Chronic Hepatitis C Virus (HCV) Infection: Treatment Considerations

from the Department of Veterans Affairs National Hepatitis C Resource Center and the HIV, Hepatitis, and Related Conditions Program in the Office of Specialty Care Services

Updated: August 27, 2018

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Frequently Used Abbreviations

The following is a list of abbreviations used throughout this document.

CTP = Child-Turcotte-Pugh	PI = protease inhibitor
DAA = direct-acting antiviral	PIB = pibrentasvir
DCV = daclatasvir (Daklinza®)	PrO = paritaprevir/ritonavir/ombitasvir (Technivie®)
DDI = drug-drug interaction	PrOD = paritaprevir/ritonavir/ombitasvir/dasabuvir (Viekira®)
EBR = elbasvir	RAS = resistance-associated substitutions
GLE = glecaprevir	RBV = ribavirin
GT = genotype	RTV or r = ritonavir
GZR = grazoprevir	SOF = sofosbuvir
HCC = hepatocellular carcinoma	SMV = simeprevir (Olysio®)
LDV = ledipasvir	SVR = sustained virologic response
LLOQ = lower limit of quantification	VEL = velpatasvir
PEG-IFN/IFN = peginterferon/interferon	VOX = voxilaprevir

I. What's New and Updates/Changes

This revision (August 27, 2018) includes algorithms for HCV genotype 1 treatment-experienced patients (Figure 1), incorporates 12 weeks (instead of 8 weeks) of glecaprevir/pibrentasvir in HCV genotype 3 treatment-naïve, non-cirrhotics and in HCV genotype 4 SOF-experienced patients, and updates on re-treatment in NS5A-experienced patients. Selection for HCV treatment should include patients who become reinfected with HCV after achieving sustained virologic response. A new section on acute HCV has been included and the transplant section has been updated. The drug-drug interactions tables have been revised to provide clinicians with guidance on the concomitant use of HCV drugs and other drugs, including HIV antiretroviral agents (Table 23 and Table 24). The Panel continues to recommend that HIV/HCV-coinfected patients receive the same HCV antiviral regimens as HCV-monoinfected patients unless ledipasvir/sofosbuvir is being considered, in which case a 12-week regimen should be used (instead of an 8-week regimen). Prior revisions incorporated HBV testing and monitoring recommendations prior to starting HCV DAA (Appendix D).

II. Summary Table

This document supplements the Veterans Affairs (VA) Pharmacy Benefits Management (PBM) Criteria For Use documents for HCV antivirals (available at: PBM Criteria For Use Documents). Information in this document may be used to support individualized treatment decisions based on the existing PBM Criteria For Use documents. The following treatment considerations are based on available medical evidence and represent the consensus of an expert panel of VA HCV clinicians. This document provides an algorithmic approach to assist in clinical decision making on HCV treatment considerations based on specific patient characteristics including genotype, treatment history, and presence or absence of cirrhosis. The practitioner should interpret these treatment considerations in the clinical context of the individual patient. The content of this document will be revised periodically as new information becomes available;

updated information is available at VA Viral Hepatitis Website. For considerations regarding patient selection for hepatitis C antiviral therapy, refer to Table 2 below.

Summary Table: Treatment Considerations and Choice of Regimen for HCV-Monoinfected and HIV/HCV-Coinfected Patients

Updated August 27, 2018**. Within each genotype/treatment history/cirrhosis status category, regimens are listed in alphabetical order; this ordering does not imply any preference for a particular regimen unless otherwise indicated. Providers should consider the most clinically appropriate option based on patient individual characteristics.* ***Refer to listing in **Table 4. HCV Direct-Acting Antiviral Agents by Drug Class.** ***Dosages and administration are noted in footnotes.***

HCV GT	Treatment History	Cirrhosis Status	Treatment Option(s) (in alphabetical order)	Alternative Option(s) (in alphabetical order)
GT1	Naïve	Non-cirrhotic	• **EBR/GZR** ○ If GT1a, test for NS5A RAS prior to treatment[e] ○ *If GT1a **without** baseline NS5A RAS:* 12 weeks ○ *If GT1b:* 12 weeks • **GLE/PIB** x 8 weeks • **LDV/SOF** ○ If HCV RNA is <6 million IU/mL and HCV-monoinfected: 8 weeks[a,b] ○ If HCV RNA is ≥6 million IU/mL: 12 weeks • **SOF/VEL** x 12 weeks	*If GT1a **with** baseline NS5A RAS[c]:* • **EBR/GZR + RBV** x 16 weeks
GT1	Naïve	Cirrhotic, CTP A	• **EBR/GZR** ○ If GT1a, test for NS5A RAS prior to treatment[e] ○ *If GT1a **without** baseline NS5A RAS:* 12 weeks ○ *If GT1b:* 12 weeks • **GLE/PIB** x 12 weeks • **LDV/SOF** x 12 weeks ○ Consider adding RBV; refer to Table 7 for details • **SOF/VEL** x 12 weeks	*If GT1a **with** baseline NS5A RAS[c]:* • **EBR/GZR + RBV** x 16 weeks
GT1	Naïve	Cirrhotic, CTP B, C	• **LDV/SOF + RBV** (600 mg/day and increase by 200 mg/day every 2 weeks as tolerated) x 12 weeks • **SOF/VEL + RBV** x 12 weeks; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)[d]	• **LDV/SOF** x 24 weeks • **SOF/VEL** x 24 weeks
GT1	Experienced *(NS5A-naïve; see Figure 1)*	Non-cirrhotic or Cirrhotic, CTP A	• **GLE/PIB** ○ *If PEG-IFN/RBV ± SOF-experienced:* 8 weeks if non-cirrhotic or 12 weeks if cirrhotic ○ *If NS3/4A PI + PEG-IFN/RBV-experienced:* 12 weeks ○ *If SMV + SOF-experienced:* 12 weeks • **SOF/VEL** ○ *If GT1b and SOF-experienced:* 12 weeks ○ *If PEG-IFN/RBV ± NS3/4A PI-experienced:* 12 weeks *If only failed PEG-IFN/RBV ± NS3/4A PI:* • **LDV/SOF** x 12 weeks; add RBV if cirrhotic	*If GT1a and SOF-experienced:* • **SOF/VEL/VOX** x 12 weeks *If GT1a **with** baseline NS5A RAS[c] and only failed PEG-IFN/RBV ± NS3/4A PI:* • **EBR/GZR + RBV** x 16 weeks

HCV GT	Treatment History	Cirrhosis Status	Treatment Option(s) (in alphabetical order)	Alternative Option(s) (in alphabetical order)
			If only failed PEG-IFN/RBV: • **EBR/GZR** ○ If GT1a, test for NS5A RAS prior to treatment[e] ○ *If GT1a **without** baseline NS5A RAS:* 12 weeks ○ *If GT1b:* 12 weeks	*If only failed PEG-IFN/RBV + NS3/4A PI and GT1a **without** baseline NS5A RAS[c] or GT1b:* • **EBR/GZR + RBV** x 12 weeks
GT1	Experienced *(NS5A-experienced; see Figure 1)*	Non-cirrhotic or Cirrhotic, CTP A	• **SOF/VEL/VOX** x 12 weeks *If only failed an NS5A inhibitor **without** NS3/4A PI (e.g., LDV/SOF):* • **GLE/PIB** x 16 weeks	
GT1	Experienced *(NS5A-naïve; see Figure 1)*	Cirrhotic, CTP B, C	• **SOF/VEL + RBV** x 12 weeks; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)[d] *If only failed PEG-IFN/RBV ± NS3/4A PI:* • **LDV/SOF + RBV** x 12 weeks; RBV 600 mg/day and increase by 200 mg/day every 2 weeks as tolerated	• **SOF/VEL** x 24 weeks *If only failed PEG-IFN/RBV ± NS3/4A PI:* • **LDV/SOF** x 24 weeks
GT1	Experienced *(NS5A-experienced; see Figure 1)*	Cirrhotic, CTP B, C	• **SOF/VEL + RBV** x 24 weeks; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)[d] *NOT FDA approved for 24 weeks*	
GT2	Naïve	Non-cirrhotic or Cirrhotic, CTP A	• **GLE/PIB** ○ *If non-cirrhotic:* 8 weeks ○ *If cirrhotic:* 12 weeks • **SOF/VEL** x 12 weeks	
GT2	Naïve	Cirrhotic, CTP B, C	• **SOF/VEL + RBV** x 12 weeks; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)[d]	• **SOF/VEL** x 24 weeks
GT2	Experienced *(SOF-experienced and NS5A-naïve)*	Non-cirrhotic or Cirrhotic, CTP A	• **GLE/PIB** ○ *If non-cirrhotic:* 8 weeks ○ *If cirrhotic:* 12 weeks • **SOF/VEL** x 12 weeks	
GT2	Experienced *(NS5A-experienced)*	Non-cirrhotic or Cirrhotic, CTP A	• **SOF/VEL/VOX** x 12 weeks	
GT2	Experienced	Cirrhotic, CTP B, C	• **SOF/VEL + RBV**; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)[d] ○ *If NS5A-naïve:* 12 weeks ○ *If NS5A-experienced:* 24 weeks; *NOT FDA approved for 24 weeks*	*If NS5A-naïve:* • **SOF/VEL** x 24 weeks
GT3	Naïve	Non-cirrhotic	• **GLE/PIB** x 12 weeks • **SOF/VEL** x 12 weeks	
GT3	Naïve	Cirrhotic, CTP A	• **GLE/PIB** x 12 weeks • **SOF/VEL** x 12 weeks ○ Test for NS5A RAS[e]; add RBV if Y93H RAS present	
GT3	Naïve	Cirrhotic, CTP B, C	• **SOF/VEL + RBV** x 12 weeks; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)[d]	• **SOF/VEL** x 24 weeks

HCV GT	Treatment History	Cirrhosis Status	Treatment Option(s) (in alphabetical order)	Alternative Option(s) (in alphabetical order)
GT3	Experienced *(PEG-IFN/IFN ± RBV or SOF + RBV ± PEG-IFN)*	Non-cirrhotic or Cirrhotic, CTP A	*If PEG-IFN/IFN ± RBV-experienced* • **GLE/PIB** x 16 weeks *If SOF-experienced:* • **SOF/VEL/VOX** x 12 weeks	
GT3	Experienced *(NS5A-experienced)*	Non-cirrhotic or Cirrhotic, CTP A	• **SOF/VEL/VOX** x 12 weeks ○ *If CTP A:* Consider adding RBV [d] (no supporting data)	
GT3	Experienced	Cirrhotic, CTP B, C	• **SOF/VEL + RBV;** start at lower RBV doses as clinically indicated (e.g., baseline Hgb)[d] ○ *If NS5A-naïve:* 12 weeks ○ *If NS5A-experienced:* 24 weeks; *NOT FDA approved for 24 weeks*	*If NS5A-naïve:* • **SOF/VEL** x 24 weeks
GT4	Naïve	Non-cirrhotic or Cirrhotic, CTP A	• **EBR/GZR** x 12 weeks • **GLE/PIB** ○ *If non-cirrhotic:* 8 weeks ○ *If cirrhotic:* 12 weeks • **LDV/SOF** x 12 weeks • **SOF/VEL** x 12 weeks	
GT4	Naïve	Cirrhotic, CTP B, C	• **LDV/SOF + RBV** (600 mg/day and increase as tolerated) x 12 weeks • **SOF/VEL + RBV** x 12 weeks; start at lower RBV doses as clinically indicated[d]	• **LDV/SOF** x 24 weeks • **SOF/VEL** x 24 weeks
GT4	Experienced *(SOF-experienced and NS5A-naïve)*	Non-cirrhotic or Cirrhotic, CTP A	• **GLE/PIB** x 12 weeks • **SOF/VEL** x 12 weeks	
GT4	Experienced *(NS5A-experienced)*	Non-cirrhotic or Cirrhotic, CTP A	• **SOF/VEL/VOX** x 12 weeks	
GT4	Experienced	Cirrhotic, CTP B, C	• **SOF/VEL + RBV;** start at lower RBV doses as clinically indicated (e.g., baseline Hgb)[d] ○ *If NS5A-naïve:* 12 weeks ○ *If NS5A-experienced:* 24 weeks; *NOT FDA approved for 24 weeks*	*If NS5A-naïve:* • **SOF/VEL** x 24 weeks

[a] 12-week regimen should be used in HIV/HCV-infected patients.
[b] Consideration should be given to 12 weeks of treatment in African Americans and those with quantifiable (>LLOQ) HCV RNA at week 4 on treatment.[1]
[c] It is unclear whether the 1-fold shift in EBR concentrations observed in vitro with the M28V mutation reduces efficacy.[2] May consider the addition of RBV and extending treatment to 16 weeks if clinically appropriate.
[d] RBV Dosages:

- RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food
  - CTP B and C patients receiving LDV/SOF: RBV 600 mg/day with food and increase as tolerated
  - CTP B and C patients receiving SOF/VEL: prescribing information recommends RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)

[e] Testing of HCV RAS for patients can be performed through the VHA Public Health Reference Laboratory (email V21PHRL@va.gov) or a commercial laboratory (see Section XV, Appendix B).

DAA Dosages:

- EBR/GZR (50/100 mg, Zepatier®): 1 tablet orally daily
- GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food
- LDV/SOF (90/400 mg, Harvoni®): 1 tablet orally daily
- SOF/VEL (400/100 mg, Epclusa®): 1 tablet orally daily
- SOF/VEL/VOX (400/100/100 mg, Vosevi®): 1 tablet orally daily with food

Note: EBR/GZR, GLE/PIB, LDV/SOF, SOF/VEL, or SOF/VEL/VOX should not be used in reduced dosages or restarted if discontinued. DCV + SOF ± RBV can be considered if DDI precludes the use of other HCV regimens (see Appendix A, Table 23 and Table 24, www.hep-druginteractions.org, and manufacturer prescribing information).

CTP Score Calculator: www.mdcalc.com/child-pugh-score-cirrhosis-mortality

III. Introduction

Key Points

- Successful antiviral treatment of chronic HCV infection decreases the risk of disease progression and death.
- Treatment of Veterans with HCV should be based on evidence-based guidelines such as those in this document.
- Evaluation of patients prior to initiation of treatment is essential (see Table 3).

The goal of hepatitis C antiviral treatment is to achieve a sustained virologic response (SVR), defined as HCV RNA level below the limit of quantification in the blood 12 or more weeks after completing antiviral treatment. Achieving an SVR is, for the vast majority of patients, synonymous with curing hepatitis C. Achieving an SVR decreases the risk of disease progression to cirrhosis, liver cancer, liver failure, and death.

Although the timing of treatment for individual patients may depend on the stage of liver disease and patients' readiness for treatment, Veterans Health Administration (VHA) expects to treat all Veterans with chronic HCV infection who wish to be treated and are suitable for treatment. Furthermore, VHA will use the optimal drug treatments available, after analysis of efficacy/effectiveness, safety, and costs. Providing appropriate treatment to Veterans requires time, expertise, care coordination (e.g., Primary Care, Mental Health, Pharmacy, Social Work), and adequate resources, including but not limited to funding.

The following treatment considerations summarize the current best practices in the treatment of chronic HCV infection within VHA. These considerations are based on review of published data and abstracts, American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) Recommendations for Testing, Managing, and Treating Hepatitis C (www.hcvguidelines.org), publicly available summaries from reviews by the United States Food and Drug Administration (FDA), and input from VHA thought leaders involved in the care of Veterans with HCV infection.

Limitations

There are limitations in the design of some clinical trials of direct-acting antiviral (DAA) agents in the treatment of hepatitis C. These limitations include: 1) small number of patients with cirrhosis, especially advanced cirrhosis; 2) lack of head-to-head trials of DAA regimens; 3) lack of blinding in some trials; 4) exclusion of patients with chronic hepatitis B virus (HBV) infection, human immunodeficiency virus (HIV) infection, cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and alcohol or substance use. The committee weighed the strengths, weaknesses, and gaps in the evidence to make decisions based on existing and sometimes suboptimal data from studies with potential biases or uncertain generalizability. Some of the limitations of studies are noted in the "Comments" column in the treatment consideration tables. The content in this document will be updated as new data become available.

Grading the evidence

Treatment considerations were developed using weighting and grading of the quality of evidence according to criteria used in the United States Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* (Table 1).[3] Each panel member participated in the preparation and review of the draft considerations and the committee approved the consensus statements reflected in the final document. The final considerations were reviewed and endorsed by the HIV, Hepatitis, and Related Conditions Program in the Office of Specialty Care Services. Additional resources pertaining to the care of the HCV-infected patient are available at the VA Viral Hepatitis website (www.hepatitis.va.gov).

