included in the AASLD/IDSA guidelines. The following recommendations are included in these guidelines:

When to Treat:
AASLD/IDSA: Treatment for all patients regardless of disease severity is recommended, except those with short life expectancy that cannot be remediated by treatment or transplantation.\(^3\) Little evidence exists to support initiation of treatment in patients with limited life expectancy. Prior to treatment, the guideline continues to emphasize the need to assess the patient’s understanding of treatment goals and provision of education on adherence and follow-up.

WHO: HCV treatment should be considered for all persons with CHC, including persons who inject drugs. Persons with cirrhosis should be prioritized for treatment because they are at increased risk of HCC and death due to liver failure.\(^20\)

VA: All patients with CHC who did not have medical contraindications are potential candidates for treatment. Patients with advanced liver disease are likely to derive the greatest benefit from treatment.\(^21\) The urgency of treatment should be based on the risk of developing decompensated cirrhosis or dying from liver or liver-related disease, and prolonging graft survival in transplant recipients. In particular, patients with cirrhosis or advanced fibrosis, selected patients with HCC awaiting liver transplant, post-transplant recipients, patients with serious extra-hepatic manifestations of HCV, and women of childbearing potential who desire to conceive a child in the next 12 months should be considered for antiviral treatment in the near term. Patients with mild liver disease (METAVIR F0-2) have less urgency for treatment in the short-term, but should be informed of current treatments and the potential to cure HCV. Patients with mild liver disease (METAVIR F0-2) and no extra-hepatic manifestations can be treated in the near term if the patient desires treatment and is otherwise a candidate for HCV treatment.

Direct Acting Antiviral Abbreviations: DCV/SOF (Daclatasvir + sofosbuvir): Daklinza\(^®\) + Sovaldi\(^®\); EBR/GZR (elbasvir/grazoprevir): Zepatier\(^®\); LDV/SOF (ledipasvir/sofosbuvir): Harvoni\(^®\); OMB/PTV-R + DAS (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak\(^®\)/Viekira XR\(^®\); OMB/PTV-R (ombitasvir, paritaprevir and ritonavir): Technivie\(^®\); SOF/VEL (sofosbuvir/velpatasvir): Epclusa\(^®\); SOF (sofosbuvir): Sovaldi\(^®\)
Who Should Treat:
With all-oral shorter course regimens, treatment may be increasingly available outside of specialty clinics. Guidelines recommend that therapy should be managed by medical specialists with experience in the treatment of CHC infection and the physician prescribing should have knowledge of monitoring and ensuring patient adherence with therapy. The VA guideline states treatment can be provided by non-specialists trained in the management of CHC and who have access to specialists for support (Expert Opinion). However, patients with decompensated cirrhosis should be seen by a specialist with experience in the management of advanced disease.

Fast Progressing:
Progression of fibrosis from stage 0 (no fibrosis) to stage 4 (cirrhosis) is variable but takes place at approximately 0.10-0.15 fibrosis units per decade. The AASLD/IDSA guidelines includes the following patient populations to be at greater risk for rapidly progressive fibrosis and cirrhosis:
- HIV coinfection
- HBV coinfection and other coexistent liver disease (nonalcoholic steatohepatitis [NASH]): Several observational studies have found coinfected patients have more severe liver disease than those with monoinfection. However, there are no longitudinal studies to evaluate the rate of fibrosis progression in coinfected subjects and most data comes from studies with a small sample size and retrospective design. Additional studies with similar limitations have conflicting results. There are no published studies evaluating DAA regimens in patients with HBV/HCV coinfection.

Extrahepatic Manifestations:
The literature has linked HCV to a number of extrahepatic symptoms involving the skin, musculoskeletal, renal, cardiovascular and nervous systems. There are no studies evaluating the effects of DAA-based regimens on progression of extrahepatic complications and most of the literature consists of observational studies demonstrating an association which are at risk for selection bias. The quality of the evidence for these associations is extremely variable, and it is difficult to make definitive conclusions regarding the effect of DAAs on progression of extrahepatic manifestations. The following extrahepatic manifestations have been identified:
- Cryoglobulinemia and lymphoproliferative disorder
- Dermatologic manifestations: leukocytoclastic vasculitis, porphyria cutanea tarda, lichen planus
- Insulin Resistance and Type 2 Diabetes: There is growing observational evidence that HCV increases the risk of T2DM through induction of insulin resistance and that T2DM can accelerate the course of CHC.
- Lymphomas (B-cell non-Hodgkin lymphoma)

Alcohol and Drug Abuse Recommendations:
AASLD/IDSA: Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection. Persons identified as abusing alcohol and having alcohol dependence require treatment and consideration for referral to an addiction specialist. For individuals with acute HCV infection who have a history of recent injection drug use, referral to an addiction medicine specialist is recommended when appropriate.

WHO: An alcohol intake assessment is recommended for all persons with HCV infection followed by the offer of a behavioral alcohol reduction intervention for persons with moderate-to-high alcohol intake. Persons who inject drugs should be assessed for antiviral treatment. Persons who inject drugs are at increased
risk of HCV-related disease and transmission, as well as for all-cause morbidity and mortality, and therefore require specialized care and should be considered as a priority for HCV treatment.

VA: All patients should be evaluated for current alcohol and other substance use, with validated screening instruments such as AUDIT-C (www.hepatitis.va.gov/provider/tools/audit-c.asp). Patients with a history of substance or alcohol use disorders should be considered for HCV antiviral therapy on a case-by-case basis. There are no published data supporting a minimum length of abstinence as an inclusion criterion for HCV antiviral treatment, while multiple studies show successful treatment of patients who have short durations of abstinence or infrequent use of alcohol. Thus, automatic disqualification of patients as treatment candidates based on length of abstinence is unwarranted and strongly discouraged. The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once a month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. Patients with active substance or alcohol use disorders may be considered for therapy on a case-by-case basis, and care should be coordinated with substance use treatment specialists.

