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Drug Class Update: Hepatitis C Direct-Acting Antivirals

Date of Review: September 2018

Date of Last Review: September 2017
End Date of Literature Search: 08/2018

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To evaluate new comparative evidence of the benefits and harms of direct-acting antivirals (DAAs) for the treatment of chronic hepatitis C (CHC). Additionally, evidence for effectiveness of DAAs in people who inject drugs (PWIDs) will be reviewed.

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?
4. Is there new evidence that achieving a sustained viral response (SVR) with DAAs results in long term improvement in clinically meaningful outcomes, including mortality, cirrhosis, liver transplantation, serious extrahepatic manifestations and hepatocellular carcinoma (HCC)?
5. Is there data that DAAs are effective and safe for the treatment of CHC in PWIDs?

Conclusions:
- There is insufficient evidence to evaluate whether eliminating hepatitis C virus (HCV) with the DAAs improves death or clinical manifestations of HCV associated cryoglobulinemia.[1]
- There is insufficient evidence that treatment with DAAs are effective in the treatment of acute HCV to reduce progression to CHC or cirrhosis, decrease mortality, or improve quality of life.[2]
- There are no data from randomized controlled trials evaluating the impact of treatment programs including needle syringe programs and/or opioid substitution therapy with methadone or buprenorphine in reducing the transmission of HCV in PWID.[3]
- There are no data suggesting a minimum length of abstinence to improve outcomes associated with treatment of CHC or that patients are less likely to achieve SVR with similar adherence.

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Date: September 2018

- There is low quality evidence based on observational data only with moderate to high risk of bias due to potential confounding that opioid substitution therapy alone (relative risk [RR] 0.50; 95% CI 0.40 to 0.63) or in combination with needle syringe programs (RR 0.26; 95% CI 0.07 to 0.89) reduces HCV incidence among PWID and that needle syringe programs alone do not reduce HCV incidence among PWID (RR 0.79; 95% CI 0.39 to 1.61).[3]
- There is low quality evidence SVR rates at 12 weeks (SVR12) with SOF/VEL with or without opioid substitution therapy or EBR/GZR with opioid substitution therapy in PWID are greater than or equal to 90% and SVR24 rates with EBR/GZR in patients receiving opioid substitution therapy are approximately 85%.

Recommendations:
- Approve updated prior authorization (PA) criteria (**Appendix 4**)
- Continue to allow treatment of HCV in PWID through current prior authorization criteria while supporting harm reduction treatment programs, including opioid substitution treatment programs, when available.

Summary of Prior Reviews and Current Policy
- There is low quality evidence that the DAA regimens are effective in achieving a SVR rate of greater than or equal to 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 12 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).
- 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 DAAs are limited to open-label, uncontrolled, or historically controlled trials.
    - Trials often exclude patients with chronic hepatitis B virus (HBV), HIV, cancer, 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.
- 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

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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 2 or greater, or patients with extrahepatic manifestations or HIV at any stage of fibrosis, and patients in the setting of solid organ transplant.

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.[4] The global prevalence is 1.6%, and in the United States (U.S.) approximately 50% of affected individuals remain unaware of their diagnosis.[5] 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 develop cirrhosis (8-16% of all people infected with HCV), and the time to progress to cirrhosis varies at an average of 40 years.[5] Approximately 20% of individuals infected with HCV will clear the virus. HCV is divided into seven major genotypes (GT) 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.[4] The most common subgenotypes of GT1 are 1a and 1b. Cure rates for GT 1a and 1b infection may differ depending on the treatment 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.[6]

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 observational data of an association of SVR and reductions in mortality, liver failure, and cancer.[4] 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.[5] SVR has previously been shown as an invalid surrogate for clinical outcomes for the efficacy of interferons.[5] 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.[7]

The two major predictors of SVR are viral genotype and pre-treatment viral load.[8] 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.[9]

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 DAAs will be most beneficial in patients at highest risk for cirrhosis-related events.[10] 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.[11] 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.[5]

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.[12] 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.[13] 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.[13] 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).[14] 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.[15]

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.[16] 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.[17] 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.

Table 1. Direct-acting Antiviral Regimens for Chronic Hepatitis C.*

Drug Brand Name	Generic name	Indications	Decompensated Cirrhosis	Mechanism of Action	Duration
Daklinza® and Solvaldi®	Daclatasvir + sofosbuvir	CHC GT 1 or GT 3	GT 1, 3 with RBV	NS5A inhibitor with NS5B inhibitor	12 weeks
Epclusa®	Sofosbuvir/velpatasvir	CHC GT 1-6	GT 1-6, with RBV	NS5B inhibitor/NS5A inhibitor	12 weeks
Harvoni®	Ledipasvir/sofosbuvir	CHC GT 1; GT 4; GT 5; GT 6	GT 1 with RBV	NS5A inhibitor/ NS5B inhibitor	8, 12, or 24 weeks