Table 1. Grading System

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement B: Moderate recommendation for the statement C: Optional recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints II: One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes III: Expert opinion

Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Department of Health and Human Services. Available at aidsinfo.nih.gov. Page A-3, Table 2. Accessed July 16, 2018.[3]

Clinical benefit of achieving SVR (i.e., cure)

SVR, defined as an HCV RNA level in the blood below the limit of quantification based on reverse-transcription polymerase chain reaction (RT-PCR) at least 12 weeks after completion of treatment, is the primary endpoint of successful therapy. There is documented concordance of SVR at 12 and 24 weeks (referred to as SVR_{12} and SVR_{24}, respectively) with reported positive and negative predictive values upward of 98% in DAA-based studies. Based on these data, the FDA now recommends testing for HCV RNA at 12 weeks after completion of treatment (i.e., SVR_{12}) as the primary endpoint for HCV clinical trials; this is endorsed by the AASLD, European Association for the Study of the Liver, and American Gastroenterological Association.[4-6] This document uses the term "SVR" without specification of SVR_{12} or SVR_{24} because the two are considered clinically equivalent.

Achieving an SVR with HCV treatment improves clinical outcome. Liver fibrosis may improve (regress) after achieving an SVR. Patients with cirrhosis who achieve an SVR also have reduced progression of their liver disease and reduced risk of HCC, liver failure, and death related to liver disease, as well as reduced all-cause mortality.[7] Thus, there is compelling evidence that curing patients of HCV infection, including patients with cirrhosis, has clinically meaningful improvements in outcomes.

Principles of patient identification, evaluation, and treatment

Key Points

- All patients with chronic HCV who do not have medical contraindications are potential candidates for antiviral treatment.
- Ongoing substance use involving alcohol, illicit drugs, and marijuana, or participation in an opioid replacement program, should <u>not</u> be an automatic exclusion criterion for HCV treatment. 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.
- Pre-treatment assessment, including determination of liver disease severity, comorbidities, assessment of potential DDIs, and patient likelihood of adherence to treatment and monitoring should be performed prior to starting HCV treatment.
- Selection of an appropriate regimen and treatment duration for patients depends on subtype, stage of liver disease, baseline level of HCV viremia, prior treatment history, and concomitant medications.

Identification, evaluation, and treatment of Veterans with hepatitis C will require efforts from multiple levels of an integrated health system. Guidelines endorsed by VHA, United States Preventive Services Task Force, and the Centers for Disease Control and Prevention recommend one-time screening for all persons born between 1945 and 1965, and risk factor-based testing for those born outside this time frame. Screening and diagnosis most commonly takes place in primary care settings. Once diagnosed, patients with detectable HCV RNA are included in the VA National Hepatitis C Clinical Case Registry, a VA-

wide electronic database established for accurate tracking of VA's HCV population and population health interventions at the facility level.

New HCV treatments allow a much larger portion of the HCV population to be treatment candidates, and to have a high likelihood of treatment success. However, providers who are considering treatment of HCV-infected patients must be knowledgeable about the optimal selection of patients for antiviral therapy, appropriate use and choice of HCV medications, and monitoring throughout the treatment course. Specifically, providers need to perform a pre-treatment assessment, including determination of liver disease severity, comorbidities, and patient likelihood of adherence to treatment and monitoring. Assessment of potential DDIs (e.g., acid-reducing agents, statins) with HCV antiviral therapy is critical prior to starting HCV treatment.

HCV experts include hepatologists, general gastroenterologists, infectious disease specialists, and other individual providers with expertise in HCV such as mid-level providers or clinical pharmacists with advanced training. In addition to specialists, HCV treatment can be provided by non-specialists, including general internist or family medicine physicians who have been educated and trained in HCV therapy and have access to specialists for support, either through direct contact or telemedicine. Furthermore, trained advanced practice nurses, nurse practitioners, physician assistants, or clinical pharmacists can independently evaluate and manage patients receiving HCV antiviral therapy. Mid-level providers and clinical pharmacists play an important role in providing patient education about HCV and antiviral treatment (side effects, DDIs, missed doses, etc.), assessment of adverse events, ordering blood tests and monitoring patients throughout the treatment course, as well as prescribing DAA agents.

Principles for patient selection for HCV treatment

All patients with chronic HCV who do not have medical contraindications are potential candidates for antiviral treatment, including patients who become reinfected with HCV after SVR. Patients with advanced liver disease are likely to derive the greatest benefit from treatment.

The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver or liver-related disease, and prolonging graft survival in liver 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) 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.

Ongoing substance use involving alcohol, illicit drugs, and marijuana, or participation in an opioid replacement program, should <u>not</u> be an automatic exclusion criterion for HCV treatment. There are no published data supporting a minimum length of abstinence or showing that these patients are less likely to achieve SVR with HCV treatment if they remain adherent. 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. Patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, PTSD), as documented by psychiatric evaluation, who are engaged in mental health treatment should be considered for HCV therapy on a case-by-case basis. 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.

Treatment is not indicated in patients with a life expectancy of less than 12 months (e.g., irreversible, progressive, non-liver-related comorbidities or aggressive hepatocellular cancer) unless there is reason to anticipate that duration or quality of life can be improved by eradication of HCV.

Patient adherence

Evaluating a patient's potential adherence to medical recommendations and the prescribed regimen is crucial to the patient selection process. Factors that may complicate adherence, such as active substance use, depression, neurocognitive disorders, and lack of social support, should be adequately evaluated and addressed before initiating medications. Providers should incorporate strategies for measuring and supporting adherence within their clinics.

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

Liver Disease Category	Considerations	Evidence Grade
No cirrhosis	Inform patients of the availability of curative treatments and offer treatment in a time period that is clinically appropriate.	B-III
Compensated cirrhosis	Treatment is recommended for appropriate patients with compensated cirrhosis. Refer to Table 16, "Diagnosis of Advanced Fibrosis and Compensated Cirrhosis ," for guidance on diagnosis of cirrhosis.	A-I
Decompensated cirrhosis, defined by one of the following: CTP score ≥7, ascites, hepatic encephalopathy, variceal bleeding or jaundice	Treatments are available for appropriate patients with decompensated cirrhosis. Consult a specialist with experience in management of HCV.	A-II
Hepatocellular carcinoma (HCC)	Consider treatment for patients with controlled HCC (based on consultation with the gastroenterologist or oncologist), including selected patients on the liver transplant list.	A-II
Post-transplant recipients	Effective treatments are available for patients who have HCV after liver transplantation. Because of the potential for drug interactions between DAA agents and immunosuppressive agents, consultation with a specialist who has experience in the management of liver transplantation and HCV is highly recommended.	A-II

Liver Disease Category	Considerations	Evidence Grade
Serious extra-hepatic manifestations of HCV	Patients with serious extra-hepatic manifestations of HCV, such as leukocytoclastic vasculitis, membranoproliferative glomerulonephritis, or symptomatic cryoglobulinemia should receive treatment as soon as possible. Consult a specialist with experience in management of HCV.	A-III
HIV/HCV coinfection	Treatment is recommended for appropriate patients with HIV/HCV coinfection because of the risk of rapid progression of liver disease. Consult a specialist with experience in treating HIV prior to starting HCV treatment as some DAA agents interact with HIV antiviral regimens.	A-I

Abbreviations: CTP = Child-Turcotte-Pugh; DAA = direct-acting antiviral

Patient identification

A population health-based approach for selection of patients for treatment should be considered. The HCV Clinical Case Registry (CCR) and the VA Hepatitis C Dashboard are available at each VA facility and are accessible for HCV clinicians. Using the CCR or the VA Hepatitis C Dashboard, providers can generate facility-specific reports on the numbers and names of patients with HCV stratified by advanced fibrosis and cirrhosis (See Table 16. Diagnosis of Advanced Fibrosis and Compensated Cirrhosis), genotype, prior treatment experience, and other clinical considerations. The availability and customizability of the information obtained from local CCR reports or the VA Hepatitis C Dashboard can optimize identification of patients with the most urgent need for treatment.

Pre-treatment evaluation

Before initiating DAA therapy for patients with HCV, the information listed in Table 3 should be obtained.

Table 3. Pre-Treatment Evaluation[8]

Essential pre-treatment information
• HCV genotype (including subtype, e.g., 1a or 1b) • HCV RNA (quantitative viral load), preferably within the past 6 months • Biochemical markers of liver injury and assessment of hepatic function, including serum ALT, AST, serum albumin, serum bilirubin (including direct bilirubin), and INR • Hemoglobin, hematocrit, WBC, and platelet count • Serum creatinine, estimated glomerular filtration rate • Clinical assessment for cirrhosis (refer to Table 16) • If cirrhotic, exclusion of HCC based on appropriate imaging study (± AFP) within the prior 6 months • Previous HCV treatment history and outcome • HIV status and, if HIV seropositive, current antiretroviral regimen and degree of viral suppression • HAV serologies • HBV serologies and status; refer to Appendix D for guidance • If using ribavirin, confirm: 1) use of two forms of birth control in patient and sex partners; and 2) female patients are not pregnant prior to starting treatment

Treatment response

Assessment of HCV RNA during and after therapy is critical to determining treatment response. The FDA recommends use of a sensitive, real-time, reverse-transcription polymerase chain reaction (RT-PCR) assay for monitoring HCV RNA levels during and after treatment with DAA agents. For more information, see Section IX, Laboratory Monitoring.

Definitions of treatment response

- **SVR:** HCV RNA below LLOQ at least 12 weeks after treatment completion.
- **Relapse:** HCV RNA below LLOQ during treatment and/or at the end of treatment, but subsequent quantifiable HCV RNA following treatment cessation.
- **Non-response:** detectable HCV RNA throughout treatment.

Table 4. HCV Direct-Acting Antiviral Agents by Drug Class

Agents listed from earliest to latest FDA approval date. Box around more than one agent indicates that these agents are combined in one tablet.

NS3/4 Protease Inhibitor	NS5A Replication Complex Inhibitors	NS5B Nucleoside Inhibitors	NS5B Nonnucleoside Inhibitors	*Brand Name*
		Sofosbuvir*		*Sovaldi®*
Simeprevir*				*Olysio®*
	Ledipasvir	Sofosbuvir		*Harvoni®*
Paritaprevir/ritonavir	Ombitasvir		Dasabuvir	*Viekira®*
Paritaprevir/ritonavir	Ombitasvir			*Technivie®*
	Daclatasvir*			*Daklinza®*
Grazoprevir	Elbasvir			*Zepatier®*
	Velpatasvir	Sofosbuvir		*Epclusa®*
Voxilaprevir	Velpatasvir	Sofosbuvir		*Vosevi®*
Glecaprevir	Pibrentasvir			*Mavyret™*

* Should not be used as monotherapy

Interpretation of resistance-associated substitutions (RAS)

Key Points

- Baseline NS5A resistance testing is recommended in GT1a-infected patients prior to initiating EBR/GZR to determine the treatment duration and if ribavirin is required.
- Baseline NS5A resistance testing is recommended in GT3 patients with cirrhosis (CTP A) if SOF/VEL is being considered to determine if ribavirin is required.
- NS3/4 and/or NS5A RAS testing can be performed by the VHA Public Health Reference Laboratory (email V21PHRL@va.gov) or a commercial laboratory (see Section XV, Appendix B) if the results would guide treatment options.

Polymorphisms are amino acid substitutions within a particular HCV protein that may or may not confer resistance to a DAA. Polymorphisms that confer resistance are called resistance-associated substitutions (RAS, also known as resistance-associated variants [RAVs]). RAS exist at baseline in a minority of patients and emerge during treatment in most patients who fail to achieve SVR with DAA treatment. NS5A RAS

testing should be performed at baseline (prior to initial treatment) for GT1a-infected patients who are being considered for treatment with EBR/GZR and for GT3 patients with cirrhosis (CTP A) who may receive SOF/VEL. If needed, expert consultation can assist with evaluating the risks versus benefits of treatment in patients with RAS (see Section XIV, Resources).

With the availability of newer agents, which have been proven effective in prior DAA failures with RAS, situations in which RAS testing could influence the regimen choice are less frequent. HCV RAS testing should be performed only if the results would guide re-treatment options. NS5B testing is not recommended because of the low potential for resistance to sofosbuvir, and is no longer available through the VHA Public Health Reference Laboratory (PHRL).

NS5A RAS testing can be obtained by sending a plasma sample to the PHRL at VA Palo Alto or a commercial laboratory (see Section XV, Appendices). The information from these tests can be used to determine the optimal treatment regimen for a given patient. The decision to request RAS testing lies with the provider, and depends on viral and clinical factors including HCV genotype, the known prevalence of baseline (naturally occurring) resistance mutations, HCV treatment history, and projected HCV drug options for a given patient.

Table 5. Recommendations for Performing Pre-Treatment RAS Testing

Patient Characteristics	Genotype	DAA Agent to Be Considered[a]	RAS Test: NS3/4	RAS Test: NS5A	RAS Test: NS5B
Treatment-naïve	GT1a	**EBR/GZR**	No	Yes[b]	No
	GT1b	**Any DAA regimen**	No	No	No
	GT2	**Any DAA regimen**	No	No	No
	GT3, CTP A	**SOF/VEL**	No	Yes[b]	No
	GT4	**Any DAA regimen**	No	No	No
Failed non-NS5A-containing regimen (e.g., PEG-IFN/RBV ± NS3/4A PI; SOF + RBV ± PEG-IFN)	GT1a	**EBR/GZR**	No	Yes	No
	GT1	**LDV/SOF**	No	Yes	No
	GT1	**SOF/VEL**	No	No	No
	GT1	**GLE/PIB**	No	No	No
	GT1	**SOF/VEL/VOX**	No	No	No
	GT2	**GLE/PIB**	No	No	No
	GT2	**SOF/VEL or SOF/VEL/VOX**	No	No	No
	GT3	**GLE/PIB**	No	No	No
	GT3	**SOF/VEL/VOX**	No	No	No
Failed NS5A-containing regimen without NS3/4A PI	GT1	**GLE/PIB**	No	No	No
	GT1, GT2, GT3	**SOF/VEL/VOX**	No	No	No
Failed NS5A-containing regimen	GT1, GT2, GT3	**SOF/VEL/VOX**	No	No	No

[a] RBV may be required as part of the regimen for patients who have failed prior treatment (in Section IV, see Table 7 and Table 8, and Genotype 1-Infected Patients Who Have Failed Treatment with DAA-Based Therapy).
[b] NS5A RAS testing not required if RBV is included in the treatment regimen.

IV. Chronic HCV Genotype 1 Infection

Including HIV/HCV coinfection

Refer to Section XII, Groups with Special Considerations for Therapy, on HCV treatment in patients with HIV/HCV coinfection.

Key Points

- EBR/GZR, GLE/PIB, or SOF/VEL/VOX should not be used in patients with moderate to severe hepatic impairment (CTP B and C).
- GLE/PIB or SOF/VEL/VOX should be taken with food. Refer to Appendix A, Table 23 and Table 24, for drug-drug interactions.
- If LDV/SOF is used in HIV/HCV-infected patients, the treatment duration should be 12 weeks. In HCV-monoinfected patients, consideration should be given to 12 weeks of LDV/SOF treatment in African Americans and those with quantifiable (>LLOQ) HCV RNA at week 4 on treatment.
- Baseline NS5A resistance testing is recommended in GT1a-infected patients prior to initiating EBR/GZR to determine the regimen and treatment duration.
- NS3/4 and/or NS5A RAS testing can be performed by the VHA Public Health Reference Laboratory (email V21PHRL@va.gov) or a commercial laboratory (see Section XV, Appendix B), if the results would guide treatment options.