**Testing for Liver Cirrhosis:**

**AASLD/IDSA:** The use of biopsy, imaging, and/or noninvasive markers appropriate to evaluate advanced fibrosis should be considered in HCV patients planning on treatment (Class I, Level A). Guidelines also recommend that a biopsy should be considered for any patient with discordant results between 2 modalities that would affect clinical decision making. If direct biomarkers or elastography are not available, the AST-to-platelet ratio index (APRI) or FIB-4 index score can help, although neither test is sensitive enough to rule out significant fibrosis.

**WHO:** In resource-limited settings, it is suggested that the APRI or FIB-4 test be used for the assessment of hepatic fibrosis rather than other noninvasive tests that require more resources such as elastography or FibroTest (Conditional recommendation, low quality of evidence). FibroScan, which is more accurate than APRI and FIB-4, may be preferable in settings where the equipment is available and the cost of the test is not a barrier to testing.

**VA:** Testing recommendations include clinical findings (low platelet count), abdominal imaging for features of portal hypertension, liver fibrosis imaging (FibroScan and Acoustic Radiation force impulse [APRI]), serum markers of fibrosis (APRI, FIB-4, FibroSure, FibroTest), and liver biopsy as options. Liver biopsy should be reserved for situations in which the risks and limitations of the procedure are outweighed by the benefits of obtaining information via this technique.

**Decompensated Cirrhosis:**

All guidelines recommend patients with decompensated cirrhosis be considered for treatment on a case by case basis and should involve an experienced specialist who is able to manage complications.

**Recommendations for performing pre-treatment resistant testing:**

The VA guidelines recommend that NS5A resistance-associated variants (RAV) testing should be performed at baseline prior to initial treatment for GT 1a-infected patients who are being treated with EBR/GZR and for GT3 patients who are being treated with DCV. Patients who fail DAA treatment usually have RAVs to one or more classes of DAAs and should have testing done for each of the drug classes before being considered for re-treatment.
Retreatment:
The AASLD/IDSA guidelines have retreatment recommendations for those who have failed treatment with PEG/RBV or PEG/RBV + a NS3 PI (telaprevir, boceprevir, or simeprevir) that are similar to initial treatment recommendations for GT1 (Table 2). For those who have failed sofosbuvir plus RBV, LDV/SOF is the recommended therapy for GT1 based on limited data. At the time of this update, there were no published data on retreatment of SOF-based failure with non-sofosbuvir regimens. For NS5A treatment-experienced patients, the guidelines recommend deferral of treatment, pending additional data. If urgent treatment is necessary, it is recommended that the retreatment regimen be tailored based on resistance testing, a treatment duration of 24 weeks should be used and ribavirin should be added. No recommendations are provided for this NS5A treatment failures for GT 2-6. Additionally, for GT3 SOF treatment-experienced patients, deferral of treatment is also recommended unless urgent retreatment is required.

Recommended Treatment Options:
Treatment options based on genotype and treatment history are included in the following table:

<table>
<thead>
<tr>
<th>GT</th>
<th>Treatment History</th>
<th>Cirrhosis Status</th>
<th>Veterans Affairs Guidelines</th>
<th>AASLD/IDSA Guidelines</th>
<th>WHO Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Naïve or Experienced (PEG-INF/RBV only)</td>
<td>Non-cirrhotic</td>
<td>EBR/GZR x 12 weeks **&lt;br&gt;LDV/SOF x 12 weeks</td>
<td>EBR/GZR x 12 weeks**&lt;br&gt;LDV/SOF x 8-12 weeks&lt;br&gt;OMB/PTV-R + DAS + RBV x 12 weeks&lt;br&gt;SOF/VEL x 12 weeks&lt;br&gt;DCV/SOF x 12 weeks</td>
<td>DCV/SOF x 12 weeks&lt;br&gt;LDV/SOF x 8-12 weeks</td>
</tr>
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<td>Cirrhotic</td>
<td>LDV/SOF + RBV x 8-12 weeks</td>
<td>EBR/GZR x 12 weeks**&lt;br&gt;LDV/SOF x 12 weeks&lt;br&gt;SOF/VEL x 12 weeks&lt;br&gt;OMB/PTV-R + DAS x 12 weeks</td>
<td>DCV/SOF +/– RBV x 12 weeks&lt;br&gt;LDV/SOF +/– RBV x 12 weeks</td>
<td>DCV/SOF x 12 weeks</td>
</tr>
<tr>
<td>1</td>
<td>Decompensated Cirrhosis</td>
<td>LDV/SOF + RBV x 12 weeks</td>
<td>EBR/GZR x 12 weeks**&lt;br&gt;LDV/SOF x 12 weeks&lt;br&gt;SOF/VEL x 12 weeks&lt;br&gt;OMB/PTV-R + DAS x 12 weeks</td>
<td>DCV/SOF x 12 weeks</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Experienced (prior sofosbuvir)</td>
<td>Non-cirrhotic or cirrhosis</td>
<td>EBR/GZR x 12 weeks +/- RBV</td>
<td>LDV/SOF + RBV x 12 weeks&lt;br&gt;SOF + RBV X 12 weeks&lt;br&gt;DCV/SOF + RBV X 12 weeks</td>
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<td>1</td>
<td>Experienced (Prior NS3A/4A inhibitor)</td>
<td>Non-cirrhotic (or cirrhotic CTP A)</td>
<td>EBR/GZR + RBV x 12 weeks</td>
<td>LDV/SOF X 12 weeks&lt;br&gt;SOF/VEL x 12 weeks&lt;br&gt;DCV/SOF X 12 weeks&lt;br&gt;EBR/GZR + RBV X 12 weeks</td>
<td>N/A</td>
</tr>
<tr>
<td>1</td>
<td>Experienced (Prior NS5A-containing regimen or SMV)</td>
<td>Test for RAPs to NS5A prior to re-treatment. Consult with an expert based on results.</td>
<td>Deferral of treatment, pending more data. Testing for RAVs should be done.</td>
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<td>SOF + RBV x 12 weeks</td>
<td>SOF/VEL x 12 weeks</td>
<td>SOF + RBV X 12 weeks</td>
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</tr>
<tr>
<td>2</td>
<td>Decompensated</td>
<td>SOF + RBV x 16 weeks</td>
<td>SOF/VEL + RBV X 12 weeks&lt;br&gt;DCV/SOF + RBV X 12 weeks</td>
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<tr>
<td>2</td>
<td>Experienced (Prior PEG-INF/RBV)</td>
<td>Non-cirrhotic or Cirrhotic</td>
<td>SOF + RBV x 16 weeks</td>
<td>SOF/VEL x 12 weeks</td>
<td>N/A</td>
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<tr>
<td>2</td>
<td>Experienced (SOF + RBV)</td>
<td>Non-cirrhotic or Cirrhotic</td>
<td>The optimal DAA-based therapy for this patient population is not known. Consult with an expert</td>
<td>DCV/SOF x 24 weeks&lt;br&gt;SOF/VEL + RBV X 12 weeks</td>
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<td>LDV/SOF + RBV x 12 weeks*</td>
<td>DCV/SOF x 12 weeks&lt;br&gt;SOF/VEL X 12 weeks</td>
<td>DCV/SOF X 12 weeks&lt;br&gt;DCV/SOF + RBV X 24 weeks&lt;br&gt;SOF/VEL + RBV X 12 weeks</td>
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<tr>
<td>3</td>
<td>Cirrhotic</td>
<td>DCV/SOF + RBV x 12 weeks</td>
<td>SOF/VEL + RBV X 12 weeks&lt;br&gt;DCV/SOF + RBV X 24 weeks</td>
<td>SOF/VEL + RBV X 12 weeks</td>
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<td>Decompensated Cirrhosis</td>
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<table>
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<tr>
<th>Experience</th>
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<th>Regimen 1</th>
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<th>Regimen 3</th>
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<td>Experienced (Prior PEG-IFN/RBV only)</td>
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<tr>
<td></td>
<td>Cirrhotic</td>
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<td>SOF/VEL x 12 weeks</td>
<td>DCV/SOF + RBV x 24 weeks</td>
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<tr>
<td>Experienced (SOF + RBV)</td>
<td>Non-cirrhotic or Cirrhotic</td>
<td>The optimal DAA-based therapy for this patient population is based on expert opinion. Recommend NS5A resistance testing.</td>
<td>Deferral if retreatment is not urgent</td>
<td>N/A</td>
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<td>EBV/GZR x 12 weeks</td>
<td>OMB/PTV- R + RBV x 12 weeks</td>
<td>DCV/SOF x 12 weeks</td>
</tr>
<tr>
<td></td>
<td>Cirrhotic</td>
<td>EBV/GZR x 12 weeks</td>
<td>OMB/PTV- R + RBV x 12 weeks</td>
<td>DCV/SOF x 24 weeks</td>
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<tr>
<td></td>
<td>Decompensated Cirrhosis</td>
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<td>SOF/VEL x 12 weeks</td>
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<tr>
<td>Experienced (Prior PEG-IFN/RBV only)</td>
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<td>SOF/VEL x 12 weeks</td>
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<tr>
<td>Naïve or Experienced (Prior PEG-IFN/RBV only)</td>
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<td>LDV/SOF x 12 weeks</td>
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</table>