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Mavyret®	Glecaprevir/pibrentasvir	CHC GT 1-6 without cirrhosis or compensated cirrhosis and GT 1 previously treated with a NS5A inhibitor or an NS3/4a protease inhibitor	Contraindicated	NS3/4A protease inhibitor/NS5A inhibitor	8-16 weeks
Olysio®	Simeprevir	CHC GT 1 in combination with sofosbuvir	Not approved	NS3/4A protease inhibitor	12 -24 weeks
Sovaldi®	Sofosbuvir	CHC GT 1; GT 2; GT 3; GT 4 Used in combination with other antivirals	Not approved	Nucleotide analog NS5B polymerase inhibitor	12 weeks
Vosevi®	sofosbuvir/velpatasvir/voxilaprevir	CHC GT 1-6 TE with NS5A inhibitor; GT 1a or 3 TE with sofosbuvir and without an NS5A inhibitor	Contraindicated	NS5B inhibitor/NS5A inhibitor/NS3 protease inhibitor	12 weeks
Zepatier®	Elbasvir / grazoprevir	CHC GT 1; GT 4	Contraindicated	NS3/4A protease inhibitor/ NS5A inhibitor	12 or 16 weeks
Abbreviations: CHC = chronic hepatitis C; GT = genotype, RBV: ribavirin; TE: treatment-experienced *Viekira Pak/Viekira XR and Technivie have been discontinued and will no longer be available after January 2019					

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. If these trials are not available, trials using a historical SVR will be considered. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Institute for Clinical and Economic Review (ICER), 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 evidence-based clinical practice 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.

For use of the DAAs in PWID, observational trials will be considered.

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New Systematic Reviews:
After review, 9 systematic reviews were excluded due to poor quality, wrong study design of included trials (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).[18-26]

A systematic review from the Cochrane Collaboration evaluated the benefits and harms of treatment options for HCV-associated cryoglobulinemia with active manifestations of vasculitis.[1] One such therapeutic approach is eliminating HCV infection. The primary outcomes were death and decreasing clinical manifestations (i.e. kidney disease, skin vasculitis, musculoskeletal symptoms, liver involvement, interstitial lung involvement, and widespread vasculitis). Ten studies met inclusion criteria and were identified for review, all of which evaluated immunosuppressive medications (rituximab), interferon therapy or extracorpeal therapies. Although elimination of HCV with DAAs is the current mainstay of treatment, there were no published or ongoing studies evaluating the DAAs in patients with HCV-associated cryoglobulinemia.

A second systematic review from the Cochrane Collaboration assessed the comparative benefits and harms of pharmacological interventions in the treatment of acute HCV.[2] Interferon and DAAs have been used to attempt to eradicate acute HCV and prevention progression to CHC. The primary outcomes of interest were mortality, adverse events, and quality of life. Ten trials were identified and included in the review (n=488). All of the trials compared interferon or pegylated interferon to other interventions. Overall, there was very low-quality evidence that interferon-alfa may decrease the incidence of CHC as measured by SVR. However, there was no evidence on quality of life, reduction in cirrhosis, decompensated liver disease and liver transplantation. These results are also not applicable today since DAAs have become the standard of care. None of the trials compared DAAs to any other interventions.

The efficacy and safety of 12 weeks of LDV/SOF versus LDV/SOF + RBV in patients with CHC GT 1 with cirrhosis or who have failed prior therapy was evaluated in a recent systematic review of randomized controlled trials. [27] Current guidelines recommend LDV/SOF + RBV or extending the duration of LDV/SOF to 24 weeks in patients with cirrhosis or with failure of previous treatment. However, this is based on expert opinion only. The authors of this review had no conflicts of interest to disclose. Study quality was assessed independently by two authors using the Cochrane Collaboration risk of bias tool. Only four trials met inclusion criteria and were included in the review. The proportion of patients with cirrhosis ranged from 20% to 100% in the included studies, and all studies excluded those with HIV coinfection, chronic hepatitis B, and decompensated cirrhosis. All of the trials had a high risk of bias associated with non-blinded methods and for being funded and conducted by Gilead Sciences, the manufacturer of LDV/SOF. Among cirrhotic patients who failed previous therapy, the pooled relative risk (RR) of not achieving SVR12 after completing 12 weeks of LDV/SOF compared to 12 weeks of LDV/SOF + RBV was 1.21 (95% CI 0.42 to 3.48). However, with the wide confidence interval and pooled effect size over a 20% increase in the risk of failure to achieve SVR, the authors concluded the study could not confirm that 12 weeks of LDV/SOF is noninferior to LDV/SOF + RBV. Furthermore, adverse effects were significantly less common in those not receiving RBV (RR 0.11; 95% CI 0.04 to 0.29).

New Guidelines:
After review, two guidelines were excluded due to poor quality.[28,29]

Guidelines from the Veterans Affairs (VA) National Hepatitis C Resource Center were updated in October 2017 to include all available agents and update options for re-treatment (**Table 2**).[14] In addition to updated treatment regimens, the guidelines recommend RAS testing only be performed if results would guide re-

treatment options. Additional recommendations are included before for easy comparison to other treatment guidelines. The guidelines continue to recommend that HIV/HCV-coinfected patients receive the same HCV antiviral regimens as HCV monoinfected patients unless LDV/SOF is being considered, in which case a 12-week regimen should be used (instead of an 8-week regimen).

Additional Guidelines for Clinical Context:

The World Health Organization (WHO) updated their guidelines for the screening care and treatment of persons with CHC in April 2016,[30] 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 September 2017 to include the latest DAA regimens (SOF/VEL/VOX and G/P) and in May 2018.[6] The AASLD/IDSA guidelines are routinely updated to reflect rapidly changing evidence with the DAAs.[6] 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 guidelines are provided for clinical context, but decisions based on these guidelines should be made with caution.