Table 6. Treatment Regimens for GT1

*See **Table 7 and Table 8** for details. Within each category, regimens are listed in alphabetical order; this ordering does not imply any preference for a particular regimen unless otherwise indicated.*

Treatment-naïve without or with cirrhosis (CTP A)

- *EBR/GZR (50/100 mg, Zepatier®): 1 tablet orally daily for 12 weeks if GT1a without baseline NS5A RAS[e] or GT1b*
- *GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food*
  - *If non-cirrhotic: 8 weeks*
  - *If cirrhotic: 12 weeks*
- *LDV/SOF (90/400 mg, Harvoni®): 1 tablet orally daily*
  - *If HCV-monoinfected, non-cirrhotic, and baseline HCV RNA <6 million IU/mL: 8 weeks[a,b]*
  - *If cirrhotic, baseline HCV RNA ≥6 million IU/mL or HIV/HCV coinfected: 12 weeks*
  - *Consider adding RBV[d] in cirrhotic patients (refer to **Table 7** for details)*
- *SOF/VEL (400/100 mg, Epclusa®): 1 tablet orally daily for 12 weeks*

Treatment-naïve with decompensated cirrhosis (CTP B or C)

- *LDV/SOF (90/400 mg, Harvoni®): 1 tablet orally daily + RBV (600 mg/day and increase by 200 mg/day every 2 weeks only as tolerated) for 12 weeks*
- *SOF/VEL (400/100 mg, Epclusa®): 1 tablet orally daily + RBV[d] for 12 weeks; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)*

Table 6. Treatment Regimens for GT1

Treatment-experienced (NS5A- and SOF-naïve [e.g., failed PEG-IFN/RBV ± NS3/4A PI]) without or with cirrhosis (CTP A)

- *EBR/GZR (50/100 mg, Zepatier®): 1 tablet orally daily for 12 weeks if GT1b, or if failed only PEG-IFN/RBV and GT1a without baseline NS5A RAS*[e]
- *GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food*
  - *If PEG-IFN/RBV-experienced: 8 weeks if non-cirrhotic or 12 weeks if cirrhotic*
  - *If NS3/4A PI + PEG-IFN/RBV-experienced: 12 weeks*
- *LDV/SOF (90/400 mg, Harvoni®): 1 tablet orally daily for 12 weeks; add RBV*[d] *if cirrhotic*
- *SOF/VEL (400/100 mg, Epclusa®): 1 tablet orally daily for 12 weeks*

Treatment-experienced (NS5A-naïve and SOF-experienced) without or with cirrhosis (CTP A)

- *GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food*
  - *If PEG-IFN/RBV + SOF-experienced: 8 weeks if non-cirrhotic or 12 weeks if cirrhotic*
  - *If SMV + SOF-experienced: 12 weeks*
- *SOF/VEL (400/100 mg, Epclusa®): 1 tablet orally daily for 12 weeks if GT1b*

Treatment-experienced (prior NS5A-containing regimen) without or with cirrhosis (CTP A)

- *GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food for 16 weeks if failed only an NS5A inhibitor without NS3/4A PI (e.g., LDV/SOF)*
- *SOF/VEL/VOX (400/100/100 mg, Vosevi™): 1 tablet orally daily with food for 12 weeks*

Treatment-experienced with decompensated cirrhosis (CTP B or C)

- *SOF/VEL (400/100 mg, Epclusa®): 1 tablet orally daily + RBV*[d]*; start at lower RBV doses as clinically indicated (e.g., baseline Hgb);*
  - *If NS5A-naïve: 12 weeks*
  - *If NS5A-experienced: 24 weeks; NOT FDA approved for 24 weeks*

[a] 12-week regimen should be used in HIV/HCV-infected patients.

[b] Consideration should be given to 12 weeks of treatment in African Americans and those with quantifiable (>LLOQ) HCV RNA at week 4 on treatment.[1]

[c] It is unclear whether the 1-fold shift in EBR concentrations observed in vitro with the M28V mutation reduces efficacy.[2] May consider the addition of RBV and extending treatment to 16 weeks if clinically appropriate.

[d] RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food.

[e] NS5A RAS testing can be performed through the VHA Public Health Reference Laboratory (email **V21PHRL@va.gov**) or a commercial laboratory (see Section XV, **Appendix B**) if results will change management.

Table 7. Treatment Regimens and SVR Rates in Treatment-Naïve Patients[a]

Based on patient characteristics, providers should consider the most clinically appropriate option when selecting a hepatitis C antiviral regimen. SVR rates cannot be compared between trials because of differences in study populations and clinical trial methodology. ***Within each category, regimens are listed in alphabetical order; this ordering does not imply preference for a particular regimen unless otherwise indicated.***

Treatment history & HCV genotype	Cirrhosis status	Regimen	Duration	Evidence grade	SVR% (N/N) in clinical trials	Comments
Naïve, GT1 ***GT1a without NS5A RAS*** ***GT1a with NS5A RAS***[d] **GT1b**	Non-cirrhotic	**EBR/GZR** **EBR/GZR + RBV** **EBR/GZR**	12 weeks 16 weeks 12 weeks	A-I	98% (441/450)[9] 100% (6/6)[9] 99% (129/131)[10]	**If GT1a, test for NS5A RAS.**[d] Incudes treatment-experienced cirrhotic patients.[9] 78% non-cirrhotic, 22% cirrhotic.[10] See monitoring recommendations below.[e]
Naïve, GT1	Non-cirrhotic	**GLE/PIB**	8 weeks	A-I	99% (348/351)[11,12]	Includes PEG-IFN/IFN ± RBV or SOF + RBV ± PEG-IFN-experienced patients.
Naïve, GT1 ***HCV RNA <6 million IU/mL, HCV monoinfection***	Non-cirrhotic	**LDV/SOF**	8 weeks[b,c]	A-I	97% (119/123)[13]	Higher relapse rates with 8 weeks vs. 12 weeks of LDV/SOF if baseline HCV RNA ≥6 million IU/mL: 10% (9/92) vs. 1% (1/85), respectively.[13]
Naïve, GT1	Non-cirrhotic	**LDV/SOF**	12 weeks	A-I	96% (82/85)[13] 99% (179/180)[14]	SVR 97% (178/184, + RBV)[14]
Naïve, GT1	Non-cirrhotic	**SOF/VEL**	12 weeks	A-I	99% (323/328)[15]	Includes cirrhotic and PEG-IFN/RBV ± NS3/4 PI)-experienced patients.
Naïve, GT1 ***GT1a without NS5A RAS*** ***GT1a with NS5A RAS***[d] **GT1b**	Cirrhotic, CTP A	**EBR/GZR** **EBR/GZR + RBV** **EBR/GZR**	12 weeks 16 weeks 12 weeks	A-I	98% (441/450)[9] 100% (6/6)[9] 99% (129/131)[10]	**If GT1a, test for NS5A RAS**[d]**.** Incudes treatment-experienced non-cirrhotic patients.[9] 78% non-cirrhotic, 22% cirrhotic.[10] See monitoring recommendations below.[e]
Naïve, GT1	Cirrhotic, CTP A	**GLE/PIB**	12 weeks	A-I	99% (89/90)[11]	Includes PEG-IFN/IFN ± RBV or SOF + RBV ± PEG-IFN-experienced patients.
Naïve, GT1	Cirrhotic, CTP A	**LDV/SOF** (consider adding RBV)	12 weeks	A-I	94% (32/34)[14]	SVR 100% (33/33, + RBV)[14]
Naïve, GT1	Cirrhotic, CTP A	**SOF/VEL**	12 weeks	A-I	99% (323/328)[15]	Includes non-cirrhotic and PEG-IFN/RBV ± NS3/4 PI)-experienced patients.[15]

Treatment history & HCV genotype	Cirrhosis status	Regimen	Duration	Evidence grade	SVR% (N/N) in clinical trials	Comments
Naïve, GT1	Cirrhotic, CTP B or C	**LDV/SOF + RBV**	12 weeks	A-I	CTP B: 87% (26/30)[16] CTP C: 86% (19/22)[16]	24 weeks: CTP B: SVR 89% (24/27)[16] CTP C: SVR 87% (20/23)[16] RBV initiated at 600 mg/day, increase by 200 mg/day every 2 weeks only as tolerated.[16] Includes treatment-experienced patients.[16]
Naïve, GT1	Cirrhotic, CTP B or C	**SOF/VEL + RBV**	12 weeks	A-I	96% (65/68)[17]	24 weeks: SVR 92% (65/71) [17]

[a] Refer to Section XII, Groups with Special Considerations for Therapy, on HCV treatment in patients with HIV/HCV coinfection and Appendix A, Table 24.

[b] 12-week regimen should be used in HIV/HCV-infected patients.

[c] Consideration should be given to 12 weeks of treatment in African Americans and those with quantifiable (>LLOQ) HCV RNA at week 4 on treatment.[1]

[d] NS5A RAS at amino acid positions 28, 30, 31, or 93. It is unclear whether the 1-fold shift in EBR concentrations observed in vitro with the M28V mutation reduces efficacy.[2] May consider the addition of RBV and extension of treatment to 16 weeks if clinically appropriate. Testing of HCV RAS can be performed through the VHA Public Health Reference Laboratory (email V21PHRL@va.gov) or a commercial laboratory (see Section XV, Appendix B).

[e] Monitor liver function tests at baseline, treatment week 8, and week 12 (if receiving 16 weeks of therapy) and as clinically indicated thereafter. Monitor for hepatic decompensation (e.g., ascites, jaundice, encephalopathy) while on treatment (see Section IX, Laboratory Monitoring).

Dosages:

- EBR/GZR (50/100 mg, Zepatier®): 1 tablet orally daily
- GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food
- LDV/SOF (90/400 mg, Harvoni®): 1 tablet orally daily
- SOF/VEL (400/100 mg, Epclusa®): 1 tablet orally daily
- RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food; 600 mg/day and increase as tolerated in CTP B and C patients receiving LDV/SOF. CTP B and C patients receiving SOF/VEL: prescribing information recommends RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)

Note: EBR/GZR, GLE/PIB, LDV/SOF, or SOF/VEL should not be used in reduced dosages or restarted if discontinued. DCV + SOF ± RBV can be considered if DDI precludes the use of other HCV regimens (see Appendix A, Table 23 and Table 24, www.hep-druginteractions.org, and manufacturer prescribing information).

Table 8. Genotype 1: Treatment Regimens and SVR Rates in Treatment-Experienced Patients[a]

Based on patient characteristics, providers should consider the most clinically appropriate option when selecting a hepatitis C antiviral regimen. SVR rates cannot be compared between trials because of differences in study populations and clinical trial methodology. Within each category, regimens are listed in alphabetical order; this ordering does not imply preference for a particular regimen unless otherwise indicated.

Treatment history & HCV genotype	Cirrhosis status	Regimen	Duration	Evidence grade	SVR% (N/N) in clinical trials	Comments
Experienced, GT1 *(PEG-IFN/RBV ± NS3/4A PI)* **GT1a without NS5A RAS** **GT1a with NS5A RAS[b]** **GT1b**	Non-cirrhotic	 **EBR/GZR + RBV** (no RBV if PEG-IFN/RBV only) **EBR/GZR + RBV** **EBR/GZR + RBV** (no RBV if PEG-IFN/RBV only)	 12 weeks 16 weeks 12 weeks	A-II	Failed NS3/4A PI + PEG-IFN/RBV: 96% (76/79, + RBV)[18] Failed PEG-IFN/RBV: 98% (441/450, – RBV)[9] 100% (6/6, – RBV)[9] 100% (35/35, – RBV)[19]	**If GT1a, test for NS5A RAS[b].** See Section XV, Appendix B. GT1a population incudes treatment-naïve and cirrhotic patients.[9] 65% were non-cirrhotic; 34% cirrhotic.[19] See monitoring recommendations below.[c]
Experienced, GT1 *(PEG-IFN ± RBV or SOF + RBV ± PEG-IFN)*	Non-cirrhotic	**GLE/PIB**	8 weeks	A-I	Failed PEG-IFN ± RBV or SOF + RBV ± PEG-IFN: 99% (348/351)[11,12] Failed PEG-IFN/RBV ± SOF: 99% (89/90)[11]	Includes treatment-naive patients.[11,12]
Experienced, GT1 *(NS3/4A PI-based regimen and NS5A-naïve)*	Non-cirrhotic	**GLE/PIB**	12 weeks	A-I	100% (14/14)[20]	
Experienced, GT1 *(PEG-IFN/RBV ± NS3/4A PI)*	Non-cirrhotic	**LDV/SOF** (consider adding RBV)	12 weeks	A-I	95% (83/87, – RBV)[21] 100% (89/89, + RBV)[21]	46-61% failed boceprevir- or telaprevir-based therapy.[21]
Experienced, GT1 *(NS5A-containing regimen without an NS3/4A PI)*	Non-cirrhotic	**GLE/PIB**	16 weeks	A-II	94% (17/18)[20]	Includes GT4-6.[20] 12 weeks: SVR 88% (14/16)[20]
Experienced, GT1 *(NS5A-experienced)*	Non-cirrhotic	**SOF/VEL/VOX**	12 weeks	A-I	97% (146/150)[22] GT1a: 96% (97/101)[22] GT1b: 100% (45/45)[22]	Includes cirrhotic patients.[22] Patients failed LDV/SOF (51%), DCV-containing regimen (27%), PrOD (11%), and other (13%) including SOF/VEL or EBR/GZR.[22]

Treatment history & HCV genotype	Cirrhosis status	Regimen	Duration	Evidence grade	SVR% (N/N) in clinical trials	Comments
Experienced, GT1 *(PEG-IFN/RBV ± NS3/4A PI)* GT1a without NS5A RAS GT1a with NS5A RAS[b] GT1b	Cirrhotic, CTP A	 **EBR/GZR + RBV** (no RBV if PEG-IFN/RBV only) **EBR/GZR + RBV** **EBR/GZR + RBV** (no RBV if PEG-IFN/RBV only)	 12 weeks 16 weeks 12 weeks	A-II	Failed NS3/4A PI + PEG-IFN/RBV: 96% (76/79, + RBV)[18] Failed PEG-IFN/RBV: 98% (441/450, – RBV)[9] 100% (6/6, – RBV)[9] 100% (35/35, – RBV)[19]	**If GT1a, test for NS5A RAS[b]**; see Section XV, Appendix B. GT1a population incudes treatment-naïve and non-cirrhotic patients.[9] 65% non-cirrhotic; 34% cirrhotic.[19] See monitoring recommendations below.[c]
Experienced, GT1 *(SMV + SOF; or PEG-IFN/RBV ± SOF or NS3/4A PI)*	Cirrhotic, CTP A	**GLE/PIB**	12 weeks	A-I	100% (14/14)[20] 99% (89/90)[11]	Failed SMV + SOF or PEG-IFN/RBV + NS3/4A PI.[20] Failed PEG-IFN/RBV ± SOF.[11]
Experienced, GT1 *(PEG-IFN/RBV + NS3/4A PI)*	Cirrhotic, CTP A	**LDV/SOF + RBV**	12 weeks	A-I	96% (74/77)[23]	SVR 97% (75/77) with LDV/SOF x 24 weeks.[23]
Experienced, GT1 *(NS5A-containing regimen without an NS3/4A PI)*	Cirrhotic, CTP A	**GLE/PIB**	16 weeks	A-II	94% (17/18)[20]	Includes GT 4-6.[20] 12 weeks: SVR 88% (14/16)[20]
Experienced, GT1 *(NS5A-experienced)*	Cirrhotic CTP A	**SOF/VEL/VOX**	12 weeks	A-I	97% (146/150)[22] GT1a: 96% (97/101)[22] GT1b: 100% (45/45)[22]	Includes non-cirrhotic patients.[22] Previously failed LDV/SOF (51%), DCV-containing regimen (27%), PrOD (11%), and other (13%) including SOF/VEL or EBR/GZR.[22]
Experienced, GT1 *(PEG-IFN/RBV ± NS3/4A PI)*	Cirrhotic, CTP B or C	**LDV/SOF + RBV**	12 weeks	B-I	CTP B: 87% (26/30)[16] CTP C: 86% (19/22)[16]	24 weeks: CTP B: SVR 89% (24/27)[16] CTP C: SVR 87% (20/23)[16] RBV initiated at 600 mg/day and increased by 200 mg/day every 2 weeks only as tolerated. Includes treatment-naïve patients.[16]
Experienced, GT1 *(NS5A-experienced)*	Cirrhotic, CTP B or C	**SOF/VEL + RBV**	24 weeks *NOT FDA approved for 24 weeks*	B-II	97% (33/34)[24]	Previously failed SOF/VEL-containing regimens for 4, 6, 8, or 12 weeks; 26% cirrhotic; 18% baseline NS5A RAS.[24]

[a] Refer to Section XII, Groups with Special Considerations for Therapy, on HCV treatment in patients with HIV/HCV coinfection and Appendix A, Table 23 and Table 24. Drug-Drug Interactions with HIV Antiretrovirals

[b] NS5A RAS at amino acid positions 28, 30, 31, or 93. It is unclear whether the 1-fold shift in EBR concentrations observed in vitro with the M28V mutation reduces efficacy.[2] May consider the addition of RBV and extending

treatment to 16 weeks if clinically appropriate. Testing of HCV RAS can be performed through the VHA Public Health Reference Laboratory (email V21PHRL@va.gov) or a commercial laboratory (see Section XV, Appendix B).

[c] Monitor liver function tests at baseline, treatment week 8, and week 12 (if receiving 16 weeks of therapy) and as clinically indicated thereafter. Monitor for hepatic decompensation (e.g., ascites, jaundice, encephalopathy) while on treatment (see Section IX, Laboratory Monitoring).