**No baseline NSSA RAVs**

Abbreviations: DAA = direct acting antiviral; DCV = daclatasvir; EBV/GZR = elbasvir/grazoprevir; LDV/SOF = ledipasvir/sofosbuvir; OMB/PTV-R + DAS = ombitasvir, paritaprevir and ritonavir with dasabuvir; PEG-IFN = pegylated interferon; VEL/SOF = velpatasvir/sofosbuvir; RBV = ribavirin; SOF = sofosbuvir

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**National Institute for Health and Care Excellence (NICE)**

A technology appraisal guidance was published in January 2017 regarding SOF/VEL for treating CHC. NICE recommended SOF/VEL as an option for treating CHC in adults, only if the company provides the drug with the agreed upon discount. It was recommended for HCV GT 1-6 with or without compensated cirrhosis as well as for those with decompensated cirrhosis (with ribavirin), except for untreated GT2 without cirrhosis. This recommendation was based on review of the four key randomized controlled phase III trials evaluating SOF/VEL on SVR. The committee concluded that the trials showed high SVRs (89% to 100%) regardless of HCV genotype, cirrhosis stage or treatment history. However, there was a high risk of bias in the open-label trials. The committee also concluded that the adverse events associated with SOF/VEL are generally tolerable. Additionally, they concluded there is insufficient evidence to consider those with drug-resistant mutations separately to the overall population.

**New FDA Safety Alerts:**

In October 2016, the FDA warned about the risk of hepatitis B virus (HBV) reactivation in any patient with a current or previous infection with HBV undergoing treatment with DAAs. This HBV reactivation can result in serious liver problems or death. Twenty four cases of HBV reactivation while receiving DAAS were found in the literature. HBV occurred an average of 52 days (range of 4-8 weeks) after starting treatment. Three patients progressed to decompensated liver disease and 2 of the patients died. The mechanism of HBV reactivation is not known. Since patients with HBV co-infection were excluded from all phase III trials of DAAs, HBV reactivation was not identified in clinical trials.
FDA recommends that all patients should be screened for evidence of current or prior HBV infection prior to starting treatment with DAAs; monitor is recommended for HBV reactivation during treatment and following treatment. Clinical guidelines were updated to recommend that all patients be tested for HBsAg, HBsAb, and HBeAb status. In patients with serologic evidence of HBV, baseline HBV DNA should be measured prior to DAA treatment and monitored during therapy and for several weeks after. Antiviral therapy for HBV infection should be given if criteria for treatment are met.

**New Indications:**
In April 2017, the FDA approved SOF (Sovaldi) and LDV/SOF (Harvoni) to treat HCV in children ages 12 to 17 weighing at least 35 kilograms. These are the only two DAAs approved for children with HCV. It is estimated that there are 23,000 to 46,000 children in the U.S. with HCV.

Sofosbuvir was approved in combination with ribavirin for those with GT 2 or 3 without cirrhosis or with compensated cirrhosis based on an ongoing unpublished, open-label study in 13 adolescents with GT2 (12 weeks) and 37 adolescents with GT3 (24 weeks). Results are not available on clinicaltrials.gov. According to the FDA, 100% of patients with GT2 and 97% of patients with GT3 achieved SVR12.