The AASLD/IDSA guidelines were updated in May 2018 with the following changes:

1. Treatment of CHC in pregnancy:
    a. Universal screening of all pregnant women, ideally at the initiation of prenatal care.
    b. Treatment during pregnancy is not recommended due to the lack of safety and efficacy data with DAAs.
    c. For women of reproductive age with CHC, antiviral therapy is recommended before pregnancy is considered.
2. Management of CHC in PWID:
    a. Annual HCV testing is recommended
    b. Substance use disorder treatment programs and needle/syringe exchange programs should offer routine, opt-out HCV-antibody testing with linkage to care for those infected
    c. PWID should be offered to harm reduction services when available (needle/syringe service programs and substance use disorder treatment programs)
    d. Active or recent drug use or a concern for reinfection is not a contraindication to HCV treatment
3. Management of CHC in men who have sex with men (MSM):
    a. Annual HCV testing is recommended for sexually active HIV-infected MSM.
    b. HCV testing at HIV pre-exposure prophylaxis (PrEP) initiation and at least annually is recommended at least annually thereafter in HIV-uninfected MSM.
    c. All MSM should be counseled about the risk of sexual HCV transmission with high risk sexual and drug practices
    d. Antiviral treatment should be coupled with ongoing counseling about the risk of HCV reinfection, and education about methods to reduce HCV reinfection risk after cure
4. Management of CHC in correctional settings
    a. Jails should implement opt-out HCV testing

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b. Chronically infected individuals whose jail sentence is sufficiently long to complete a recommended course of antiviral therapy should receive treatment while incarcerated
c. Jails and prisons should facilitate continuation of HCV therapy for individuals on treatment at the time of incarceration

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.[6] 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.

VA: All patients with CHC who do not have medical contraindications are potential candidates for treatment. Patients with advanced liver disease are likely to derive the greatest benefit from treatment.[14] 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.

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).[14] 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.[31] 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.[32] 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.[33] 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.[34] There are no RCTs evaluating the effects of DAA-based regimens on progression of extrahepatic complications, and most of the literature consists of observational studies with risk for selection bias which demonstrate an association between progression and treatment. 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.[35]
- 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.[6]

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.[30]

VA: Ongoing substance use involving alcohol, illicit drugs, and marijuana, or participation in an opioid replacement program, should not be an automatic exclusion criterion for HCV treatment. However, in some patients, substance use or alcohol use disorders may need to be addressed prior to initiation of HCV treatment because of the risk of non-adherence and reinfection.

Decisions regarding HCV treatment of patients with substance use disorders or severe mental health conditions should be made by an experienced provider who can assess the likelihood of adherence with medical recommendations, clinic visits, and medications. 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).[14] 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.[14]

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).[6] 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.[30]

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 [ARFI]), 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.[14]

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 being treated with SOF/VEL to determine if RBV is needed.[14]

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. For NS5A treatment-experienced patients, the guidelines recommend the newer agents, SOF/VEL/VOX or G/P with a higher strength of recommendation for SOF/VEL/VOX.[6]

Recommended Treatment Options:

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

Table 2: Guideline Recommended Treatment Options

GT	Treatment History	Cirrhosis Status	Veterans Affairs Guidelines[14]	AASLD/IDSA Guidelines[6]	WHO Guidelines[30]
1	***Naïve or Experienced (PEG-INF/RBV only)***	***Non-cirrhotic***	EBR/GZR x 12 weeks ** LDV/SOF x 8-12 weeks (8 weeks if HCV RNA <6 million IU/ml and HCV-monoinfected) G/P x 8 weeks SOF/VEL x 12 weeks	EBR/GZR x 12 weeks** LDV/SOF x 8-12 weeks (8 weeks if RNA <6 million IU/ml, non-black and HCV-monoinfected) G/P x 8 weeks SOF/VEL x 12 weeks	DCV/SOF x 12 weeks LDV/SOF x 8-12 weeks
1		***Cirrhotic***	LDV/SOF x 12 weeks EBR/GZR x 12 weeks G/P x 12 weeks SOF/VEL x 12 weeks	LDV/SOF x 12 weeks EBR/GZR x 12 weeks** G/P x 12 weeks SOF/VEL x 12 weeks	DCV/SOF +/- RBV x 12 weeks LDV/SOF +/- RBV x 12 weeks
1		***Decompensated Cirrhosis***	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 weeks	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 weeks DCV/SOF + RBV x 12 weeks	DCV/SOF x 12 weeks
1	***Experienced (prior sofosbuvir)***	***Non-cirrhotic or compensated cirrhosis***	G/P x 8-12 weeks SOF/VEL x 12 weeks	G/P x 12 weeks SOF/VOL x 12 weeks (GT 1 b) SOF/VEL/VOX x 12 weeks (GT 1a)	N/A
1	***Experienced (Prior NS3A/4A inhibitor)***	***Non-cirrhotic or compensated cirrhosis***	G/P x 8-12 weeks (8 weeks if non-cirrhotic) SOF/VEL x 12 weeks LDV/SOF +/- RBV x 12 weeks	G/P x 12 weeks SOF/VEL x 12 weeks LDV/SOF X 12 weeks	N/A
1	***Experienced (prior NS5A-containing regimen)***	***Non-cirrhotic or compensated cirrhosis***	SOF/VEL/VOX x 12 weeks-24 weeks	SOF/VEL/VOX x 12 weeks	N/A
2	***Naïve***	***Non-cirrhotic***	SOF/VEL x 12 weeks G/P x 8 weeks	SOF/VEL x 12 weeks G/P x 8 weeks	SOF + RBV X 12 weeks
2		***Cirrhotic***	SOF/VEL +/- x 12 weeks	SOF/VEL x 12 weeks G/P x 12 weeks	SOF + RBV x 16 weeks
2		***Decompensated***	SOF/VEL + RBV x 12 weeks	SOF/VEL + RBV x 12 weeks DCV/SOF + RBV x 12 weeks	SOF + RBV x 16 weeks
2	***Experienced (prior PEG-IFN/RBV)***	***Non-cirrhotic or Compensated Cirrhotic***	SOF/VEL x 12 weeks G/P x 8-12 weeks	SOF/VEL x 12 weeks G/P x 8-12 weeks	N/A
2	***Experienced (NS5A-experienced)***	***Non-cirrhotic or compensated cirrhosis***	SOF/VEL/VOX x 12 weeks – 24 weels	SOF/VEL/VOX x 12 weeks	N/A
2	***Experienced (SOF + RBV)***	***Non-cirrhotic or Compensated Cirrhotic***	SOF/VEL x 12 weeks G/P x 8-12 weeks	SOF/VEL x 12 weeks G/P x 12 weeks	N/A
3	***Naïve***	***Non-cirrhotic***	G/P x 8 weeks SOF/VEL X 12 weeks	G/P x 8 weeks SOF/VEL X 12 weeks	DCV/SOF X 12 weeks
3		***Compensated Cirrhotic***	SOF/VEL x 12 weeks G/P x 12 weeks	SOF/VEL x 12 weeks G/P x 12 weeks	DCV/SOF + RBV x 12 weeks
3		***Decompensated Cirrhosis***	SOF/VEL + RBV X 12 weeks	SOF/VEL + RBV x 12 weeks DCV/SOF + RBV x 12 weeks	N/A
3	***Experienced (prior PEG-IFN/RBV only)***	***Non-cirrhotic***	G/P x 16 weeks	SOF/VEL x 12 weeks	N/A

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Date: September 2018

3		***Compensated Cirrhotic***	G/P x 16 weeks	SOF/VEL/VOX x 12 weeks EBV/GZR + SOF x 12 weeks	DCV/SOF + RBV x 24 weeks
3	***Experienced (NS5A or SOF)***	***Non-cirrhotic or Compensated Cirrhotic***	SOF/VEL/VOX x 12 weeks	SOF/VEL/VOX x 12 weeks	N/A
4	***Naïve***	***Non-cirrhotic***	EBV/GZR x 12 weeks LDV/SOF x 12 weeks SOF/VEL x 12 weeks G/P x 8 weeks	EBV/GZR x 12 weeks LDV/SOF x 12 weeks SOF/VEL x 12 weeks G/P x 8 weeks	DCV/SOF x 12 weeks LDV/SOF x 12 weeks
4		***Compensated Cirrhotic***	EBV/GZR x 12 weeks LDV/SOF x 12 weeks SOF/VEL x 12 weeks G/P x 12 weeks	EBV/GZR x 12 weeks LDV/SOF x 12 weeks SOF/VEL x 12 weeks G/P x 12 weeks	DCV/SOF x 24 weeks DCV/SOF + RBV x 12 weeks LDV/SOF x 24 weeks LDV/SOF + RBV x 12 weeks
4		***Decompensated Cirrhosis***	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 week	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 week DCV/SOF + RBV X 12 week	N/A
4	***Experienced (prior PEG-IFN/RBV only)***	***Non-cirrhotic or Compensated Cirrhotic***	N/A	SOF/VEL x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks G/P x 8 -12 weeks	N/A
	Experienced (SOF)	***Non-cirrhotic or compensated cirrhotic***	G/P x 8-12 weeks SOF/VEL x 12 weeks	SOF/VEL/VOX x 12 weeks	N/A
	Experienced (NS5A)	***Non-cirrhotic or compensated cirrhotic***	SOF/VEL/VOX x 12 weeks	SOF/VEL/VOX x 12 weeks	
5/6	***Naïve or Experienced (prior PEG-IFN/RBV only)***	***Non-cirrhotic or Compensated Cirrhotic***	N/A	SOF/VEL x 12 weeks LDV/SOF x 12 weeks G/P x 8-12 weeks	LDV/SOF X 12 weeks
5/6	***Experienced (NS5A or SOF)***	***Non cirrhotic or Compensated Cirrhotic***	N/A	SOF/VEL/VOX x 12 weeks	N/A

**No baseline NS5A RAVs. Abbreviations: CTP = Child-Turcotte-Pugh; DAA = direct acting antiviral; DCV = daclatasvir; EBV/GZR = elbasvir/grazoprevir; G/P = glecaprevir/pibrentasvir, LDV/SOF = ledipasvir/sofosbuvir; OMB/PTV-R + DAS = ombitasvir, paritaprevir and ritonavir with dasabuvir; PEG-IFN = pegylated interferon; VEL/SOF = velpatasvir/sofosbuvir; RAP = resistance-associated polymorphisms; RAV = resistance-associated variant; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SOF/VEL/VOX = sofosbuvir, velpatasvir, voxilaprevir

New Formulations or Indications:
None identified

Two combination treatments (OMB/PTV-R + DAS [Viekira Pak/Viekira XR] and OMB/PTV-R [Technivie]) have been discontinued by Abbvie Pharmaceuticals. Both agents are expected to be available through January 2019.