Dosages:

- EBR/GZR (50/100 mg, Zepatier®): 1 tablet orally daily
- GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food
- LDV/SOF (90/400 mg, Harvoni®): 1 tablet orally daily
- SOF/VEL (400/100 mg, Epclusa®): 1 tablet orally daily
- SOF/VEL/VOX (400/100/100 mg, Vosevi®): 1 tablet orally daily with food
- RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food; 600 mg/day and increase as tolerated in CTP B and C patients receiving LDV/SOF. CTP B and C patients receiving SOF/VEL: prescribing information recommends RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)

Note: EBR/GZR, GLE/PIB, LDV/SOF, SOF/VEL, SOF/VEL/VOX should not be used in reduced dosages or restarted if discontinued. DCV + SOF ± RBV can be considered if DDI precludes the use of other HCV regimens (see Appendix A, Table 23 and Table 24, www.hep-druginteractions.org, and manufacturer prescribing information).

Table 9. Genotype 1: Treatment Regimens and SVR Rates in Treatment-Experienced Patients based on Subtype[a]

SVR rates cannot be compared between trials.

Treatment history & HCV genotype	Cirrhosis status	Regimen	Duration	Evidence grade	SVR% (N/N) in clinical trials	Comments
Experienced, GT1a *(NS5A-naïve and SOF-experienced)*	Non-cirrhotic or Cirrhotic, CTP A	**SOF/VEL/VOX**	12 weeks	A-I	GT1a: 98% (53/54)[22]	SVR 89% (39/44) with SOF/VEL x 12 weeks.[22]
Experienced, GT1b *(NS5A-naïve)*	Non-cirrhotic or Cirrhotic	**SOF/VEL**	12 weeks	A-I	GT1b: 99% (117/118)[15] GT1b: 95% (21/22)[22] CTP B or C: 83% (75/90, – RBV)[17]	Includes treatment-naïve[15,17] and non-cirrhotic patients.[15] 24 weeks, CTP B or C: 86% (77/90, – RBV)[17]

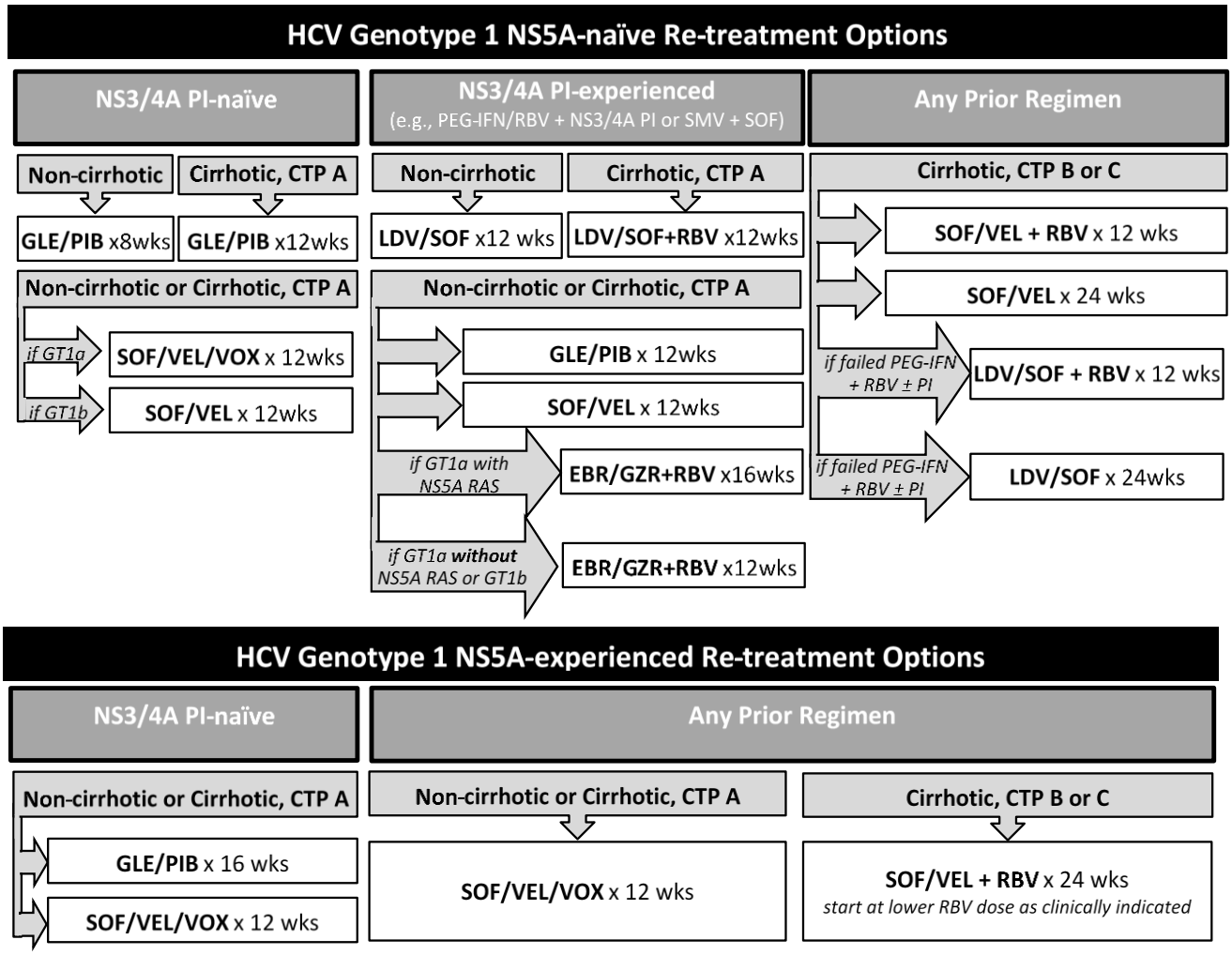
[a] In patients with HIV/HCV coinfection, see "Groups with Special Considerations for Therapy" on HCV treatment and Appendix A, Table 23 and Table 24.

Dosages:

- SOF/VEL (400/100 mg, Epclusa®): 1 tablet orally daily
- SOF/VEL/VOX (400/100/100 mg, Vosevi®): 1 tablet orally daily with food

Note: SOF/VEL or SOF/VEL/VOX should not be used in reduced dosages or restarted if discontinued. DCV + SOF ± RBV can be considered if DDI precludes the use of other HCV regimens (see Appendix A, Table 23 and Table 24, www.hep-druginteractions.org, and manufacturer prescribing information).

Figure 1. Re-Treatment Options for HCV Genotype 1 NS5A-Naïve and NS5A-Experienced Patients



Treatments for Genotype 1-Infected Patients

Given similar SVR rates with all regimens, differences in drug metabolism, adverse events, drug interactions, pill burden, and treatment duration should be considered to determine the optimal treatment regimen for a patient.

Genotype 1-Infected Patients Who Have Failed DAA-Based Therapy

Recommendations on re-treatment of patients who have failed a DAA-containing regimen should be based on the previous regimen used and the presence/absence of decompensated cirrhosis. With the availability of newer agents which have been proven effective in prior DAA failures with RAS, situations in which RAS testing could influence the regimen choice are less frequent. HCV RAS testing should be performed only if the results would guide re-treatment options. The VHA Public Health Reference Laboratory (PHRL, email V21PHRL@va.gov) and commercial laboratories offer testing for HCV RAS (see Section XV, Appendix B).

Patients who have failed an NS5A-containing regimen (i.e., daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, velpatasvir)

Re-treatment with SOF/VEL/VOX

Re-treatment with SOF/VEL/VOX for 12 weeks can be used for GT1 patients without cirrhosis and those with compensated cirrhosis (CTP A) who previously failed an NS5A inhibitor-containing regimen. A randomized, double-blind, placebo-controlled study (POLARIS-1) evaluated the efficacy of SOF/VEL/VOX for 12 weeks in 263 NS5A inhibitor-experienced patients, including 150 patients with GT1.[22] Patients previously failed LDV/SOF (51%), a DCV-containing regimen (27%), PrOD (11%), and other regimens (13%) including SOF/VEL or EBR/GZR. SVR was achieved in 96% (97/101; 95% CI: 90-99) with GT1a and 100% (45/45, 95% CI 92-99) with GT1b. Across genotypes, SVR rates were similar in patients with and without RAS; 97% (199/205) vs. 98% (42/43), respectively. These results demonstrate that baseline RAS testing may not be needed prior to using SOF/VEL/VOX. Because SOF/VEL/VOX contains an NS3/4A protease inhibitor, this regimen is not recommended in patients with decompensated cirrhosis.

Re-treatment with GLE/PIB + SOF + RBV (regimen is not FDA approved)

MAGELLAN-3 is an ongoing open-label, parallel arm study evaluating the efficacy and safety of GLE/PIB + SOF + RBV (800-1,200 mg daily) for 12 or 16 weeks in GT1-6 patients who experienced virologic failure (breakthrough or relapse) with GLE/PIB in a Phase II/III clinical trial.[25] Treatment duration is 12 weeks for noncirrhotic patients with GT1, 2, 4-6 infection who were NS5A- or NS3-naïve before GLE/PIB virologic failure. Patients with GT3, compensated cirrhosis, or NS5A- and/or NS3-experience before GLE/PIB virologic failure receive 16 weeks of GLE/PIB + SOF + RBV. Interim analysis of 23 of the projected 50 patients was presented; 6 were GT1a (26%), 1 GT1b (4%), 2 GT2 (9%), and 14 GT3 (61%). Most were treatment-naïve before GLE/PIB virologic failure (n=15, 65%) and had no to minimal fibrosis (n=16, 70%). Six patients (26%) were NS5A-experienced before GLE/PIB and seven patients (30%) had compensated cirrhosis. Pre-treatment (current study) NS5A RAS were present in 18 patients and 5 had NS5A + NS3 RAS. Overall SVR was 96% (22/23). In the 12-week arm, 100% (2/2) achieved SVR, both of whom had GT2 infection. In the 16-week arm, SVR occurred in 83% (5/6) with GT1a, 100% (1/1) with GT1b and 100% (14/14) with GT3. Adverse events were reported in 83% (19/23) with headache being most frequent

(n=6, 23%), followed by pruritus (n=5, 22%), dizziness and irritability (4 each, 17%). There was only 1 SAE (symptomatic cholelithiasis, not related to study drug). There were no Grade ≥3 reductions in hemoglobin or RBV dose reductions due to toxicity.

Re-treatment with EBR/GRZ + SOF + RBV (regimen is not FDA approved)
In the C-SWIFT open-label study, 25 GT1-infected patients were re-treated with EBR/GZR + SOF + RBV for 12 weeks if they had previously failed EBR/GZR for 4, 6, or 8 weeks.[26] The majority of patients were male (88%), Caucasian (100%), and had GT1a (88%) infection. There were 5 patients with cirrhosis (20%). Baseline RAS to NS5A were present in 20 patients (80%), NS3 in 13 patients (52%), and NS5A + NS3 in 11 patients (44%). SVR was achieved in 92% (23/25); 2 patients were lost to follow-up.

Re-treatment with SOF/VEL + RBV
For GT1 patients who have failed an NS5A inhibitor-containing regimen and have decompensated cirrhosis (CTP B, C), SOF/VEL + RBV for 24 weeks can be considered; note that 24 weeks of therapy is not FDA approved. In an open-label study, 69 GT1, 2, and 3 patients were re-treated with SOF/VEL + RBV for 24 weeks after failing SOF/VEL-containing regimens for 4, 6, 8, or 12 weeks.[24] The majority of patients were male (77%), Caucasian (88%), and had GT1 (54%) infection; 26% had cirrhosis. Among GT1 patients, SVR was achieved in 96% (27/28) without baseline RAS and 100% (6/6) with baseline RAS.

Patients who have failed an NS5A-containing regimen without an NS3/4A PI (e.g., LDV/SOF)
GLE/PIB for 16 weeks is FDA approved for GT1 patients without cirrhosis or those with compensated cirrhosis (CTP A) who have failed an NS5A-containing regimen without an NS3/4A PI (e.g., LDV/SOF). In an open-label, multicenter study (MAGELLAN-1, Part 2), patients with GT1, 4-6 who failed prior DAA-based treatment were re-treated with GLE/PIB for 12 or 16 weeks.[20] The majority of patients were male (70%) and had GT1a (71-80%). Patients had previously failed NS3/4A PI only (28-32%), NS5A inhibitor only (26-28%), or NS3/4A PI + NS5A inhibitor (32-34%). Baseline RAS to NS3/4A PI only occurred in 5-9%, NS5A inhibitor only 52-55%, and NS3/4A PI + NS5A inhibitor 9-11%. In those who had failed an NS5A inhibitor-containing regimen only, SVR rates were 88% (14/16) in the 12-week arm and 94% (17/18) in the 16-week arm. In those who had failed NS3/4A PI + NS5A inhibitor, SVR rates were 79% (11/14) and 81% (13/16) with 12 and 16 weeks of GLE/PIB, respectively. GLE/PIB should not be used in patients previously treated with both an NS3/4A PI- and NS5A-containing regimen.

Patients who have failed a non-NS5A-containing regimen
Re-treatment with EBR/GZR + RBV
In a Phase II open-label study (C-SALVAGE), 12 weeks of EBR/GZR + weight-based RBV was evaluated among 79 patients who previously failed treatment with PEG-IFN/RBV + NS3/4A PI (i.e., telaprevir [n=43], boceprevir [n=28], or SMV [n=8]).[18] In this cohort, 98% were non-CC IL28B genotype, 62% had GT1b, 43% had cirrhosis, and 84% had prior virologic failure. SVR was achieved in 96% (76/79); 3 patients experienced virologic relapse. SVR was achieved in 91% (31/34) and 100% (55/55) with and without baseline NS3 RAS, respectively. SVR was achieved in 75% (6/8) with baseline NS5A RAS. Based on expert opinion, GT1a patients with baseline NS5A RAS who previously failed treatment with PEG-IFN/RBV + NS3/4A PI should receive 16 weeks of EBR/GZR + RBV.

Re-treatment with GLE/PIB (HCV NS5A inhibitor/HCV NS3/4A protease inhibitor)

GLE/PIB for 12 weeks is FDA approved for GT1 patients without cirrhosis or those with compensated cirrhosis (CTP A) who have failed a NS3/4A PI-containing regimen. In an open-label, multicenter study (MAGELLAN-1, Part 2) patients with GT1, 4-6 who previously failed a NS3/4A PI-containing regimen were re-treated with GLE/PIB for 12 or 16 weeks.[20] The majority of patients were male (70%) and had GT1a (71-80%). Patients had previously failed NS3/4A PI only (28-32%), NS5A inhibitor only (26-28%), or NS3/4A PI + NS5A inhibitor (32-34%). Baseline RAS to NS3/4A PI only were present in 5-9%, NS5A Inhibitor only 52-55%, and NS3/4A PI + NS5A inhibitor 9-11%. In those who had failed NS3/4A PI only, SVR rates were 100% (14/14, 13/13) in the 12- and 16-week arms.

Among cirrhotic patients who have failed PEG-IFN/RBV ± SOF, re-treatment with GLE/PIB for 12 weeks can be considered. An open-label study (EXPEDITION-1) evaluated GLE/PIB for 12 weeks in 146 GT1, 2, 4-6 patients with compensated cirrhosis (CTP A) who were treatment-naïve (75%) or treatment-experienced (25%; PEG-IFN/IFN ± RBV [69%], SOF + RBV ± PEG-IFN [31%]).[11] The majority were male (62%), White (82%), with cirrhosis (91%, CTP score 5 or 6); 20% had platelets <100,000/mm^3 and 3% had total bilirubin ≥2 mg/dL. Baseline RAS to NS3 only were present in 2% (2/133), NS5A only in 40% (53/133), and NS3 + NS5A in 2% (2/133). SVR was achieved with GLE/PIB for 12 weeks in 99% (89/90) of GT1 patients.

Re-treatment with LDV/SOF ± RBV

For patients who previously failed PEG-IFN/RBV + an NS3/4A PI, LDV/SOF (without RBV) is FDA approved for 12 weeks in those without cirrhosis and for 24 weeks in those with cirrhosis, or LDV/SOF + RBV for 12 weeks with cirrhosis is also approved.[23,27] In a randomized, double-blind study (SIRIUS) comparing LDV/SOF + RBV for 12 weeks with LDV/SOF for 24 weeks among cirrhotic patients who had previously failed boceprevir or telaprevir + PEG-IFN/RBV, SVR was achieved in 96% (74/77) of those treated with LDV/SOF + RBV for 12 weeks and in 97% (75/77) of those treated with LDV/SOF for 24 weeks.[23]

Among patients who have failed SOF-based therapy but are NS5A-naïve, re-treatment with LDV/SOF + RBV for 12 weeks achieved SVR rates of 95-100%.[28] In a Phase II trial of GT1-infected patients (29% of whom had cirrhosis) who initially failed SOF + PEG-IFN/RBV (n=25) or SOF + RBV (n=21), re-treatment with LDV/SOF + RBV for 12 weeks achieved SVR in 100% (25/25) with prior SOF + PEG-IFN/RBV experience and 95% (20/21) with prior SOF + RBV experience. Thus, available data suggest that patients who fail a regimen that contains SOF (without an NS5A inhibitor) can be successfully re-treated with LDV/SOF + RBV for 12 weeks.