SOF/LDV was approved for HCV GT 1, 4, 5 or 6 without cirrhosis or mild cirrhosis based on an ongoing, unpublished and open-label study (n=100). Results are not available on clinicaltrials.gov. According to the FDA, 98% of patients achieved SVR12.

Children with GT 1 or 4 are currently being studied in a trial of OMB/PTV-R +/- DAS.

An update from the AASLD/IDSA guidelines regarding treatment of CHC in adolescent patients is in process.

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

References

34. HAVRONI (ledipasvir and sofosbuvir) Prescribing Information. Gilead Pharmaceuticals. 4/2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205834s017lbl.pdf.

### Appendix 1: Current Preferred Drug List

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<td>SIMEPREVIR SODIUM</td>
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</table>

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®
## Appendix 2: OVID Search Results

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<tr>
<td>14</td>
<td>limit 13 to (english language and humans and yr=&quot;2016 -Current&quot; and (clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or meta analysis or practice guideline or randomized controlled trial or systematic reviews))</td>
<td>68</td>
<td>Advanced</td>
<td>Display Results</td>
<td>More</td>
</tr>
</tbody>
</table>

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®
Appendix 3: Summary of Randomized Controlled Trials

Randomized Controlled Trials:
After initial review, 23 trials were manually reviewed from the literature search. The majority of trials were excluded due to wrong study design, wrong comparator, poor quality, or unapproved medication. The remaining 6 trials are briefly described in the table below.

Table 1: Description of Randomized Comparative Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Population</th>
<th>Results (Primary Outcome; SVR12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gane, 2016(^{35}) (2 phase II, open-label, single-arm trials)</td>
<td>ABT-493 (glecaprevir) + ABT-530 (pibrentasvir) +/- RBV, 12 or 16 weeks</td>
<td>GT3 and GT1, with compensated cirrhosis (n=82)</td>
<td>SVR12: GT1; 12 weeks: 26/27 (96%; 95% CI 82-99)</td>
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<td>SVR12: GT3; 12 weeks: 27/28 (96%; 95% CI 82-99)</td>
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<td></td>
<td></td>
<td></td>
<td>GT3; + RBV 27/27 (100%; 95% CI 88-100)</td>
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<tr>
<td>Kwo, 2017(^{36}) (2 phase II, open-label trials)</td>
<td>Glecaprevir/pibrentasvir dose ranging study with or without RBV</td>
<td>GT1-6 without cirrhosis</td>
<td>SVR12: GT1: 200 mg/40 mg: 38/39 (97%; 95% CI 87-100)</td>
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<td>200 mg/120 mg: 40/40 (100%; 95% CI 91-100)</td>
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<td>GT2: 200 mg/120 mg: 24/24 (10%; 95% CI 86-100)</td>
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<td>300 mg/120 mg: 24/25 (96%; 95% CI 80-99)</td>
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<td>GT3: 200 mg/40 mg: 25/30 (83%; 95% CI 66-93)</td>
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<td>200 mg/120 mg 28/30 (93%; 95% CI 79-98)</td>
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<td></td>
<td>200 mg/120 mg + RBV: 29/30 (94%; 95% CI 79-98)</td>
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<td></td>
<td></td>
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<td>300 mg/120 mg: 28/30 (93%; 95% CI 79-98)</td>
</tr>
<tr>
<td>Gane, 2016(^{37}) (phase II, open-label trial)</td>
<td>SOF/VEL/GS-9857 4, 6, and 8 weeks</td>
<td>GT 1 or 3 with or without compensated cirrhosis (n=161)</td>
<td>SVR12: GT1: Treatment-naïve; 6 weeks: 14/15 (93%; 95% CI 68-99)</td>
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<td>Treatment-naïve, with cirrhosis; 6 wk 15/18 (83%; 95% CI 59-96)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment-naïve, with cirrhosis; 6 weeks 13/15 (87%; 60 to 98)</td>
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<td></td>
<td>PEG/RBV-experienced, with cirrhosis; 8 wk</td>
</tr>
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</table>

Direct Acting Antiviral Abbreviations: DCV/SOF (Daclatasvir + sofosbuvir); Daklinza® + Sovaldi®; EBR/GZR (elbasvir/grazoprevir); Zepatier®; LDV/SOF (ledipasvir/sofosbuvir); Harvoni®; OMB/PTV-R + DAS (ombitasvir, paritaprevir and ritonavir with dasabuvir); Viekira Pak®/Viekira XR®; OMB/PTV-R (ombitasvir, paritaprevir and ritonavir); Technivie®; SOF/VEL (sofosbuvir/velpatasvir); Epclusa®; SOF (sofosbuvir): Sovaldi®
| Bourliere, 2017¹ (2 phase III RCTs) | SOF/VEL/VXP | GT1-6 previously treated with a DAA-containing regimen | Previous NS5A inhibitor 
SVR12: 
SOF/VEL/VXP: 253/263 (96%) | Previous treated with DAA, not including NS5A inhibitor 
SOF/VEL/VXP: 178/182 (98%) 
SOF/VEL: 136/151 (90%) |
|---|---|---|---|---|
| Leroy, 2016³⁸ RCT, phase III, open-label | DCV/SOF + RBV for 12 or 16 weeks | GT 3 with advanced fibrosis or compensated cirrhosis | SVR12: 
12 wk: 21/24 (87.5%; 95% CI 67.6-97.3) 
16 wk: 24/26 (92.3%; 95% CI 74.9-99.1) | |
| Kwo, 2017³⁹ Phase III, open-label, RCT | EBR/GZR x 12 weeks vs. EBR/GZR + RBV x 12 weeks vs. EBR/GZR x 16 weeks vs. EBR/GZR + RBV x 16 week | GT 1, 4, or 6 with or without cirrhosis, previously treated with PEG/RBV (n=420) | SVR12: 
12 weeks: 
EBR/GZR: 92.4% 
EBR/GZR + RBV: 94.2% | SVR12: 
16 weeks: 
EBR/GZR: 92.4% 
EBR/GZR + RBV: 98.1% |

**Direct Acting Antiviral Abbreviations:**
- **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®
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- **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®
- **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®
- **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®
- **SOF** (sofosbuvir): Sovaldi®
- **PEG/RBV**-experienced; 8 wk 
17/17 (100%; 81 to 100) 
DAA-experienced; 8 wk 
20/30 (67%; 47 to 83) 
Pl-experienced; 8 wk 
25/28 (89%, 72-98)
- **19/19 (100%; 95% CI 82-100)**
- **DAA-experienced; 8 wk** 
**4/4 (100%; 40-100)**
Appendix 4: Abstracts of Randomized Controlled Trials:


**BACKGROUND & AIMS:**
The combination of ABT-493 (NS3/4A protease inhibitor) plus ABT-530 (NS5A inhibitor) has shown high rates of sustained virologic response at post-treatment week 12 (SVR12) in noncirrhotic patients infected with hepatitis C virus (HCV) genotypes (GTs) 1-6. We describe 2 open-label phase 2 studies investigating the efficacy and safety of ABT-493 plus ABT-530 with or without ribavirin (RBV) in GT1- or GT3-infected patients with compensated cirrhosis.