New FDA Safety Alerts:
None identified

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Randomized Controlled Trials:

A total of 49 citations were manually reviewed from the initial literature search. After further review, 46 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Toyoda, 2018[36]	G/P for 8 weeks vs. 12 weeks of SOF + RBV	HCV G2 patients without cirrhosis or compensated cirrhosis (n=11) in Japan (n=136)	SVR12	SVR12: G/P: 88/90 (97.8%) SOF + RBV: 43/46 (93.5%)
Tam, 2017[37] RESCUE	GT 1 or GT 4: 1. LDV/SOF +/- RBV x 12 weeks vs. 2. LDV/SOF x 24 weeks GT 1 with HIV: 3. LDV/SOF + RBV x 12 weeks vs. 4. LDV/SOF X 24 weeks	SOF-experienced, NS5a treatment naïve 1: HCV G1 or G4 2: HCV G1 with HIV coinfection	SVR12	SVR12: *HCV G1 or G4 (non-cirrhotic):* 1. 13/16 (81%) 2. 17/18 (100%) *HCV G1 or G4 (cirrhotic):* 1. 20/25 (80%) 2. 22/24 (92%) *HIV coinfection:* 3. 4/4 (100%) 4. 3/3 (100%)
Foster, 2018[22]	Treatment-naïve: 1. EBR/GZR + SOF + RBV x 8 weeks vs. 2. EBR/GZR + SOF x 12 weeks Treatment-experienced: 3. EBR/GZR + SOF +/- RBV X 12 weeks vs. 4. EBR/GZR + SOF x 16 weeks	HCV GT 3, compensated cirrhosis with HCV RNA ≥ 10,000 IU/ml	SVR 12	SVR12: *Treatment-naïve:* 1. 21/23 (91%) 2. 23/24 (96%) *Treatment-experienced:* 3. 17/18 (94%) 4. 17/18 (100%)

Abbreviations: RCT = EBR/GZR: elbasvir/grazoprevir; GT: genotype; HCV: hepatitis C virus; G/P: glecaprevir/pibrentasvir; LDV/SOF: ledipasvir/sofosbuvir; SOF: sofosbuvir; SVR12: sustained viral response at week 12; RBV: ribavirin

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Evidence for DAA use in substance use disorder and PWID:

Injection drug use is a significant risk factor for HCV-related disease and transmission, as well as for all-cause morbidity and mortality. The biggest risk factor for infection with HCV is sharing needles and/or syringes.[3] The current OHP prior authorization policy allows treatment for HCV for PWID. If the provider is aware of current illicit injectable drug use, the patient must be enrolled in a treatment program under the care of an addiction or substance use specialist. Current guidelines recommend that recent and active drug use should not be seen as an absolute contraindication to HCV therapy. The guidelines also recommend that PWID should be offered harm reduction services when available, including needle/syringe service programs and substance use disorder treatment programs.

A recent Cochrane systematic review evaluated the effects of needle syringe programs and opioid substitution therapy for preventing transmission of HCV among PWID.[3] A literature search for RCTs, cohort studies and case-control studies was conducted. The primary outcome was HCV incidence. Overall, 28 observational studies were identified for inclusion. No RCTs were identified. The majority of the studies were prospective cohort studies that evaluated opioid substitution therapy with methadone or buprenorphine. Twelve studies were judged to be at moderate risk of bias due to confounding and 12 studies to be at high risk of bias because confounding was insufficiently addressed. Four studies were at critical risk of bias because they did not make any adjustment for confounding. Overall, there was very low evidence that needle exchange program coverage did not reduce HCV acquisition (RR 0.79; 95% CI 0.39 to 1.61) with high heterogeneity. There was low quality evidence that combined needle exchange program coverage and opioid substitution therapy did result in a decreased rate of HCV acquisition (RR 0.29; 95% CI 0.07 to 0.89) which was more pronounced than with opioid substitution therapy alone (RR 0.50; 95% CI 0.40 to 0.63) compared to no opioid substitution therapy. Although the effect size is strong, conclusions based on observational data only should not be made and further RCTs should be conducted in this patient population.

The following clinical trials were identified evaluating treatment of HCV in PWID or alcohol use disorder. Overall, randomized prospective data is limited. Most studies enroll patients receiving treatment for injection drug use with opioid substation therapy. The trial by Norton, et al. had one small arm (n=10) of patients actively using drugs not receiving opioid substation therapy and nine of the ten patients achieved SVR12. [38] There is an ongoing randomized trial in 150 PWID with chronic HCV evaluating three models of care for HCV therapy delivered in an opioid substitution treatment program and their effects on adherence and virological outcomes.[39]