A Phase III trial (ION-2) randomized 440 HCV GT1 treatment-experienced (PEG-IFN/RBV ± NS3/4 PI) patients to receive one of four regimens: 12 weeks of LDV/SOF (n=109), 12 weeks of LDV/SOF + RBV (n=111), 24 weeks of LDV/SOF (n=109), or 24 weeks of LDV/SOF + RBV (n=111).[21] Across the groups, 41-46% of patients were non-responders and 54-59% were relapsers or had experienced virologic breakthrough. Overall, 46-61% of patients had previously received PI-based treatment with either boceprevir or telaprevir. In each treatment group, 20% of patients had cirrhosis. In the four treatment arms described above, SVR rates were 94% (95% CI: 87-97), 96% (95% CI: 91-99), 99% (95% CI: 95-100), and 99% (95% CI: 95-100), respectively. In patients who previously failed PI-based therapy, SVR rates

were 94-97% (95% CI: 85-100) with LDV/SOF for 12 weeks and 98-100% (95% CI: 89-100) with LDV/SOF for 24 weeks. Among patients with cirrhosis, SVR rates in those receiving 12 weeks of treatment were 86% (19/22; 95% CI: 65-97) with LDV/SOF and 82% (18/22; 95% CI: 60-95) with LDV/SOF + RBV, and SVR in those receiving 24 weeks of treatment was 100% with LDV/SOF (22/22; 95% CI: 85-100) and LDV/SOF + RBV (22/22; 95% CI: 85-100). Of the 62 patients who had an NS5A RAS at baseline, 89% (55/62) achieved SVR; 6 of 11 patients who relapsed after treatment had NS5A RAS at baseline.

Re-treatment with SOF/VEL
A randomized, double-blind Phase III trial (POLARIS-4) compared 12 weeks of SOF/VEL with SOF/VEL/VOX in GT1-3 patients who had failed previous DAA regimens that did not contain an NS5A inhibitor.[22] In GT1b patients, SVR rates between SOF/VEL and SOF/VEL/VOX were similar; 95% (21/22) vs. 96% (23/24), respectively. Among patients without cirrhosis, SVR rates were 94% (77/82) with SOF/VEL and 98% (96/98) with SOF/VEL/VOX.

Re-treatment with SOF/VEL/VOX
SOF/VEL/VOX for 12 weeks is FDA approved for GT1 patients without cirrhosis or those with compensated cirrhosis (CTP A) who have failed a non-NS5A-containing DAA regimen. A randomized, double-blind Phase III trial (POLARIS-4) compared 12 weeks of SOF/VEL/VOX with SOF/VEL in GT1-4 patients who had failed previous DAA regimens that did not contain an NS5A inhibitor.[22] Patients with decompensated cirrhosis were excluded. Patients had failed an SOF-containing regimen (85%) or both an NS5B inhibitor and N3/4A PI (25%). Among GT1a patients, SVR with SOF/VEL/VOX was higher than for SOF/VEL, 98% (53/54) and 89% (39/44), respectively. SVR rates between SOF/VEL/VOX and SOF/VEL were similar for GT1b; 96% (23/24) vs. 95% (21/22), respectively. Across genotypes, 46% had cirrhosis and 49% had baseline NS3 or NS5A RAS. Among patients with cirrhosis, SVR rates for SOF/VEL/VOX were higher than for SOF/VEL, 98% and 86%, respectively. Overall, there was no significant difference in SVR rates with SOF/VEL/VOX with or without baseline NS3 or NS5A RAS; SVR 100% (83/83) vs. 99% (85/86), respectively. This study demonstrates that patients with prior DAA experience can be treated without baseline RAS testing, even among patients with compensated cirrhosis (CTP A).

Summary of Pivotal Trials in Genotype 1-Infected Patients

Elbasvir/grazoprevir (HCV NS5A inhibitor/HCV NS3/4A protease inhibitor) ± ribavirin

In a double-blind, randomized Phase III trial (C-EDGE), 12 weeks of EBR/GZR was evaluated in 421 GT1-, 4-, or 6-infected treatment-naïve patients.[10] SVR rates with EBR/GZR for 12 weeks were 92% (144/157) in GT1a patients and 98% (129/131) in GT1b patients.[9] SVR rates in GT1-infected patients with cirrhosis were 97% (66/68) and 94% (207/220) in non-cirrhotics.

In an open-label, randomized Phase II study (C-WORTHY), 123 GT1 treatment-naïve patients with cirrhosis received EBR/GZR + RBV for 12 weeks (n=31), EBR/GZR for 12 weeks (n=29), EBR/GZR + RBV for 18 weeks (n=32), or EBR/GZR for 18 weeks (n=31).[29] SVR rates for the groups were: 90% (28/31) with EBR/GZR + RBV for 12 weeks, 97% (28/29) with EBR/GZR for 12 weeks, 97% (31/32) with EBR/GZR + RBV for 18 weeks, and 94% (29/31) EBR/GZR for 18 weeks. In another arm of the study, the efficacy and

safety of 12 or 18 weeks of EBR/GZR ± RBV were evaluated in GT1 null responders to PEG-IFN/RBV.[29] Among patients receiving EBR/GZR for 12 weeks, SVR was 91% (30/33) without RBV and 94% (30/32) with RBV. Among patients receiving EBR/GZR for 18 weeks, SVR was 97% (31/32) without RBV and 100% (33/33) with RBV, including SVR 100% (5/5) with RAS to NS5A prior to treatment.

In an open-label Phase III trial (C-EDGE), 12 or 16 weeks of EBR/GZR ± weight-based RBV was evaluated among 420 patients (377 with GT1, 37 with GT4, and 6 with GT6) who had failed PEG-IFN/RBV treatment.[19] The overall SVR was 92% (97/105) with EBR/GZR for 12 weeks, 94% (98/104) with EBR/GZR + RBV for 12 weeks, 92% (97/105) with EBR/GZR for 16 weeks, and 97% (103/106) with EBR/GZR + RBV for 16 weeks. In prior partial or null responders, SVR was achieved in 100% (62/62) with EBR/GZR + RBV for 16 weeks including 6/6 with baseline NS5A RAS prior to treatment. Among GT1 patients, SVR rates were 90% (90/96) with EBR/GZR for 12 weeks and 97% (93/96) with EBR/GZR + RBV for 16 weeks.[9] Among GT1a patients, SVR rates were 90% (55/61) with EBR/GZR for 12 weeks and 95% (55/58) with EBR/GZR + RBV for 16 weeks. In GT1b patients, SVR rates were 100% (35/35) with EBR/GZR for 12 weeks and 100% (38/38) with EBR/GZR + RBV for 16 weeks. SVR rates were similar in GT1 cirrhotic patients treated with EBR/GZR for 12 weeks or EBR/GZR + RBV for 16 weeks; SVR 94% vs. 100%, respectively.[9]

Impact of Baseline HCV RAS on SVR Rates with Elbasvir/Grazoprevir in Genotype 1-Infected Patients
SVR rates from treatment-naïve patients who received EBR/GZR ± RBV from pooled analysis of Phase III clinical trials and those who did not achieve SVR for non-virologic failure were reviewed.[9]

Genotype 1a
NS3: In GT1a-infected patients, the NS3 Q80K polymorphism did not appear to impact treatment response. RAS at other NS3 resistance-associated positions were not associated with reduced efficacy.

NS5A: The presence of one or more HCV NS5A RAS at positions M28, Q30, L31, or Y93 was associated with reduced efficacy of EBR/GZR for 12 weeks, regardless of prior treatment history or cirrhosis status. The addition of RBV and extension of treatment with EBR/GZR to 16 weeks achieved favorable SVR rates. Among patients treated with 12 weeks of EGR/GZR, SVR rates were 98% (441/450) without baseline NS5A RAS (M28, Q30, L31, or Y93) compared with SVR 70% (39/56) with baseline NS5A RAS. Although data are limited, among GT1a-infected patients with NS5A RAS who received EBR/GZR + RBV for 16 weeks, 100% (6/6) achieved SVR. The prevalence of NS5A RAS at any of these positions in GT1a-infected patients was 12% (37/309) in the United States across Phase II and Phase III clinical trials. Thus, NS5A RAS testing is recommended in GT1a-infected patients prior to initiating EBR/GZR to determine the regimen (requirement for RBV) and treatment duration.[9]

Genotype 1b
NS3: In GT1b-infected subjects, baseline NS3 RAS did not impact treatment response.

NS5A: In GT1b-infected subjects treated with EBR/GZR for 12 weeks, SVR rates (non-virologic failure-censored) were 94% (48/51) and 99% (247/248) for those with and without one or more NS5A RAS at positions 28, 30, 31, or 93.

Glecaprevir/pibrentasvir (HCV NS3/4A protease inhibitor/HCV NS5A inhibitor)

An integrated analysis of data pooled from ENDURANCE 1-4, SURVEYOR-I and -II, and EXPEDITION-4 examined the efficacy of 8 (n=828) or 12 (n=1,076) weeks of GLE/PIB in non-cirrhotic GT1-6 patients. Patients were treatment-naïve (74-79%) or treatment-experienced (21-26%; PEG-IFN/IFN ± RBV [96-97%], SOF + RBV ± PEG-IFN [4%]).[12] The population was mostly male (51-54%) and White (77-83%) with F0-F1 disease (81-82%). High SVR rates occurred in GT1 patients receiving GLE/PIB for 8 and 12 weeks; 99% (383/387) vs. 100% (400/401), respectively. Across genotypes, only 1% (7/828) and 0.3% (3/1,076) relapsed in the 8- and 12-week group, respectively. Baseline NS3 or NS5A RAS had minimal impact on SVR with 8 or 12 weeks of GLE/PIB, whereas baseline NS3 + NS5A RAS significantly reduced the likelihood of SVR (78% (7/9); OR = 0.017, [95% CI: 0.003–0.098]; $p < .0001$). This study supports the use of GLE/PIB for 8 weeks in GT1 patients who are non-cirrhotic and treatment-naïve or treatment-experienced (PEG-IFN/IFN ± RBV or SOF + RBV ± PEG-IFN).

An open-label study (EXPEDITION-1) evaluated GLE/PIB for 12 weeks in 146 GT1, 2, 4-6 patients with compensated cirrhosis (CTP A) who were treatment-naïve (75%) or treatment-experienced (25%; PEG-IFN/IFN ± RBV [69%], SOF + RBV ± PEG-IFN [31%]).[11] The majority were male (62%), White (82%), with cirrhosis (91%, CTP score 5 or 6); 20% had platelets <100,000/mm^3 and 3% had total bilirubin ≥2 mg/dL. Baseline RAS to NS3 only were present in 2% (2/133), NS5A only in 40% (53/133), and NS3 + NS5A in 2% (2/133). SVR was achieved with GLE/PIB for 12 weeks in 99% (89/90) with GT1. This study supports the use of GLE/PIB for 12 weeks in GT1 patients with cirrhosis who are treatment-naïve or treatment-experienced (PEG-IFN/RBV ± SOF).

Ledipasvir/sofosbuvir (HCV NS5A inhibitor/HCV nucleotide NS5B polymerase inhibitor)

ION-1 was a randomized, open-label Phase III clinical trial of LDV/SOF in treatment-naïve patients with HCV GT1 infection.[14] Four treatment arms were compared: LDV/SOF for 12 or 24 weeks, with and without RBV. Of 865 patients enrolled, 67% were GT1a, 12% were Black, 70% were IL-28B non-CC genotype, and 16% had cirrhosis. High SVR rates (97-99%) were observed in all treatment arms with no statistically significant differences observed with the 24-week duration arm or with the addition of RBV. In subgroup analyses, high SVR rates (97-100%) were observed in all four treatment arms regardless of race, IL-28B genotype, subtype (1a vs. 1b), higher baseline HCV RNA, and the presence or absence of cirrhosis. Based on the findings of this study, 12 weeks of LDV/SOF (without RBV) is expected to produce high SVR rates in HCV GT1 treatment-naïve patients across a broad range of pre-treatment characteristics.

ION-3 evaluated the safety and efficacy of 8 weeks and 12 weeks of LDV/SOF among 647 treatment-naïve, HCV GT1-monoinfected patients without cirrhosis.[13] Patients were randomly assigned to receive one of three treatment regimens: 8 weeks of LDV/SOF (n=215), 8 weeks of LDV/SOF + RBV (n=216), or 12 weeks of LDV/SOF (n=216). Randomization was stratified according to HCV GT1a (80% of patients) or 1b (20% of patients). The majority of patients had METAVIR F0-F2 (50-59%) and 13% had F3. Overall, SVR in the 8-week LDV/SOF arm was 94% (95% CI: 90-97) and 93% in the RBV-containing arm (95% CI: 89-96), and SVR in the 12-week LDV/SOF arm was 95% (95% CI: 92-98). In a post-hoc analysis, patients with a baseline HCV RNA <6 million IU/mL achieved SVR rates of 97% (119/123) in the 8-week arm and 96% (126/131) in the 12-week arm. Relapse rates in the 8-week arm receiving LDV/SOF occurred in 10%

(9/92) of patients with a baseline HCV RNA level ≥6 million IU/mL but in only 1% (1/85) of patients with HCV RNA <6 million IU/mL. LDV/SOF for 8 weeks can be considered in non-cirrhotic, treatment-naïve HCV GT1-monoinfected patients with a baseline HCV RNA <6 million IU/mL. However, 8 weeks of LDV/SOF is not recommended for patients with HIV/HCV coinfection or cirrhosis, or for previously treated patients.

Genotype 1-Infected Patients with Cirrhosis, Compensated

Up to 20% of patients in Phase III studies of LDV/SOF (i.e., ION-1, 2, and 3) had compensated cirrhosis. Among treatment-naïve patients receiving LDV/SOF for 12 weeks, the SVR rates among patients without cirrhosis were similar to those with cirrhosis. However, among treatment-experienced patients in the ION-2 study receiving treatment for 12 weeks, the SVR was 86% (19/22) with LDV/SOF and 82% (18/22) with LDV/SOF + RBV. SVR was 100% among patients receiving 24 weeks of LDV/SOF (22/22) or LDV/SOF + RBV (22/22). Based on these data, the FDA recommends that treatment-experienced patients with cirrhosis receive LDV/SOF for 24 weeks.

LDV/SOF + RBV for 12 weeks achieved a high SVR rate in treatment-experienced patients with cirrhosis. SIRIUS was a prospective, double-blind, placebo-controlled study of LDV/SOF + RBV for 12 weeks (n=77) compared with LDV/SOF (n=77) for 24 weeks in patients with compensated cirrhosis who had failed treatment with PEG-IFN/RBV and, subsequently, with PEG-IFN/RBV + NS3/4A PI.[23] Median age was 56 years, 94% of patients had non-IL-28B CC genotype, 17% had platelet counts <100,000/mm^3, and 13% had albumin levels <3.5 g/dL. SVR occurred in 96% (74/77) with LDV/SOF + RBV for 12 weeks (3 relapsed) compared with an SVR in 97% (75/77) with LDV/SOF for 24 weeks (2 relapsed). Adverse events were infrequent. Hemoglobin decreased to <10 g/dL in 1 patient in each treatment arm. There were no deaths. Based on these data, 12 weeks of LDV/SOF + RBV is safe and effective in treatment-experienced patients with compensated cirrhosis who failed PEG-IFN/RBV + NS3/4A PI.