**METHODS:**
Patients with GT1 infection received 200 mg ABT-493 plus 120 mg ABT-530 for 12 weeks. Patients with GT3 infection were randomized 1:1 to receive 300 mg ABT-493 plus 120 mg ABT-530 with or without once-daily 800 mg RBV for 12 weeks; treatment-experienced patients who were not treated with RBV received 16 weeks of therapy. Efficacy was measured by SVR12, defined as an HCV-RNA level less than 25 IU/mL. Adverse events and laboratory parameters were evaluated throughout the study.

**RESULTS:**
Twenty-seven patients with GT1 infection and 55 patients with GT3 infection were enrolled. The majority were treatment-naive (84%) and male (65%). In patients with GT1 infection, SVR12 was achieved by 96% (26 of 27; 95% confidence interval [CI], 82-99) of patients, with 1 relapse. Among GT3-infected patients, SVR12 was achieved in 96% (27 of 28; 95% CI, 82-99) of patients in the RBV-free arm (1 relapse), and in 100% (27 of 27; 95% CI, 88-100) in the RBV-containing arm. The most common adverse events were headache, fatigue, and nausea. Laboratory abnormalities were rare; no patient discontinued treatment.

**CONCLUSIONS:**
In cirrhotic HCV GT1- or GT3-infected patients, ABT-493 plus ABT-530 with or without RBV achieved SVR12 rates of 96%-100% and was well tolerated. ClinicalTrials.gov identifiers NCT02243280 and NCT02243293.


**BACKGROUND & AIMS:**
Hepatitis C virus (HCV) therapy that is highly efficacious, pangenotypic, with a high barrier to resistance and short treatment duration is desirable. The efficacy and safety of 8- and 12-week treatments with glecaprevir (ABT-493; NS3/4A protease inhibitor) and pibrentasvir (ABT-530; NS5A inhibitor) were evaluated in non-cirrhotic patients with chronic HCV genotype 1-6 infection.

**METHODS:**

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®
SURVEYOR-I and SURVEYOR-II were phase II, open-label, multicenter, dose-ranging trials including patients with chronic HCV genotype 1-6 infection who were either previously untreated or treated with pegylated interferon plus ribavirin. Patients received once-daily glecaprevir plus pibrentasvir at varying doses with or without ribavirin for 8 or 12 weeks. The primary efficacy endpoint was the percentage of patients with a sustained virologic response at post-treatment week 12 (SVR12).

RESULTS:
Of the 449 patients who received varying doses of glecaprevir plus pibrentasvir, 25%, 29%, 39%, and 8% had HCV genotype 1, 2, 3, and 4-6 infection, respectively. Twelve-week treatment achieved SVR12 in 97-100%, 96-100%, 83-94%, and 100% in genotypes 1, 2, 3, and 4-6, respectively. Eight-week treatment with 300mg glecaprevir plus 120mg pibrentasvir in genotype 1-, 2-, or 3-infected patients yielded 97-98% SVR12 with no virologic failures. Three (0.7%) patients discontinued treatment due to adverse events; most events were mild (grade 1) in severity. No post-nadir alanine aminotransferase elevations were observed.

CONCLUSIONS:
Glecaprevir plus pibrentasvir was well tolerated and achieved high sustained virologic response rates in HCV genotypes 1-6-infected patients without cirrhosis following 8- or 12-week treatment durations.

LAY SUMMARY:
The combination of direct-acting antivirals glecaprevir and pibrentasvir comprise a once-daily, all-oral, pangenotypic treatment for HCV genotype 1-6 infection. This article describes results from two phase II trials investigating a range of doses at treatment durations of 8 or 12 weeks in 449 patients without cirrhosis. Efficacy of the optimal dose, as determined by rates of sustained virologic response at post-treatment week 12, ranged from 92%-100%; treatment was well tolerated and significant laboratory abnormalities were rare.


BACKGROUND & AIMS:
We performed a phase 2 trial of the efficacy and safety of 4, 6, and 8 weeks of sofosbuvir, given in combination with the NS5A inhibitor velpatasvir and the NS3/4A protease inhibitor GS-9857, in patients with hepatitis C virus (HCV) infection.

METHODS:
We enrolled 161 treatment-naïve or previously treated patients infected with HCV genotypes 1 or 3 with or without compensated cirrhosis at 2 centers in New Zealand, from September 2014 through March 2015. All patients received sofosbuvir (400 mg) and velpatasvir (100 mg) plus GS-9857 (100 mg) once daily. The primary efficacy end point was sustained virologic response at 12 weeks after therapy (SVR12). The duration of therapy was determined by baseline patient characteristics: 4 or 6 weeks for treatment-naïve patients without cirrhosis, 6 weeks for treatment-naïve patients with cirrhosis, and 6 or 8 weeks for treatment-experienced patients with or without cirrhosis.
RESULTS:
Four weeks of sofosbuvir, velpatasvir, and GS-9857 produced an SVR12 in 4 of 15 (27%) treatment-naive patients with HCV genotype 1 without cirrhosis. Six weeks of this combination produced a SVR12 in 14 of 15 (93%) treatment-naive patients with HCV genotype 1 without cirrhosis, in 13 of 15 (87%) treatment-naive genotype 1 patients with cirrhosis, in 15 of 18 (83%) treatment-naive patients with HCV genotype 3 with cirrhosis, and in 20 of 30 (67%) patients with HCV genotype 1 who had failed an all-oral regimen of 2 or more direct-acting antiviral agents. Eight weeks of the drug combination produced an SVR12 in 17 of 17 (100%) patients with HCV genotype 1, in 19 of 19 (100%) patients with HCV genotype 3 and cirrhosis who had failed pegylated interferon plus ribavirin, in 25 of 28 (89%) patients with HCV genotype 1 who had failed protease inhibitor-based triple therapy, and in 4 of 4 (100%) patients with HCV genotype 3 who had failed an all-oral regimen of ≥2 direct-acting antiviral agents. The most common reported adverse events were headache, nausea, and fatigue.