Study	Comparison	Population	Primary Outcome	Results
Norton, 2017[38] Observational cohort study	1. no active or history of drug use 2. no active drug use, receiving OAT 3. active drug use, not on OAT 4. active drug use, on OAT	Patients who received HCV treatment in a primary care clinic in the Bronx, NY (n=89)	SVR12	SVR12: 1. 41/43 (95%) 2. 15/15 (100%) 3. 9/10 (90%) 4. 20/21 (95%)
Grebely, 2018[40]	SOF/VEL x 12 weeks	HCV GT 1-6 with recent injection drug use (past 6 months) (n=103); 57% receiving OST	SVR12	SVR12: 97/103 (94%)

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Open-label, single arm, phase 4				
Dore, 2017[41] RCT, DB, PC	EBR/GZR (immediate treatment group [ITG] vs. deferred treatment group [DTG]) DTG: 12wks placebo + 4 weeks de-randomization + 12 weeks treatment	HCV GT 1, GT 4 or GT 6, treatment naïve, receiving OAT with methadone or buprenorphine	SVR12	SVR12: ITG: 184/201 (91.5%) DTG: 85/95 (89.5%) SVR24: ITG: 170/201 (84.6%) DTG: 81/95 (85.3%)

Abbreviations: DB = double blind; EBR/GZR: elbasvir/grazoprevir; GT = genotype; HCV: hepatitis C virus; OAT = opioid agonist therapy; PC = placebo controlled; RCT = randomized controlled trial; SVR12: sustained viral response at week 12; SOF/VEL: sofosbuvir/velpatasvir

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Date: September 2018

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36. Toyoda H, Chayama K, Suzuki F, et al. Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 2 hepatitis C virus infection. *Hepatology (Baltimore, Md).* 2017.
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Appendix 1: Current Preferred Drug List

Route	Formulation	Brand	Generic	PDL
ORAL	TABLET	EPCLUSA	sofosbuvir/velpatasvir	Y
ORAL	TABLET	ZEPATIER	elbasvir/grazoprevir	Y
ORAL	TABLET	MAVYRET	glecaprevir/pibrentasvir	Y
ORAL	TABLET	VOSEVI	sofosbuvir/velpatas/voxilaprev	Y
ORAL	TABLET	DAKLINZA	daclatasvir dihydrochloride	N
ORAL	TABLET	DAKLINZA	daclatasvir dihydrochloride	N
ORAL	TABLET	DAKLINZA	daclatasvir dihydrochloride	N
ORAL	TABLET	HARVONI	ledipasvir/sofosbuvir	N
ORAL	TAB DS PK	VIEKIRA PAK	ombita/paritap/riton/dasabuvir	N
ORAL	TAB BP 24H	VIEKIRA XR	ombita/paritap/riton/dasabuvir	N
ORAL	TABLET	TECHNIVIE	ombitasvir/paritaprev/ritonav	N
ORAL	TABLET	SOVALDI	sofosbuvir	N

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Appendix 2: Abstracts of Comparative Clinical Trials

1. Toyoda H, Chayama K, Suzuki F, Sato K, et al. Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 2 hepatitis C virus infection. Hepatology. 2017 Sep 2. doi: 10.1002/hep.29510. [Epub ahead of print]

Glecaprevir (nonstructural protein 3/4A protease inhibitor) and pibrentasvir (nonstructural protein 5A inhibitor) (G/P), a coformulated once-daily, all oral, ribavirin (RBV)-free, direct-acting antiviral regimen, was evaluated for safety and efficacy in hepatitis C virus genotype 2 (GT2)-infected Japanese patients, including those with compensated cirrhosis. CERTAIN-2 is a phase 3, open-label, multicenter study assessing the safety and efficacy of G/P (300/120 mg) once daily in treatment-naive and interferon ± RBV treatment-experienced Japanese patients without cirrhosis but with GT2 infection. Patients were randomized 2:1 to receive 8 weeks of G/P (arm A) or 12 weeks of sofosbuvir (400 mg once daily) + RBV (600-1000 mg weight-based, twice daily) (arm B). The primary endpoint was noninferiority of G/P compared to sofosbuvir + RBV by assessing sustained virologic response at posttreatment week 12 (SVR12) among patients in the intent-to-treat population. SVR12 was also assessed in treatment-naive and interferon ± RBV treatment-experienced patients with GT2 infection and compensated cirrhosis who received G/P for 12 weeks in the CERTAIN-1 study. A total of 136 patients were enrolled in CERTAIN-2. SVR12 was achieved by 88/90 (97.8%) patients in arm A and 43/46 (93.5%) patients in arm B. No patient in arm A experienced virologic failure, while 2 did in arm B. The primary endpoint was achieved. In CERTAIN-1, 100% (18/18) of GT2-infected patients with compensated cirrhosis achieved SVR12. Treatment-emergent serious adverse events were experienced by 2 patients without cirrhosis in each arm and no patient with cirrhosis.

2.. Tam E, Luetkemeyer AF, Mantry PS, Satapathy SK, Ghali P, Kang M, RESCUE and ACTG A5348 study investigators. Ledipasvir/sofosbuvir for treatment of hepatitis C virus in sofosbuvir-experienced, NS5A treatment-naïve patients: Findings from two randomized trials. Liver Int. 2018 Jun;38(6):1010-1021. doi: 10.1111/liv.13616. Epub 2017 Dec 5.