Genotype 1-Infected Patients with Cirrhosis, Decompensated

LDV/SOF in combination with RBV should be used for treatment of GT1-infected patients with decompensated cirrhosis whenever possible. SVR rates are reduced when RBV is not administered in combination with LDV/SOF for 12 weeks. In a Phase II open-label study of treatment-naïve patients with CTP B cirrhosis treated with LDV/SOF for 12 weeks, the SVR was 65% (13/20).[30]

LDV/SOF + RBV (starting at 600 mg/day and titrated up as tolerated) for 12 or 24 weeks was evaluated in a prospective study of GT1- or GT4-infected patients who were treatment-naïve or treatment-experienced with CTP B (n=59) or with CTP C (n=49).[16] Inclusion criteria included bilirubin ≤10 mg/dL, hemoglobin ≥10 g/dL, platelets >130,000/mm^3 and eGFR ≥40 mL/min. Patients were excluded from SVR analysis if they underwent transplantation. Among the 57 CTP B patients, SVR rates were 87% (26/30) and 89% (24/27) with LDV/SOF + RBV for 12 weeks and 24 weeks, respectively. In patients with CTP C, SVR rates were 86% (19/22) and 87% (20/23) with LDV/SOF + RBV for 12 and 24 weeks, respectively. Mean bilirubin and albumin concentrations improved significantly between baseline and post-treatment week 4 for CTP B and for CTP C patients in the 12- and 24-week arms. MELD score improved in most patients. There were 4 treatment-related serious adverse events (anemia [2], hepatic encephalopathy [1], peritoneal hemorrhage [1]), 2 in CTP B and 2 in CTP C patients. Three patients discontinued treatment due to adverse events. Ten patients died, which was assessed as complications related to

hepatic decompensation. These data suggest that LDV/SOF + RBV (starting at 600 mg/day) for 12 weeks can be considered for patients with decompensated cirrhosis and eGFR >40 mL/min. RBV can be increased by 200 mg/day every 2 weeks if the hemoglobin is >10 g/dL.

Sofosbuvir/velpatasvir (HCV nucleotide NS5B polymerase inhibitor/HCV NS5A inhibitor)

ASTRAL-1 was a Phase III double-blind placebo-controlled randomized trial of treatment-naïve and treatment-experienced (PEG-IFN/RBV ± NS3/4 PI) patients with GT1, 2, 4, 5, and 6, treated with SOF/VEL for 12 weeks.[15] Among GT1a patients who received SOF/VEL, 23% (49/210) had cirrhosis and 37% (78/210) were treatment-experienced (94% [74/78] received PEG-IFN/RBV ± NS3/4 PI). Among the GT1b, 20% (24/118) were cirrhotic and 27% (32/118) were treatment-experienced (11 [34%] DAA + PEG-IFN/RBV, 14 [43%] PEG-IFN/RBV and 7 [23%] other). Of the GT1 patients who received SOF/VEL, SVR was achieved in 99% (323/328); SVR 98% (206/210) with GT1a and SVR 99% (117/118) with GT1b. There were no virologic failures during therapy. Of the 4 GT1a patients who did not achieve SVR, 1 discontinued due to a mental health event; 1 treatment-naïve non-cirrhotic patient experienced virologic relapse after therapy and was found to have a Q30R mutation in NS5A; and 2 were lost to follow-up. The one GT1b patient who did not achieve SVR had an NS5A Q30R mutation and was also PEG-IFN/RBV-experienced.

Genotype 1-Infected Patients with Cirrhosis, Decompensated

ASTRAL-4 was a prospective, open-label, Phase III trial of 267 patients with HCV genotypes 1-6 and decompensated cirrhosis who were treatment-naïve and treatment-experienced (PEG-IFN/RBV ± NS3/4 PI; 55%).[17] Patients were randomized to receive SOF/VEL for 12 weeks, SOF/VEL + RBV (weight-based dosing) for 12 weeks, or SOF/VEL for 24 weeks. Of 267 patients, 78% (n=207) had HCV GT1, 4% (n=12) GT2, 15% (n=39) GT3, 3% (n=8) GT4, and less than 1% (n=1) GT6; no patients had GT5. Only 6% were Black and 2% were Asian. The majority of patients were CTP B (score 7-9, 89%); 6% were CTP A (score ≤6) and 4% were CTP C (score 10). Mild or moderate ascites was present in 78% and severe in 3%. Among 207 patients with HCV GT1, SVR was achieved in 88% (88% [44/50] GT1a, 89% [16/18] GT1b) with SOF/VEL for 12 weeks, 96% (94% [51/54] GT1a, 100% [14/14] GT1b) with SOF/VEL + RBV for 12 weeks, and 92% (93% [51/55] GT1a, 88% [14/16] GT1b) with SOF/VEL for 24 weeks. SVR was achieved in 89% (64/72) with baseline NS5A RAS compared with SVR 92% (169/183) in those without. Nine deaths occurred during the study, which was evenly divided among the treatment groups; none were considered related to therapy.

Sofosbuvir/velpatasvir/voxilaprevir (HCV nucleotide NS5B polymerase inhibitor/HCV NS5A inhibitor/HCV NS3/4A protease inhibitor)

POLARIS-2 compared the efficacy of SOF/VEL/VOX for 8 weeks compared with SOF/VEL for 12 weeks among 464 DAA-naïve GT1 patients.[31] SVR rates for 12 weeks of SOF/VEL were 99% (170/172) for GT1a and 97% (57/59) for GT1b. SVR rates for 8 weeks of SOF/VEL/VOX were 92% for GT1a (155/169) and 97% for GT1b (61/63). Among GT1a patients who received 8 weeks of SOF/VEL/VOX, those with baseline NS3 or NS5a RAS had a lower rate of SVR (89%) compared with those without baseline RAS (95%). The 8-week regimen of SOF/VEL/VOX should not be used in patients with GT1a, and is not FDA approved for use in treatment-naïve patients.

V. Chronic HCV Genotype 2 Infection

Including HIV/HCV coinfection

Refer to Section XII, Groups with Special Considerations for Therapy, on HCV treatment in patients with HIV/HCV coinfection.

Key Points

- GLE/PIB or SOF/VEL/VOX should not be used in patients with moderate to severe hepatic impairment (CTP B and C).
- GLE/PIB or SOF/VEL/VOX should be taken with food. Refer to Appendix A, Table 23 and Table 24 for drug-drug interactions.

Table 10. Treatment regimens for GT2

See Table 11 for details

Treatment-naïve or treatment-experienced (PEG-IFN/IFN ± RBV or SOF + RBV ± PEG-IFN) without or with cirrhosis (CTP A)

- *GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food*
  - *If non-cirrhotic: 8 weeks*
  - *If cirrhotic: 12 weeks*
- *SOF/VEL (400/100 mg) 1 tablet orally daily for 12 weeks*

Treatment-experienced (NS5A-experienced) without or with cirrhosis (CTP A)

- *SOF/VEL/VOX (400/100/100 mg, Vosevi®): 1 tablet orally daily with food for 12 weeks*

Treatment-naïve or treatment-experienced patients with decompensated cirrhosis (CTP B or CTP C)

- *SOF/VEL (400/100 mg, Epclusa®) 1 tablet orally daily + RBV; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)*
  - *If NS5A-naïve: 12 weeks*
  - *If NS5A-experienced: 24 weeks*

Table 11. Genotype 2: Treatment Regimens and SVR Rates[a]

Regimens with optimal efficacy, favorable tolerability and toxicity profile, and ease of use. SVR rates cannot be compared between trials.

Treatment history & HCV genotype	Cirrhosis status	Regimen	Duration	Evidence grade	SVR% (N/N) in clinical trials	Comments
Naïve, GT2	Non-cirrhotic	**GLE/PIB**	8 weeks	A-I	98% (193/197)[12]	Includes PEG-IFN/IFN ± RBV or SOF + RBV ± PEG-IFN-experienced patients.[12]
Naïve, GT2	Non-cirrhotic	**SOF/VEL**	12 weeks	A-I	100% (104/104)[15] 99% (99/100)[32]	Includes treatment-experienced and cirrhotic patients.[15]
Naïve, GT2	Cirrhotic, CTP A	**GLE/PIB**	12 weeks	A-I	100% (31/31)[11]	Includes PEG-IFN/IFN ± RBV or SOF + RBV ± PEG-IFN-experienced patients.[11]
Naïve, GT2	Cirrhotic, CTP A	**SOF/VEL**	12 weeks	A-I	100% (15/15)[32]	
Naïve, GT2	Cirrhotic, CTP B or C	**SOF/VEL + RBV**	12 weeks	A-II	100% (15/15)[32] 100% (4/4)[17]	Includes treatment-experienced patients.[17]
Experienced, GT2 *(PEG-IFN/IFN ± RBV or SOF + RBV ± PEG-IFN)*	Non-cirrhotic	**GLE/PIB**	8 weeks	A-I	98% (193/197)[12]	Includes treatment-naïve patients.
Experienced, GT2 *(PEG-IFN/IFN ± RBV or SOF + RBV ± PEG-IFN)*	Cirrhotic, CTP A	**GLE/PIB**	12 weeks	A-I	100% (31/31) (31/31)[11]	Includes treatment-naïve patients.[11]
Experienced, GT2 *(NS5A-naïve)*	Non-cirrhotic or Cirrhotic, CTP A	**SOF/VEL**	12 weeks	A-I	100% (15/15)[32] 97% (32/33)[22]	
Experienced, GT2 *(NS5A-experienced)*	Non-cirrhotic or Cirrhotic, CTP A	**SOF/VEL/VOX**	12 weeks	A-II	100% (5/5)[22]	Includes cirrhotic patients.[22]
Experienced, GT2	Cirrhotic, CTP B or C	**SOF/VEL + RBV**	12-24 weeks	A-II/III	100% (4/4)[17]	Includes treatment-naïve patients.[17]

[a] Refer to Section XII, Groups with Special Considerations for Therapy, on HCV treatment in patients with HIV/HCV coinfection.

Dosages:

- GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food
- SOF/VEL (400/100 mg, Epclusa®): 1 tablet orally daily
- SOF/VEL/VOX (400/100/100 mg, Vosevi®): 1 tablet orally daily with food
- RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food; in CTP B and C patients, start at lower RBV dosages as clinically indicated (e.g., baseline Hgb)

Note: GLE/PIB, SOF/VEL, or SOF/VEL/VOX should not be used in reduced dosages or restarted if discontinued. DCV + SOF ± RBV (not FDA approved for GT2) can be considered if DDI precludes the use of other HCV regimens (see Appendix A, Table 23 and Table 24, www.hep-druginteractions.org, and manufacturer prescribing information).

Treatment of Chronic HCV Genotype 2

Glecaprevir/pibrentasvir (HCV NS3/4A protease inhibitor/HCV NS5A inhibitor)

An integrated analysis of data pooled from ENDURANCE 1-4, SURVEYOR-I and -II, and EXPEDITION-4 examined the efficacy of 8 (n=828) or 12 (n=1,076) weeks of GLE/PIB in non-cirrhotic GT1-6 patients.[12] Patients were treatment-naïve (74-79%) or treatment-experienced (21-26%; PEG-IFN/IFN ± RBV [96-97%], SOF + RBV ± PEG-IFN [4%]). The population was mostly male (51-54%) and White (77-83%) with F0-F1 disease (81-82%). High SVR rates occurred in GT2 patients receiving GLE/PIB for 8 and 12 weeks; 98% (193/197) vs. 99% (232/234), respectively. This study supports the use of GLE/PIB for 8 weeks in GT2 patients who are non-cirrhotic and treatment-naïve or treatment-experienced (IFN- or SOF-based therapy).

In an open-label study (EXPEDITION-1) of GLE/PIB for 12 weeks in 146 GT1, 2, 4-6 patients with compensated cirrhosis (CTP A) who were treatment-naïve (75%) or treatment-experienced (25%; PEG-IFN/IFN ± RBV [69%], SOF + RBV ± PEG-IFN [31%]), SVR was achieved in 100% (31/31) with GT2.[11] This study supports the use of GLE/PIB for 12 weeks in GT2 patients with cirrhosis who are treatment-naïve or treatment-experienced (IFN- or SOF-based therapy).

Sofosbuvir/velpatasvir (HCV nucleotide NS5B polymerase inhibitor/HCV NS5A inhibitor)

The efficacy of SOF/VEL was studied in genotype 2 patients enrolled in the ASTRAL-1, ASTRAL-2, and ASTRAL-4 studies.

ASTRAL-1 was a Phase III, double-blind, placebo-controlled, randomized trial of treatment-naïve and treatment-experienced patients with genotypes 1, 2, 4, 5, and 6, treated with SOF/VEL for 12 weeks.[15] SVR was achieved in 100% (104/104) of GT2-infected patients treated with SOF/VEL.

ASTRAL-2 was a Phase III, open-label, randomized controlled trial among GT2 patients. Patients were randomized to 12 weeks of SOF/VEL (n=134) or SOF + RBV (n=132).[32] In both treatment arms, 14% had cirrhosis and 14-15% were treatment-experienced. Data were not provided on the previous treatment regimens. SVR was significantly higher with SOF/VEL compared with SOF + RBV (SVR 99% [133/134] vs. 94% [124/132)], respectively; p = .018). Virologic relapse occurred in 5% (6/132) of patients treated with SOF + RBV before 12 weeks and 2 patients were lost to follow-up. In the SOF/VEL group, there were no relapsers and 1 patient was lost to follow-up. Among treatment-naïve patients without cirrhosis, 99% (99/100) achieved SVR with SOF/VEL compared with 96% (92/96) with SOF + RBV. Among treatment-naïve patients with cirrhosis, 100% (15/15) achieved SVR with SOF/VEL compared with SVR 93% (14/15) in the SOF + RBV arm. Among treatment-experienced patients without cirrhosis, patients treated with SOF/VEL achieved an SVR 100% (15/15) compared with SVR 81% (13/16) with SOF + RBV. Very few treatment-experienced patients with cirrhosis were enrolled, but there were 4 in each treatment arm, and both arms had 100% SVR (4/4). At baseline, 60% in the SOF/VEL group had NS5A RAS and 10% had NS5B RAS yet no patient had a virologic failure. Overall ASTRAL-1 and ASTRAL-2 studies demonstrated the efficacy and safety of SOF/VEL as the first FDA-approved RBV-free regimen for GT2.

ASTRAL-4 was a prospective, open-label, Phase III trial of 267 patients with HCV genotypes 1-6 and decompensated cirrhosis who were treatment-naïve and treatment-experienced (PEG-IFN/RBV ± NS3/4 PI; 55%).[17] Patients were randomized to receive SOF/VEL for 12 weeks, SOF/VEL + RBV (weight-based dosing) for 12 weeks, or SOF/VEL for 24 weeks. The majority of patients were CTP B (score 7-9, 89%); 6% were CTP A (score ≤6) and 4% were CTP C (score 10). Mild or moderate ascites was present in 78% and severe in 3%. Among HCV GT2 patients (n=12), all achieved SVR except for 1 patient who was assigned to receive SOF/VEL for 24 weeks; this patient died of liver failure after completing 28 days of treatment.

Sofosbuvir/velpatasvir/voxilaprevir (HCV nucleotide NS5B polymerase inhibitor/HCV NS5A inhibitor/HCV NS3/4A protease inhibitor)

DAA-naïve

POLARIS-2 compared SOF/VEL/VOX for 8 weeks with SOF/VEL for 12 weeks in 116 DAA-naïve GT2 patients. SVR rates were 97% (61/63) with SOF/VEL/VOX for 8 weeks and 100% (53/53) with SOF/VEL for 12 weeks.[31] Across GT1-6, SVR rates were suboptimal among patients with compensated cirrhosis compared with those without cirrhosis receiving SOF/VEL/VOX for 8 weeks; SVR 91% (82/90) vs. SVR 96% (394/411), respectively.

DAA-experienced

In the POLARIS 1 and 4 studies, GT 2 DAA-experienced patients achieved SVR in 100% (36/36) with SOF/VEL/VOX for 12 weeks.[22] In GT2 patients with prior NS5A experience (POLARIS-1), SVR was achieved in 100% (5/5) with SOF/VEL/VOX for 12 weeks. GT2 patients previously treated with prior SOF-based regimens but were NS5A-naive were randomized to SOF/VEL/VOX or SOF/VEL for 12 weeks (POLARIS-4). SVR rates were 100% (31/31) with SOF/VEL/VOX for 12 weeks and 97% (32/33) with SOF/VEL for 12 weeks.

VI. Chronic HCV Genotype 3 Infection

Including HIV/HCV coinfection

Refer to Section XII, Groups with Special Considerations for Therapy, on HCV treatment in patients with HIV/HCV coinfection.

Key Points

- GLE/PIB or SOF/VEL/VOX should not be used in patients with moderate to severe hepatic impairment (CTP B and C).
- GLE/PIB or SOF/VEL/VOX should be taken with food. Refer to Appendix A, Table 23 and Table 24, for drug-drug interactions.