CONCLUSIONS:
Eight weeks of treatment with the combination of sofosbuvir, velpatasvir, and GS-9857 produced an SVR12 in most treatment-naive or previously treated patients with HCV genotype 1 or 3 infections, including those with compensated cirrhosis. ClinicalTrials.gov, Number: NCT02202980.


BACKGROUND:
Patients who are chronically infected with hepatitis C virus (HCV) and who do not have a sustained virologic response after treatment with regimens containing direct-acting antiviral agents (DAAs) have limited retreatment options.

METHODS:
We conducted two phase 3 trials involving patients who had been previously treated with a DAA-containing regimen. In POLARIS-1, patients with HCV genotype 1 infection who had previously received a regimen containing an NS5A inhibitor were randomly assigned in a 1:1 ratio to receive either the nucleotide polymerase inhibitor sofosbuvir, the NS5A inhibitor velpatasvir, and the protease inhibitor voxilaprevir (150 patients) or matching placebo (150 patients) once daily for 12 weeks. Patients who were infected with HCV of other genotypes (114 patients) were enrolled in the sofosbuvir-velpatasvir-voxilaprevir group. In POLARIS-4, patients with HCV genotype 1, 2, or 3 infection who had previously received a DAA regimen but not an NS5A inhibitor were randomly assigned in a 1:1 ratio to receive sofosbuvir-velpatasvir-voxilaprevir (163 patients) or sofosbuvir-velpatasvir (151 patients) for 12 weeks. An additional 19 patients with HCV genotype 4 infection were enrolled in the sofosbuvir-velpatasvir-voxilaprevir group.

RESULTS:
In the three active-treatment groups, 46% of the patients had compensated cirrhosis. In POLARIS-1, the rate of sustained virologic response was 96% with sofosbuvir-velpatasvir-voxilaprevir, as compared with 0% with placebo. In POLARIS-4, the rate of response was 98% with sofosbuvir-velpatasvir-voxilaprevir and 90% with sofosbuvir-velpatasvir. The most common adverse events were headache, fatigue, diarrhea, and nausea. In the active-treatment groups in both trials, the percentage of patients who discontinued treatment owing to adverse events was 1% or lower.

CONCLUSIONS:

Direct Acting Antiviral Abbreviations: DCV/SOF (Daclatasvir + sofosbuvir); Daklinza® + Sovaldi®; EBR/GZR (elbasvir/grazoprevir); Zepatier®; LDV/SOF (ledipasvir/sofosbuvir); Harvoni®; OMB/PTV-R + DAS (ombitasvir, paritaprevir and ritonavir with dasabuvir); Viekira Pak®/Viekira XR®; OMB/PTV-R (ombitasvir, paritaprevir and ritonavir); Technivie®; SOF/VEL (sofosbuvir/velpatasvir); Epclusa®; SOF (sofosbuvir): Sovaldi®
Sofosbuvir-velpatasvir-voxilaprevir taken for 12 weeks provided high rates of sustained virologic response among patients across HCV genotypes in whom treatment with a DAA regimen had previously failed. (Funded by Gilead Sciences; POLARIS-1 and POLARIS-4 ClinicalTrials.gov numbers, NCT02607735 and NCT02639247.).


Patients with hepatitis C virus (HCV) genotype 3 infection, especially those with advanced liver disease, are a challenging population in urgent need of optimally effective therapies. The combination of daclatasvir (DCV; pangenotypic nonstructural protein 5A inhibitor) and sofosbuvir (SOF; nucleotide nonstructural protein 5B inhibitor) for 12 weeks previously showed high efficacy (96%) in noncirrhotic genotype 3 infection. The phase III ALLY-3+ study (N = 50) evaluated DCV-SOF with ribavirin (RBV) in treatment-naïve (n = 13) or treatment-experienced (n = 37) genotype 3-infected patients with advanced fibrosis (n = 14) or compensated cirrhosis (n = 36). Patients were randomized 1:1 to receive open-label DCV-SOF (60 + 400 mg daily) with weight-based RBV for 12 or 16 weeks. The primary endpoint was sustained virological response at post-treatment week 12 (SVR12). SVR12 (intention-to-treat) was 90% overall (45 of 50): 88% (21 of 24) in the 12-week (91% observed) and 92% (24 of 26) in the 16-week group. All patients with advanced fibrosis achieved SVR12. SVR12 in patients with cirrhosis was 86% overall (31 of 36): 83% (15 of 18) in the 12-week (88% observed) and 89% (16 of 18) in the 16-week group; for treatment-experienced patients with cirrhosis, these values were 87% (26 of 30), 88% (14 of 16; 93% observed), and 86% (12 of 14), respectively. One patient (12-week group) did not enter post-treatment follow-up (death unrelated to treatment). There were 4 relapses (2 per group) and no virological breakthroughs. The most common adverse events (AEs) were insomnia, fatigue, and headache. There were no discontinuations for AEs and no treatment-related serious AEs.

CONCLUSION:
The all-oral regimen of DCV-SOF-RBV was well tolerated and resulted in high and similar SVR12 after 12 or 16 weeks of treatment among genotype 3-infected patients with advanced liver disease, irrespective of past HCV treatment experience.


BACKGROUND & AIMS:
Patients infected with hepatitis C virus (HCV) genotype 1, 4, or 6, with or without cirrhosis, previously treated with peg-interferon and ribavirin, are a challenge to treat. We performed a phase 3 randomized controlled open-label trial to assess the effects of 12 or 16 weeks of treatment with once-daily elbasvir (an HCV NS5A inhibitor, 50 mg) and grazoprevir (an HCV NS3/4A protease inhibitor, 100 mg), in a fixed-dose combination tablet, with or without twice-daily ribavirin, in this patient population.