BACKGROUND & AIMS:
We report data from two similarly designed studies that evaluated the efficacy, safety, and optimal duration of ledipasvir/sofosbuvir (LDV/SOF) ± ribavirin (RBV) for retreatment of chronic hepatitis C virus (HCV) in individuals who failed to achieve sustained virological response (SVR) with prior SOF-based, non-NS5A inhibitor-containing regimens.
METHODS:
The RESCUE study enrolled HCV mono-infected adults with genotype (GT) 1 or 4. Non-cirrhotic participants were randomized to 12 weeks of LDV/SOF or LDV/SOF + RBV. Compensated cirrhotic participants were randomized to LDV/SOF + RBV (12 weeks) or LDV/SOF (24 weeks). The AIDS Clinical Trials Group A5348 study randomized genotype 1 adults with HCV/HIV co-infection to LDV/SOF + RBV (12 weeks) or LDV/SOF (24 weeks). Both studies used SVR at 12 weeks post-treatment (SVR12) as the primary endpoint.
RESULTS:
In the RESCUE study, 82 participants were randomized and treated, and all completed treatment. Overall, SVR12 was 88% (72/82); 81-100% in non-cirrhotic participants treated with LDV/SOF or LDV/SOF + RBV for 12 weeks and 80-92% in cirrhotic participants treated with LDV/SOF + RBV for 12 weeks or LDV/SOF for

24 weeks. Adverse events (AEs), mostly mild-to-moderate in severity, were experienced by 78% of participants, with headache and fatigue most frequently reported. One serious AE, not related to treatment, was observed. No premature discontinuations of study drug, or deaths occurred. In the A5348 study, seven participants were randomized (cirrhotic n = 1; GT1a n = 5) and all attained SVR12, with no serious AEs or premature discontinuations.
CONCLUSIONS:
In this SOF-experienced, NS5A inhibitor-naïve population, which included participants with cirrhosis or HCV/HIV co-infection, high SVR12 rates were achieved.

3. Foster GR, Agarwal K, Cramp ME, Moreea S, et al. Elbasvir/grazoprevir and sofosbuvir for hepatitis C virus genotype 3 infection with compensated cirrhosis: A randomized trial. Hepatology. 2018 Jun;67(6):2113-2126. doi: 10.1002/hep.29852. Epub 2018 Apr 19.

Abstract
Many direct-acting antiviral regimens have reduced activity in people with hepatitis C virus (HCV) genotype (GT) 3 infection and cirrhosis. The C-ISLE study assessed the efficacy and safety of elbasvir/grazoprevir (EBR/GZR) plus sofosbuvir (SOF) with and without ribavirin (RBV) in compensated cirrhotic participants with GT3 infection. This was a phase 2, randomized, open-label study. Treatment-naive participants received EBR/GZR + SOF + RBV for 8 weeks or EBR/GZR + SOF for 12 weeks, and peginterferon/RBV treatment-experienced participants received EBR/GZR + SOF ± RBV for 12 weeks or EBR/GZR + SOF for 16 weeks. The primary endpoint was HCV RNA <15 IU/mL 12 weeks after the end of treatment (sustained virologic response at 12 weeks [SVR12]). Among treatment-naive participants, SVR12 was 91% (21/23) in those treated with RBV for 8 weeks and 96% (23/24) in those treated for 12 weeks. Among treatment-experienced participants, SVR12 was 94% (17/18) and 100% (17/17) in the 12-week arm, with and without RBV, respectively, and 94% (17/18) in the 16-week arm. Five participants failed to achieve SVR: 2 relapsed (both in the 8-week arm), 1 discontinued due to vomiting/cellulitis (16-week arm), and 2 discontinued (consent withdrawn/lost to follow-up). SVR12 was not affected by the presence of resistance-associated substitutions (RASs). There was no consistent change in insulin resistance, and 5 participants reported serious adverse events (pneumonia, chest pain, opiate overdose, cellulitis, decreased creatinine). High efficacy was demonstrated in participants with HCV GT3 infection and cirrhosis. Treatment beyond 12 weeks was not required, and efficacy was maintained regardless of baseline RASs.
CONCLUSION:
Data from this study support the use of EBR/GZR plus SOF for 12 weeks without RBV for treatment-naive and peginterferon/RBV-experienced people with GT3 infection and cirrhosis

Appendix 3: Medline Search Strategy

▼ **Search History** (32)

# ▲	Searches	Results
1	glecaprevir.mp.	14
2	pibrentasvir.mp.	17
3	mavyret.mp.	1
4	sofosbuvir.mp. or SOFOSBUVIR/	1299
5	velpatasvir.mp.	79
6	voxilaprevir.mp.	21
7	vosevi.mp.	1
8	epclusa.mp.	5
9	daclatasvir.mp.	504
10	daklinza.mp.	10
11	technivie.mp.	3
12	ombitasvir.mp.	249
13	paritaprevir.mp.	239
14	ritonavir.mp. or RITONAVIR/	5766
15	dasabuvir.mp.	225
16	simeprevir.mp. or SIMEPREVIR/	534
17	ledipasvir.mp.	482
18	harvoni.mp.	35

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☐	19	antiviral agents.mp. or Antiviral Agents/	72769
☐	20	direct acting antivirals.mp.	1150
☐	21	protease inhibitors.mp. or Protease Inhibitors/	40950
☐	22	ribavirin.mp. or RIBAVIRIN/	14116
☐	23	ns5a inhibitors.mp.	181
☐	24	ns5b inhibitor.mp.	78
☐	25	Hepatitis C, Chronic/ or Hepatitis C/	58411
☐	26	hepatocellular carcinoma.mp. or Carcinoma, Hepatocellular/	88176
☐	27	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	116755
☐	28	25 or 26	140262
☐	29	27 and 28	19471
☐	30	limit 29 to (english language and humans and yr="2017 -Current" and (clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews))	184
☐	31	from 30 keep 13-14, 18, 22-23, 28, 34, 36-39...	49
☐	32	from 31 keep 2-3, 5, 7, 9-10, 12-13, 15...	25

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Appendix 4: 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:

- 8-16 weeks

Requires PA:

- All direct-acting antivirals for treatment of Hepatitis C

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of chronic Hepatitis C infection?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is expected survival from non-HCV-associated morbidities more than 1 year?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.