Table 12. Treatment regimens for GT3

See Table 13 for details

Treatment-naïve without cirrhosis or with cirrhosis (CTP A)

- *GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food for 12 weeks*
- *SOF/VEL (400/100 mg, Epclusa®) 1 tablet orally daily for 12 weeks*
  - *If CTP A, test for NS5A RAS*
  - *Add RBV if Y93H RAS present*

Treatment-experienced (PEG-IFN ± RBV or SOF + RBV ± PEG-IFN) without or with cirrhosis (CTP A)

- *GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food for 16 weeks*

Treatment-experienced (NS5A-experienced) without or with cirrhosis (CTP A)

- *SOF/VEL/VOX (400/100/100 mg, Vosevi®): 1 tablet orally daily with food for 12 weeks*
  - *If CTP A, consider adding RBV (no supporting data)*

Treatment-naïve or treatment-experienced with decompensated cirrhosis (CTP B or CTP C)

- *SOF/VEL (400/100 mg, Epclusa®) 1 tablet orally daily + RBV; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)*
  - *If NS5A-naïve: 12 weeks*
  - *If NS5A-experienced: 24 weeks*

Table 13. Genotype 3: Treatment Regimens and SVR Rates[a]

SVR rates cannot be compared between trials.

Treatment history & HCV genotype	Cirrhosis status	Regimen	Duration	Evidence grade	SVR% (N/N) in clinical trials	Comments
Naïve, GT3	Non-cirrhotic	**GLE/PIB**	12 weeks	A-I	95% (149/157)[33] 95% (177/186)[12] Baseline A30K: 12 weeks: 90% (9/10)[33] 8 weeks: 75% (12/16)[33]	SVR is lower with baseline A30K.[33]
Naïve, GT3	Cirrhotic, CTP A	**GLE/PIB**	12 weeks	A-II	98% (38/40)[34]	
Naïve, GT3	Non-cirrhotic	**SOF/VEL**	12 weeks	A-I	98% (160/163)[32]	
Naïve, GT3	Cirrhotic, CTP A	**SOF/VEL** ○ Test for NS5A RAS[b] ○ Add RBV if Y93H RAS is present	12 weeks	A-I	93% (40/43)[32]	Includes treatment-experienced patients.[17]
Naïve, GT3	Cirrhotic, CTP B or C	**SOF/VEL + RBV**	12 weeks	A-I	85% (11/13)[17]	Includes treatment-experienced patients.[17]
Experienced, GT3 *(PEG-IFN/IFN ± RBV or SOF + RBV ± PEG-IFN)*	Non-cirrhotic or Cirrhotic, CTP A	**GLE/PIB**	16 weeks	A-I	96% (21/22) in non-cirrhotics[34] 96% (45/47) in CTP A[34]	Failed ***SOF + RBV ± PEG-IFN*** in 16 week arms: n=9 non-cirrhotics; n=25 CTP A
Experienced, GT3 *(NS5A-experienced)*	Non-cirrhotic or CTP A	**SOF/VEL/VOX** ○ If CTPA, consider adding RBV (no supporting data)	12 weeks	A-I	95% (74/78) [22]	Relapse occurred in four cirrhotic patients
Experienced, GT3	Cirrhotic, CP B or C	**SOF/VEL + RBV**	12-24 weeks *(NOT FDA approved for 24 weeks)*	B-II/III	<u>12 weeks in prior PEG-IFN/RBV ± SOF:</u> 85% (11/13)[17] <u>24 weeks in NS5A-experienced:</u> 100% (3/3) without baseline NS5A RAS[24] 77% (10/13) with baseline NS5A RAS[24]	Includes treatment-naïve patients.[17]

[a] Refer to Section XII, Groups with Special Considerations for Therapy, on HCV treatment in patients with HIV/HCV coinfection.

[b] NS5A resistance testing can be performed through the VHA Public Health Reference Laboratory (email V21PHRL@va.gov) or a commercial laboratory (see Section XV, Appendix B).

Dosages:

- GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food
- SOF/VEL (400/100 mg, Epclusa®): 1 tablet orally daily
- SOF/VEL/VOX (400/100/100 mg, Vosevi®): 1 tablet orally daily with food
- RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food; in CTP B and C patients, start at lower RBV dosages as clinically indicated (e.g., baseline Hgb)

Note: GLE/PIB, SOF/VEL, or SOF/VEL/VOX should not be used in reduced dosages or restarted if discontinued. DCV + SOF ± RBV can be considered if DDI precludes the use of other HCV regimens (see Appendix A, Table 23 and Table 24, www.hep-druginteractions.org, and manufacturer prescribing information[35]).

Table 14. Genotype 3: Alternative Regimens and SVR Rates[a]

SVR rates cannot be compared between trials.

Treatment history & HCV genotype	Cirrhosis status	Regimen	Duration	Evidence grade	SVR% (N/N) in clinical trials
Experienced, GT3 *(SOF-experienced and NS5A-naïve)*	Non-cirrhotic or Cirrhotic, CTP A	**SOF/VEL/VOX**	12 weeks	A-I	96% (52/54)[22]

[a] Refer to Section XII, Groups with Special Considerations for Therapy, on HCV treatment in patients with HIV/HCV coinfection.

Dosages:

- SOF/VEL/VOX (400/100/100 mg, Vosevi®): 1 tablet orally daily with food

Note: SOF/VEL/VOX should not be used in reduced dosages or restarted if discontinued. DCV + SOF ± RBV can be considered if DDI precludes the use of other HCV regimens (see Appendix A, Table 23 and Table 24, www.hep-druginteractions.org, and manufacturer prescribing information[35]).

Treatment of Chronic HCV Genotype 3

Glecaprevir/pibrentasvir (HCV NS3/4A protease inhibitor/HCV NS5A inhibitor)

ENDURANCE-3 compared 8 and 12 weeks of GLE/PIB vs. 12 weeks of SOF + DCV in GT3 non-cirrhotic treatment-naïve patients.[33] Patients with METAVIR scores >3 or with HBV or HIV coinfection were excluded. Most patients were F0-F1 (78-86%), White (85-90%), and had a history of injection drug use (63-66%). GLE/PIB for 8 (n=157) and 12 (n=233) weeks were non-inferior to SOF + DCV (n=115); SVR was achieved in 95% (149/157), 95% (222/233), and 97% (111/115), respectively. Relapse occurred in 3 patients and 1 patient in the GLE/PIB 8- and 12-week arms, respectively. While SVR was achieved in 100% (5/5) with Y93H at baseline in the 8-week arm, those with baseline NS3 + NS5A RAS had a lower SVR (71%, 5/7). Similarly, for those receiving GLE/PIB for 12 weeks, 86% (6/7) achieved SVR with baseline NS3 + NS5A RAS. For patients with only baseline NS5A RAS, SVR rates were 91% (39/43) and 95% (41/43) with 8 and 12 weeks of GLE/PIB, respectively. If baseline A30K was present, SVR occurred in 90% (9/10) in the 12-week arm vs. 75% (12/16) in the 8-week arm of GLE/PIB. To avoid baseline RAS testing in treatment-naïve patients without cirrhosis, 12 weeks of GLE/PIB treatment is recommended. A30K and Y93H were the most commonly detected RAS following virologic failure with GLE/PIB.

An integrated analysis of data pooled from ENDURANCE 1-4, SURVEYOR-I and SURVEYOR-II, and EXPEDITION-4 examined the efficacy of 8 (n=828) or 12 (n=1,076) weeks of GLE/PIB in non-cirrhotic GT1-6 patients.[12] The population was mostly male (51-54%) and White (77-83%) with F0-F1 disease (81-82%). All GT3 patients in this analysis were treatment-naïve. High SVR rates occurred in GT3 patients receiving GLE/PIB for 8 and 12 weeks, 95% (177/186) and 96% (258/270), respectively. Across genotypes, only 1% (7/828) and 0.3% (3/1,076) in the 8- and 12-week group relapsed, respectively. This study supports the use of GLE/PIB for 8 weeks in GT3 patients who are non-cirrhotic and treatment-naïve.

SURVEYOR-II, Part 3 was an open-label study that evaluated 12 and 16 weeks of GLE/PIB in 131 GT3 treatment-experienced and/or cirrhotic patients.[34] The majority of patients were male (77-93%), White (77-93%), treatment-experienced (70%; PEG-IFN/IFN ± RBV [54%], SOF + RBV ± PEG-IFN [46%]), and cirrhotic (66%). Baseline RAS to NS3 only were present in 2% (2/131), NS5A only in 18% (24/133), and none with NS3 + NS5A. Among treatment-naïve cirrhotic patients, GLE/PIB for 12 weeks achieved SVR in 98% (39/40). Among treatment-experienced patients without cirrhosis, SVR was achieved in 91% (20/22) and 96% (21/22) in the 12- and 16-week arms of GLE/PIB, respectively. Among treatment-experienced cirrhotic patients, SVR occurred in 96% (45/47) in the 16-week arm. This data supports the use of GLE/PIB for 16 weeks in treatment-experienced (NS5A-naïve) patients without or with cirrhosis.

Sofosbuvir/velpatasvir (HCV nucleotide NS5B polymerase inhibitor/HCV NS5A inhibitor)

The efficacy of SOF/VEL was studied in GT3 patients enrolled in the ASTRAL-3 and ASTRAL-4 studies.

ASTRAL-3 was a prospective, randomized, Phase III trial of SOF/VEL for 12 weeks (n=277) vs. SOF + RBV for 24 weeks (n=275) among treatment-naïve and -experienced (PEG-IFN/RBV ± NS5B) GT3-infected patients.[32] Only 1% were Black and 8-11% were Asian. The mean body mass index was 26-27, 29-30% had compensated cirrhosis, and 26% were treatment-experienced. The SVR was significantly higher among patients receiving 12 weeks of SOF/VEL (SVR 95%; 95% CI: 92-98) as compared with those receiving SOF + RBV for 24 weeks (SVR 80%; 95% CI: 75-85). The SVR rate in cirrhotic patients was 91% as compared with 97% in those without cirrhosis. Similarly, SVR among treatment-experienced patients receiving SOF/VEL was 90% compared with 97% among those who were treatment-naïve. In patients with cirrhosis who were treatment-naïve and treatment-experienced, SVR rates were 93% (40/43) and 89% (33/37), respectively. There were no on-treatment failures; 11 patients (4%) receiving SOF/VEL experienced virologic relapse. Of patients with baseline resistance testing performed, 16% (43/274) had detectable NS5A RAS, of whom 88% (38/43) achieved SVR. SVR was achieved in 97% (225/231) of patients without baseline NS5A RAS. The Y93H polymorphism was present in 25 patients at baseline and 21 (84%) achieved SVR. Ten patients had NS5B RAS at baseline, all of whom achieved SVR.

ASTRAL-4 was a prospective, open-label, Phase III trial of 267 patients with HCV genotypes 1-6 and decompensated cirrhosis who were treatment-naïve and treatment-experienced (PEG-IFN/RBV ± NS3/4 PI; 55%).[17] Patients were randomized to receive SOF/VEL for 12 weeks, SOF/VEL + RBV (weight-based dosing) for 12 weeks, or SOF/VEL for 24 weeks. Of 267 patients, 78% (n=207) had HCV GT1, 4% (n=12) GT2, 15% (n=39) GT3, 3% (n=8) GT4, and less than 1% (n=1) GT6; no patients had GT5. Only 6% were Black and 2% were Asian. The majority of patients were CTP B (score 7-9, 89%); 6% were CTP A (score ≤6)

and 4% were CTP C (score 10). Mild or moderate ascites was present in 78% and severe in 3%. Among patients with HCV GT3, SVR was achieved in 85% (11/13) with SOF/VEL + RBV for 12 weeks compared with 50% for the groups that received SOF/VEL alone. Of 255 patients, 28% (n=72) had baseline NS5A RAS. SVR was achieved in 89% (64/72) with baseline NS5A RAS compared with SVR 92% (169/183) in those without. Nine deaths occurred during the study, which was evenly divided among the treatment groups; none were considered to be related to therapy.

At baseline, approximately 10% of GT3-infected patients have the Y93H RAS. The presence of the Y93H RAS has been associated with reduced SVR among patients receiving SOF/VEL; the impact on SVR when RBV is included in the regimen is not well defined. Until more data are available, baseline testing for NS5A RAS is recommended prior to SOF/VEL treatment for cirrhotic or treatment-experienced patients. The addition of RBV to SOF/VEL is recommended if the Y93H RAS is present or if the patient has decompensated cirrhosis.

Sofosbuvir/velpatasvir/voxilaprevir (HCV nucleotide NS5B polymerase inhibitor/HCV NS5A inhibitor/HCV NS3/4A protease inhibitor)

POLARIS-2 compared 8 weeks of SOF/VEL/VOX with 12 weeks of SOF/VEL in 181 DAA-naïve GT3 patients without cirrhosis. SVR rates were similar between the two arms: 99% (91/92) for SOF/VEL/VOX for 8 weeks and 97% (86/89) for SOF/VEL for 12 weeks.[31]

POLARIS-3 was a Phase III open-label study that randomized 219 GT3 DAA-naïve patients with compensated cirrhosis to SOF/VEL/VOX for 8 weeks or SOF/VEL for 12 weeks. Most were White (90%) and treatment-naïve (84%). SVR rates were 96% in both arms (106/110 and 105/109, respectively). In both arms, SVR rates were high (≥97%) with and without NS3 and/or NS5A RAS. NS5A RAS were not detected with virologic relapse to SOF/VEL/VOX for 8 weeks, but Y93H was detected with relapse to SOF/VEL for 12 weeks.[31]

Genotype 3-Infected Patients Who Have Failed NS5A-Based Therapy

Sofosbuvir/velpatasvir + ribavirin

An open-label study of SOF/VEL + RBV for 24 weeks was conducted in patients (n=69) who had failed prior SOF/VEL-containing regimens for 4-12 weeks; 88% were Caucasian, 77% were men, 26% had cirrhosis, and 26% had GT3 infection. In an interim analysis of 16 GT3 patients, 81% (13/16) had baseline NS5A RAS and 77% (10/13) achieved SVR; in those without NS5A baseline RAS (19%, 3/16), 100% (3/3) achieved SVR.[24]

Sofosbuvir/velpatasvir/voxilaprevir (HCV nucleotide NS5B polymerase inhibitor/HCV NS5A inhibitor/HCV NS3/4A protease inhibitor)

In POLARIS-1 and POLARIS-4, SVR rates were 96% (126/132) with SOF/VEL/VOX for 12 weeks in DAA-experienced GT3 patients.[22] In GT3 patients with prior NS5A experience (POLARIS-1), SVR occurred in 95% (74/78) with SOF/VEL/VOX for 12 weeks; the addition of RBV in patients with compensated cirrhosis (CTP A) can be considered given that virologic relapse occurred in 4 patients in this subgroup. In GT3

patients with NS5B ± NS3/4A experience (POLARIS-4), SVR rates were 96% (52/54) with SOF/VEL/VOX for 12 weeks and 85% (42/53) with SOF/VEL for 12 weeks.

Glecaprevir/pibrentasvir + sofosbuvir + ribavirin (HCV NS3/4A protease inhibitor/HCV NS5A inhibitor/HCV nucleotide NS5B polymerase inhibitor); regimen is not FDA approved

MAGELLAN-3 is an ongoing open-label, parallel arm study evaluating the efficacy and safety of GLE/PIB + SOF + RBV (800-1,200 mg daily) for 16 weeks that includes GT3 patients with compensated cirrhosis or NS5A- and/or NS3-experience before GLE/PIB virologic failure.[25] Interim analysis of 23 of the projected 50 GT1-6 patients was recently presented; 6 were GT1a (26%), 1 GT1b (4%), 2 GT2 (9%), and 14 GT3 (61%). Most were treatment-naïve before GLE/PIB virologic failure (n=15, 65%) and had no to minimal fibrosis (n=16, 70%). Six patients (26%) were NS5A-experienced before GLE/PIB and seven patients (30%) had compensated cirrhosis. Pre-treatment (current study) NS5A RAS were present in 18 patients and 5 had NS5A + NS3 RAS. Overall SVR was 96% (22/23). In the 16-week arm, SVR occurred in 100% (14/14) with GT3. Adverse events were reported in 83% (19/23) with headache being most frequent (n=6, 23%), followed by pruritus (n=5, 22%), dizziness and irritability (4 each, 17%). There was only 1 SAE (symptomatic cholelithiasis, not related to study drug). There were no Grade ≥3 reductions in hemoglobin or RBV dose reductions due to toxicity.