METHODS:
We analyzed data from 420 patients (35% with cirrhosis, 64% with a null or partial response to peg-interferon and ribavirin) who were randomly assigned (1:1:1:1) to groups given elbasvir and grazoprevir once daily, with or without twice-daily ribavirin, for 12 or 16 weeks, at 65 study centers in 15 countries in Europe, Asia, and Central and North America. Randomization was stratified by cirrhosis status and type of peg-interferon and ribavirin treatment failure. HCV

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RNA was measured using COBAS TaqMan v2.0. The primary end point was HCV RNA <15 IU/mL, 12 weeks after completion of treatment (SVR12). We aimed to determine whether the proportion of patients achieving an SVR12 in any group was greater than the reference rate (58%).

RESULTS:
With 12 weeks of treatment, an SVR12 was achieved by 92.4% of patients given elbasvir and grazoprevir and 94.2% of patients given elbasvir and grazoprevir with ribavirin. With 16 weeks of treatment, an SVR12 was achieved by 92.4% of patients given elbasvir and grazoprevir and 98.1% of patients given elbasvir and grazoprevir with ribavirin. Among patients treated for 12 weeks without ribavirin, virologic failure occurred in 6.8%, 0%, and 12.5% of patients with HCV genotype 1a, 1b, or 4 infection, respectively. Among patients given elbasvir and grazoprevir for 12 weeks, virologic failure occurred in 0% of patients infected with HCV genotypes 1 and 4 who relapsed after completing peg-interferon and ribavirin, and 7.5% infected with HCV genotypes 1 and 4, respectively, with a null or partial response to peg-interferon and ribavirin. Among patients treated for 16 weeks who received ribavirin, there were no incidences of virologic failure.

Common adverse events were fatigue (23.1%), headache (19.8%), and nausea (11.0%).

CONCLUSIONS:
The combination tablet of elbasvir and grazoprevir, with or without ribavirin, was highly efficacious in inducing an SVR12 in patients with HCV genotype 1, 4, or 6 infection failed by previous treatment with peg-interferon and ribavirin, including patients with cirrhosis and/or a prior null response. The treatment was generally well tolerated. ClinicalTrials.gov Number: NCT02105701.
Appendix 5: Proposed Prior Authorization Criteria

### Hepatitis C Direct-Acting Antivirals

**Goals:**
- Approve use of cost-effective treatments supported by the medical evidence.
- Provide consistent patient evaluations across all hepatitis C treatments.
- Ensure appropriate patient selection based on disease severity, genotype, and patient comorbidities.

**Length of Authorization:**
- 8-12 weeks

**Requires PA:**
- All direct-acting antivirals for treatment of Hepatitis C

<table>
<thead>
<tr>
<th>Approval Criteria</th>
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<tbody>
<tr>
<td>1. What diagnosis is being treated?</td>
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<td>2. Is the request for treatment of chronic Hepatitis C infection?</td>
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<tr>
<td>3. Is expected survival from non-HCV-associated morbidities more than 1 year?</td>
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Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®
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| 4. Has all of the following pre-treatment testing been documented:  
  a. Genotype testing in past 3 years;  
  b. Baseline HCV RNA level in past 6 months;  
  c. Current HIV status of patient  
  d. Current HBV status of patient  
  e. Pregnancy test in past 30 days for a woman of child-bearing age; and  
  f. History of previous HCV treatment and outcome? |

**Yes:** Record results of each test and go to #5

**No:** Pass to RPh. Request updated testing.

Note: Direct-acting antiviral agents can re-activate hepatitis B in some patients. Patients with history of HBV should be monitored carefully during and after treatment for flare-up of hepatitis. **Prior to treatment with a DAA, all patients should be tested for HBsAG, HBsAb, and HBcAb status.**

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## Approval Criteria

| 5. Has the patient failed treatment with any of the following HCV NS5A inhibitors: a) Daclatasvir plus sofosbuvir; b) Ledipasvir/sofosbuvir; c) Paritaprevir/ritonavir/ombitasvir plus dasabuvir; d) Elbasvir/grazoprevir; or e) Sofosbuvir/velpatasvir)? | **Yes:** Pass to RPh. Deny; medical appropriateness. 
Note: If urgent retreatment is needed, resistance testing must be done to indicate susceptibility to prescribed regimen. 
Refer to medical director for review. | **No:** Go to #6 |
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<td><strong>Note:</strong> Patients who failed treatment with sofosbuvir +/- ribavirin or PEGylated interferon can be retreated (see table below).</td>
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<tr>
<td>6. Which regimen is requested?</td>
<td>Document and go to #7</td>
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| 7. Does the patient have HIV coinfection AND: A biopsy, imaging test (transient elastography [FibroScan], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE], or serum test if the above are not available (FIBROSpect II; Fibrometer; enhanced liver fibrosis [ELF]) to indicate fibrosis (METAVIR F2) AND the patient and is under treatment by a specialist with experience in HIV? | **Yes:** Go to #12 
Note: Other imaging and blood tests are not recommended based on evidence of poor sensitivity and specificity compared to liver biopsy. 
For results falling in a range (e.g. F2 to F3), fibrosis stage should be categorized as the higher F stage for the purpose of treatment, or require one additional, more specific test (per HERC AUROC values) to be obtained to determine the stage of fibrosis. However, additional testing cannot be limited to biopsy. After one additional test, if a range still exists, the highest F score in the range will be used for determining coverage. | **No:** Go to #8 |