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Approval Criteria		
4. Has <u>all</u> 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; <u>and</u> f. History of previous HCV treatment and outcome? 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.	**Yes:** Record results of each test and go to #5 Note: If the patient has HIV or HBV co-infection, it is highly recommended that a specialist be consulted prior to treatment. <u>Currently treatment is not recommended during pregnancy due to lack of safety and efficacy data</u>	**No**: Pass to RPh. Request updated testing.
5. Which regimen is requested?	Document and go to #6	
6. Does the patient have HIV coinfection and is under treatment by a specialist with experience in HIV? Note: persons with HIV/HCV coinfection are at risk for rapidly progressing fibrosis	**Yes:** Go to #11	**No:** Go to #7

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Approval Criteria		
7. Does the patient have: a) A biopsy, imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE]) to indicate portal fibrosis with septa (METAVIR F2) advanced fibrosis (METAVIR F3) or cirrhosis (METAVIR F4); **OR** Clinical, radiologic or laboratory evidence of complications of cirrhosis (ascites, portal hypertension, hepatic encephalopathy, hepatocellular carcinoma, esophageal varices)?	**Yes:** Go to #10 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], Fibrosure) can be used to confirm METAVIR F2 or greater but cannot be used for denial. For results falling in a range (e.g. F1 to F2), 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 http://www.oregon.gov/OHA/HPA/CSI-HERC/Pages/Evidence-based-Reports-Blog.aspx?View=%7b2905450B-49B8-4A9B-AF17-5E1E03AB8B6B%7d&SelectedID=237) 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

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Approval Criteria		
8. 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)?~~ a) Lymphoproliferative disease, including type 2 or 3 cryoglobulinemia with end-organ manifestations (i.e., leukocytoclastic vasculitis); or b) Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis; or c) Porphyria cutanea tarda or lichen planus d) Lymphomas (B-cell non-Hodgkin lymphoma) e) Type 2 Diabetes	**Yes:** Go to #10	**No:** Go to #9
9. Is the patient in one of the following transplant settings: a) Listed for a transplant and treatment is essential to prevent recurrent hepatitis C infection post-transplant; or b) Post solid organ transplant?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. If METAVIR F4: Is the regimen prescribed by, or in consultation with, a hepatologist, gastroenterologist, or infectious disease specialist? **OR** 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** If METAVIR ≤F2: The regimen does not need to be prescribed by or in consultation with a specialist.	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness. Forward to DMAP for further manual review to determine appropriateness of prescriber.

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Approval Criteria		
11. In the previous 6 months: a) Does the patient actively abuse alcohol (>14 drinks per week for men or >7 drinks per week for women or binge alcohol use (>4 drinks per occasion at least once a month); OR b) Has the patient been diagnosed with a substance use disorder; OR c) Is the prescriber aware of current alcohol abuse or illicit injectable drug use?	**Yes:** Go to #12	**No:** Go to #13
12. Is the patient enrolled in a treatment program under the care of or in consultation with an addiction/substance use treatment specialist?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.
13. Is there documented attestation that ~~Will~~ the patient and provider will 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?	**Yes**: Go to #14	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the prescribed drug: a) Elbasvir/grazoprevir for GT 1a infection; or b) Daclatasvir + sofosbuvir for GT 3 infection?	**Yes**: Go to #15	**No:** Go to #16
15. Has the patient had a baseline NS5a resistance test that documents a resistant variant to one of the agents in #16? Note: Baseline NS5A resistance testing is required.	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #16 Document test and result.

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **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®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

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Approval Criteria		
16. Is the prescribed regimen include a NS3/4a protease inhibitor (elbasvir, glecaprevir, simeprevir, paritaprevir, voxilaprevir)?	**Yes:** Go to #17	**No:** Go to #18
17. Does the patient have moderate-severe hepatic impairment (Child-Pugh B or Child-Pugh C)?	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #18
18. Is the prescribed regimen for the retreatment after failure of a DAA due to noncompliance or lost to follow-up?	**Yes:** Pass to RPh; Deny and refer to medical director for review	**No:** Go to #19
19. Is the prescribed drug regimen a recommended regimen based on the patient's genotype, treatment status (retreatment or treatment naïve) and cirrhosis status (see **Table 1**)?	**Yes:** Approve for 8-16 weeks based on duration of treatment indicated for approved regimen	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *9/18 (MH); 9/17; 9/16; 1/16; 5/15; 3/15; 1/15; 9/14; 1/14*
Implementation: *TBD; 1/1/2018; 2/12/16; 4/15; 1/15*

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