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir); **EBR/GZR** (elbasvir/grazoprevir); **LDV/SOF** (ledipasvir/sofosbuvir); **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir); **Viekira Pak/Viekira XR**; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir); **Technivie**; **SOF/VEL** (sofosbuvir/velpatasvir); **Epclusa**; **SOF** (sofosbuvir): Sovaldi®
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<th>Approval Criteria</th>
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<tbody>
<tr>
<td>8. Does the patient have:</td>
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<tr>
<td>a) A biopsy, imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE]) to indicate <strong>portal fibrosis with septa (METAVIR F2)</strong> advanced fibrosis (METAVIR F3) or cirrhosis (METAVIR F4); or</td>
</tr>
<tr>
<td>Clinical, radiologic or laboratory evidence of complications of cirrhosis (ascites, portal hypertension, hepatic encephalopathy, hepatocellular carcinoma)?</td>
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<table>
<thead>
<tr>
<th>Yes: Go to #11</th>
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<tbody>
<tr>
<td>Note: Other imaging and blood tests are not recommended based on evidence of poor sensitivity and specificity compared to liver biopsy. However, if imaging testing is not regionally available, a serum test (FIBROsPect II; Fibrometer; enhanced liver fibrosis [ELF]) can be used to confirm METAVIR F3 or F4.</td>
</tr>
<tr>
<td>For results falling in a range (e.g. F2 to F3), fibrosis stage should be categorized as the higher F stage for the purpose of treatment, or require one additional, more specific test (per HERC AUROC values [<a href="http://www.oregon.gov/oha/herc/CoverageGuidances/Liver-Fibrosis-CG.pdf">http://www.oregon.gov/oha/herc/CoverageGuidances/Liver-Fibrosis-CG.pdf</a>]) to be obtained to determine the stage of fibrosis. However, additional testing cannot be limited to biopsy. After one additional test, if a range still exists, the highest F score in the range will be used for determining coverage.</td>
</tr>
</tbody>
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<p>| No: Go to #9 |</p>
<table>
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<tr>
<th>Approval Criteria</th>
<th>Yes: Go to #11</th>
<th>No: Go to #10</th>
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<tbody>
<tr>
<td>9. Does the patient have one of the following extrahepatic manifestations of Hepatitis C (with documentation from a relevant specialist that their condition is related to HCV)?</td>
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<tr>
<td>a) Type 2 or 3 cryoglobulinemia with end-organ manifestations (i.e., leukocytoclastic vasculitis); or</td>
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<td>b) Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis; or</td>
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<td>c) Porphyria cutanea tarda or lichen planus</td>
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<tr>
<td>d) Lymphomas (B-cell non-Hodgkin lymphoma)</td>
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<td>e) Type 2 Diabetes</td>
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<td>10. Is the patient in one of the following transplant settings:</td>
<td></td>
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<tr>
<td>a) Listed for a transplant and treatment is essential to prevent recurrent hepatitis C infection post-transplant; or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) Post solid organ transplant?</td>
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</tbody>
</table>

Direct Acting Antiviral Abbreviations: DCV/SOF (Daclatasvir + sofosbuvir); Daklinza® + Sovaldi®; EBR/GZR (elbasvir/grazoprevir); Zepatier®; LDV/SOF (ledipasvir/sofosbuvir); Harvoni®; OMB/PTV-R + DAS (ombitasvir, paritaprevir and ritonavir with dasabuvir); Viekira Pak®/Viekira XR®; OMB/PTV-R (ombitasvir, paritaprevir and ritonavir); Technivie®; SOF/VEL (sofosbuvir/velpatasvir); Epclusa®; SOF (sofosbuvir): Sovaldi®
### Approval Criteria

| 11. If METAVIR F4: Is the regimen prescribed by, or in consultation with, a hepatologist, gastroenterologist, or infectious disease specialist? **OR**
<table>
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<tr>
<td><strong>Yes:</strong> Go to #12</td>
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</table>
| If METAVIR F3: Is the regimen prescribed by, OR is the patient in the process of establishing care with or in consultation with a hepatologist, gastroenterologist, or infectious disease specialist? **OR**
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<tbody>
<tr>
<td><strong>Yes:</strong> Go to #13</td>
</tr>
<tr>
<td>If METAVIR &lt;F2: The regimen does not need to be prescribed by or in consultation with a specialist?</td>
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<td>---</td>
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<tr>
<td><strong>Yes:</strong> Go to #14</td>
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<tr>
<th>12. In the previous 6 months:</th>
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<tbody>
<tr>
<td>• Has the patient actively abused alcohol (&gt;14 drinks per week for men or &gt;7 drinks per week for women or binge alcohol use (&gt;4 drinks per occasion at least once a month); OR</td>
</tr>
<tr>
<td>• Has the patient been diagnosed with a substance use disorder; OR</td>
</tr>
<tr>
<td>• Is the prescriber aware of current alcohol abuse or illicit injectable drug use?</td>
</tr>
<tr>
<td>---</td>
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<tr>
<td><strong>Yes:</strong> Go to #13</td>
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<tr>
<th>13. Is the patient enrolled in a treatment program under the care of an addiction/substance use treatment specialist?</th>
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<tbody>
<tr>
<td><strong>Yes:</strong> Go to #14</td>
</tr>
</tbody>
</table>

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®
## Approval Criteria

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<tr>
<th>Question</th>
<th>Yes:</th>
<th>No:</th>
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<tbody>
<tr>
<td>14. Will the patient and provider comply with all case management interventions and adhere to monitoring requirements required by the Oregon Health Authority, including measuring and reporting of a post-treatment viral load?</td>
<td>Go to #15</td>
<td>Pass to RPh. Deny; medical appropriateness.</td>
</tr>
<tr>
<td>15. Is the prescribed drug:</td>
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<tr>
<td>a) Elbasvir/grazoprevir for GT 1a infection; or</td>
<td></td>
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<tr>
<td>b) Daclatasvir + sofosbuvir for GT 3 infection?</td>
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<tr>
<td>16. Has the patient had a baseline NS5a resistance test show a resistant variant to one of the agents in #16?</td>
<td>Pass to RPh; deny for appropriateness</td>
<td>Go to #17</td>
</tr>
<tr>
<td>17. Is the prescribed drug regimen a recommended regimen based on the patient’s genotype and cirrhosis status?</td>
<td>Approve for 8-12 weeks based on duration of treatment indicated for approved regimen</td>
<td>Pass to RPh. Deny; medical appropriateness.</td>
</tr>
</tbody>
</table>

Table 1: Recommended Treatment Regimens for Chronic Hepatitis C.

[Pending P&T Committee Recommendations]