Elbasvir/grazoprevir + sofosbuvir + ribavirin (HCV NS5A inhibitor/HCV NS3/4A protease inhibitor/HCV nucleotide NS5B polymerase inhibitor); regimen is not FDA approved

C-ISLE was an open-label, randomized study conducted in the United Kingdom of EBR/GZR + SOF ± RBV (800-1,400 mg/day) in GT3 patients (n = 100) of whom 69% were Caucasian, 29% were Asian, 68% were men, 53% were treatment experienced with SOF + PEG-IFN/RBV or DCV + SOF + RBV, and 51% had baseline NS5A RAS.[36] The mean FibroScan® value was 25.4 kPa and mean platelet count was 148,000/mm^3. In treatment-experienced patients re-treated with EBR/GZR + SOF for 12 weeks, SVR was achieved in 100% (17/17); the RBV-containing arm also achieved SVR in 100% (17/17).

VII. Chronic HCV Genotype 4 Infection

Including HIV/HCV coinfection*

** Refer to Section XII, Groups with Special Considerations for Therapy, on HCV treatment in patients with HIV/HCV coinfection.*

Key Points

- EBR/GZR, GLE/PIB or SOF/VEL/VOX should not be used in patients with moderate to severe hepatic impairment (CTP B and C).
- GLE/PIB or SOF/VEL/VOX should be taken with food. Refer to Appendix A, Table 23 and Table 24 for drug-drug interactions.

Table 15. Treatment Regimens for GT4

Within each category, regimens are listed in alphabetical order; this ordering does not imply preference for a particular regimen unless otherwise indicated.

Treatment-naïve without or with cirrhosis (CTP A)

- *EBR/GZR (50/100 mg, Zepatier®): 1 tablet orally daily for 12 weeks*
- *GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food*
  - *If non-cirrhotic: 8 weeks*
  - *If cirrhotic: 12 weeks*
- *LDV/SOF (90/400 mg, Harvoni®): 1 tablet orally daily for 12 weeks*
- *SOF/VEL (400/100 mg, Epclusa®): 1 tablet orally daily for 12 weeks*

Treatment-naïve with decompensated cirrhosis (CTP B or C)

- *LDV/SOF (90/400 mg, Harvoni®): 1 tablet orally daily + RBV (600 mg/day and increase by 200 mg/day every 2 weeks only as tolerated) for 12 weeks*
- *SOF/VEL (400/100 mg, Epclusa®): 1 tablet orally daily + RBV for 12 weeks; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)*

Treatment-experienced (SOF-experienced and NS5A-naïve) without or with cirrhosis (CTP A)

- *GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food for 12 weeks*
- *SOF/VEL (400/100 mg, Epclusa®): 1 tablet orally daily + RBV for 12 weeks; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)*

Treatment-experienced (NS5A-experienced) without or with cirrhosis (CTP A)

- *SOF/VEL/VOX (400/100/100 mg, Vosevi®): 1 tablet orally daily with food for 12 weeks*

Treatment-experienced with decompensated cirrhosis (CTP B or CTP C)

- *SOF/VEL (400/100 mg, Epclusa®) 1 tablet orally daily + RBV; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)*
  - *If NS5A-naïve: 12 weeks*
  - *If NS5A-experienced: 24 weeks; NOT FDA approved for 24 weeks*

Dosages: RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food; 600 mg/day and increase as tolerated in CTP B and C patients receiving LDV/SOF. CTP B and C patients receiving SOF/VEL: prescribing

information recommends RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food; start at lower RBV doses as clinically indicated (e.g., baseline Hgb)

Note: GLE/PIB, SOF/VEL or SOF/VEL/VOX should not be used in reduced dosages or restarted if discontinued.

Treatment of Chronic HCV Genotype 4

Elbasvir/grazoprevir

The C-EDGE Treatment-Naïve study was a Phase III randomized, blinded, placebo-controlled, parallel-group trial of EBR/GZR for 12 weeks in GT1-, 4-, or 6-infected patients (n=421).[10] The patients were randomized in a 3:1 ratio of immediate treatment or placebo with deferred treatment, and after a follow-up period, these placebo patients then received open-label EBR/GZR for 12 weeks. SVR was achieved in 100% (18/18) of GT4 patients randomized to the immediate-treatment arm.

The C-EDGE Treatment-Experienced study was a Phase III trial of EBR/GZR ± RBV for 12 or 16 weeks in GT1-, 4-, or 6-infected patients who had been previously treated with PEG-IFN/RBV.[19] The study permitted the inclusion of HIV/HCV-coinfected and cirrhotic patients with GT1, 4, or 6 infection. SVR rates for GT4-infected patients were: 78% (7/9) with EBR/GZR for 12 weeks, 93% (14/15) with EBR/GZR + RBV for 12 weeks, 60% (3/5) with EBR/GZR for 16 weeks, and 100% (8/8) with EBR/GZR + RBV for 16 weeks. The distributions of patients with cirrhosis, HIV/HCV coinfection and prior treatment response within these treatment groups were not reported. These findings suggest that treatment-experienced patients with GT4 should be treated with EBR/GZR + RBV for 16 weeks.

Glecaprevir/pibrentasvir

An integrated analysis of data pooled from ENDURANCE 1-4, SURVEYOR-I and SURVEYOR-II, and EXPEDITION-4 examined the efficacy of 8 (n=828) or 12 (n=1,076) weeks of GLE/PIB in non-cirrhotic GT1-6 patients.[12] Patients were treatment-naïve (74-79%) or treatment-experienced (21-26%; PEG-IFN/IFN ± RBV [96-97%], SOF + RBV ± PEG-IFN [4%]). The population was mostly male (51-54%) and White (77-83%) with F0-F1 disease (81-82%). High SVR rates occurred in GT4 patients receiving GLE/PIB for 8 and 12 weeks; 93% vs. 99%, respectively. Across genotypes, only 1% (7/828) and 0.3% (3/1,076) in the 8- and 12-week group relapsed, respectively. Baseline NS3 or NS5A RAS had minimal impact on SVR with 8 or 12 weeks of GLE/PIB, whereas baseline NS3 + NS5A RAS significantly reduced the likelihood of SVR (78% (7/9); OR = 0.017, [95% CI: 0.003-0.098], $p < .0001$). This study supports the use of GLE/PIB for 8 weeks in GT4 patients who are non-cirrhotic and treatment-naïve or treatment-experienced with IFN-based therapy. In SOF-experienced patients, GLE/PIB for 12 weeks should be considered. GLE/PIB should not be used in NS5A-experienced patients with RAS to both NS5A and NS3/4A PI.

An open-label study (EXPEDITION-1) evaluated GLE/PIB for 12 weeks in 146 GT1, 2, 4-6 patients with compensated cirrhosis (CTP A) who were treatment-naïve (75%) or treatment-experienced (25%; PEG-IFN/IFN ± RBV [69%], SOF + RBV ± PEG-IFN [31%]). SVR was achieved in 100% (16/16) with GT4.[11] This study supports the use of GLE/PIB for 12 weeks in GT4 patients with cirrhosis who are treatment-naïve or treatment-experienced (IFN- or SOF-based therapy).

Ledipasvir/sofosbuvir

LDV/SOF for 12 weeks was evaluated in 21 patients with GT4 infection in the NIAID SYNERGY study.[37] The cohort included treatment-naïve and treatment-experienced patients who failed PEG-IFN/RBV; 33% had F3 disease, and 10% had F4 disease. SVR was achieved in 95% (19/20).

Sofosbuvir/velpatasvir

In a Phase III, double-blind, placebo-controlled, randomized trial (ASTRAL-1) of treatment-naïve and treatment-experienced (PEG-IFN/RBV ± NS3/4 PI) patients, 116 GT4 patients were treated with SOF/VEL for 12 weeks; SVR was achieved in 100%.[15] In a Phase III, prospective, open-label trial (ASTRAL-4) of 8 GT4 patients with decompensated cirrhosis who were treatment-naïve and treatment-experienced (PEG-IFN/RBV), patients were randomized to receive SOF/VEL for 12 weeks, SOF/VEL + RBV for 12 weeks, or SOF/VEL for 24 weeks; SVR was achieved in 100%.[38]

Sofosbuvir/velpatasvir/voxilaprevir

DAA-naïve

POLARIS-2 compared SOF/VEL/VOX for 8 weeks to SOF/VEL for 12 weeks in 120 DAA-naïve GT4 patients. SVR rates were 92% (58/63) with SOF/VEL/VOX for 8 weeks and 98% (56/57) with SOF/VEL for 12 weeks.[31] Across GT1-6, SVR rates were suboptimal among patients with compensated cirrhosis compared with those without cirrhosis receiving SOF/VEL/VOX for 8 weeks; SVR 91% (82/90) vs. SVR 96% (394/411), respectively.

DAA-experienced

In the POLARIS 1 and 4 studies, GT4 DAA-experienced patients achieved SVR in 95% (39/41) with SOF/VEL/VOX for 12 weeks.[22] In GT4 patients with prior NS5A experience (POLARIS-1), SVR was achieved in 91% (20/22) with SOF/VEL/VOX for 12 weeks. SVR rates were 100% (19/19) in GT4 patients who were NS5A-naïve but failed a prior SOF-based regimen (POLARIS-4) following re-treatment with SOF/VEL/VOX for 12 weeks.

VIII. Identifying Treatment Candidates Based on Liver Disease Stage

Key Points

- Identification of patients with advanced liver disease is critical in order to select patients with greater urgency for treatment.
- Cirrhosis can be diagnosed by a variety of non-invasive means; 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.
- Treatment of patients with decompensated cirrhosis should involve an experienced and knowledgeable specialist.

HCV is a slowly progressive disease, usually requiring more than 20-40 years to progress to cirrhosis; however, the natural history of HCV is variable and not all patients with chronic HCV will develop cirrhosis during their lifetime. Fibrosis may progress more quickly in some patients, particularly among those who drink alcohol regularly or have coinfection with HIV or HBV. Before a patient develops cirrhosis, the short-term risk of a liver-related complication is low. Once a patient progresses to compensated cirrhosis, there is a higher risk of developing decompensated cirrhosis and/or HCC. Achieving SVR among patients with compensated cirrhosis reduces the risk of developing decompensated cirrhosis and HCC. Thus, patients with cirrhosis are more likely to have a morbidity and mortality benefit from an SVR and require more urgent need for DAA treatment.

Patients with decompensated cirrhosis (CTP B or C; CTP score ≥7) have a poor prognosis, with a median survival of 24 months or less. The decision to treat patients with decompensated cirrhosis should be made by an experienced and knowledgeable specialist who remains involved during the treatment course.

Table 16. Diagnosis of Advanced Fibrosis and Compensated Cirrhosis

Method	Comment
Clinical Findings	• Physical exam findings (splenomegaly, palmar erythema, or spider angioma) • Low platelet count (<140,000-150,000/mm^3)* or other serum markers of fibrosis/cirrhosis (see below) • Abdominal imaging findings (see below)
Abdominal Imaging • Ultrasound • Computed tomography (CT) • Magnetic resonance imaging (MRI)	• Surface abnormalities (e.g., nodularity, and left lobe/caudate lobe hypertrophy) are suggestive of cirrhosis. • Features of portal hypertension (e.g., splenomegaly, recanalization of umbilical vein, collaterals) and ascites are strongly suggestive of cirrhosis.
Liver Fibrosis Imaging • Vibration-controlled transient elastography (FibroScan®) • Acoustic radiation force impulse (ARFI) imaging • 2-dimensional shear wave elastography (Aixplorer®) • Magnetic resonance elastography (MRE)	• Vibration-controlled transient elastography (FibroScan®), acoustic radiation force impulse (ARFI) imaging, 2-dimensional shear wave elastography (Aixplorer®), and magnetic resonance elastography (MRE) can be used for estimating the extent of liver fibrosis. • FibroScan® value of ≥9.5-10 kilopascals has been associated with advanced fibrosis in those with chronic HCV. • ARFI value of >1.75 meters/second has been associated with histologic cirrhosis.
Serum Markers of Fibrosis/Cirrhosis • Platelet count • APRI • FIB-4 • FibroSure®, FibroTest®, FIBROSpect®	• Platelet count less than 140,000-150,000/mm^3 has a high accuracy for the diagnosis of cirrhosis in the absence of other factors that may affect platelet count such as HIV, idiopathic thrombocytopenia, etc. • APRI and FIB-4 scores are easily calculated using standard clinical labs (http://www.hepatitisc.uw.edu/page/clinical-calculators/apri, http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4). • APRI >1.5 has been associated with advanced fibrosis (METAVIR F3); APRI >2.0 has been associated with cirrhosis (METAVIR F4) in the setting of chronic HCV infection. • FIB-4 >3.25 has been associated with advanced fibrosis (METAVIR F3-F4) in the setting of chronic HCV infection. • FibroSure®, FibroTest®, and FIBROSpect® are proprietary, costly serum fibrosis assays that may be used in the diagnosis of cirrhosis.
Liver Biopsy	• Liver biopsy may be considered, but it is invasive and limited by potential sampling error. • METAVIR or Batts-Ludwig stage 4 fibrosis (on a scale from 0 to 4) or Ishak stage 5 or 6 fibrosis (on a scale from 0 to 6) confirms the diagnosis of cirrhosis.

Abbreviations: APRI = [(AST/upper limit of normal AST) x 100]/platelet count (10^9/L);
FIB-4 = [Age (years) x AST]/platelet count (10^9/L) x $ALT^{1/2}$

* A low platelet count in the context of chronic HCV infection is predictive of histologic cirrhosis. Other risk factors for low platelet count should be evaluated.

Liver Disease Stage

Diagnosis of Advanced Fibrosis and Compensated Cirrhosis

See Table 16. Noninvasive and invasive methods to determine the presence and stage of fibrosis continue to evolve.

Serum markers

Routine blood tests can assist in identifying patients with advanced liver disease and, in some instances, predict the likelihood of decompensation or HCC. Serum markers of fibrosis (e.g., APRI, FIB-4, FibroSure®) are quite good at diagnosing cirrhosis (see Table 16).

Platelet counts are another noninvasive tool to identify cirrhotic patients with some degree of portal hypertension. A platelet count of <140,000-150,000/mm^3 has a high sensitivity for the diagnosis of cirrhosis in patients with chronic HCV in the absence of other factors that may affect platelet count such as HIV, idiopathic thrombocytopenia, etc. Patients with platelet counts of <150,000/mm^3 have increased risk of developing HCC, and those with platelet counts of <100,000/mm^3 have an even higher risk.

Radiological studies

A nodular liver or splenomegaly (>13 cm) on imaging (e.g., ultrasound, CT scan or MRI) suggest cirrhosis, but a normal examination does not exclude the presence of cirrhosis. Furthermore, these modalities cannot determine fibrosis stage. Therefore, these abdominal imaging studies are useful if they show features of cirrhosis, but they cannot exclude cirrhosis and cannot determine the stage of fibrosis.

Imaging tools for hepatic fibrosis assessment

Three specialized ultrasound-based modalities can be used to assess liver fibrosis: 1) vibration-controlled transient elastography (VCTE/FibroScan®); 2) acoustic radiation force impulse (ARFI) imaging; and 3) 2-dimensional shear wave elastography (Aixplorer®, Supersonic Imagine). Magnetic resonance elastography (MRE) using MRI is another modality that can be used. These modalities correlate with stage of histologic fibrosis, and cutoffs that correspond to histologic cirrhosis have been developed. Additional information on these tests can be found at www.hepatitis.va.gov/provider/reviews/liver-fibrosis.asp. However, it is important for clinicians to understand that the functional parameters are different for each technology and for each disease state in which they are used. For example, in patients who have been cured of their hepatitis C, there is currently a lack of validated data to understand what their noninvasive fibrosis assessment means. Obesity is a confounding factor for many of these tests, and there is also a learning curve for operators of the modality, with greater reliability after performing more tests. As a result, clinical correlation is recommended when interpreting the FibroScan® or other test results. Not every VA facility has these modalities available.

Liver biopsy

Cirrhosis determination can be made using a histologic assessment of tissue obtained by liver biopsy. However, liver biopsy carries several limitations: not all facilities offer this procedure; the specimen quality depends upon the equipment used and the skill of the proceduralist; it is invasive, expensive, and prone to sampling error and variability in histopathologic interpretation; and it carries a small risk of

complications to the patient. The complication risks include significant bleeding (approximately 1 in 500 cases) and mortality (approximately 1 in 2,000-3,000 cases).

IX. Laboratory Monitoring

Key Points

- Patients should have an HCV RNA level assessed at week 4 of treatment.
- If the HCV RNA is quantifiable* at week 4 or at any time point thereafter, reassess HCV RNA in 2-4 weeks. If the repeated HCV RNA increases (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all treatment should be strongly considered.
- HCV RNA levels should be assessed at least **12 weeks after completion of treatment** to determine whether SVR was achieved.
- Patients receiving EBR/GZR should have hepatic function test performed after 8 weeks of treatment (and after 12 weeks of treatment for patients who receive 16 weeks of EBR/GZR+RBV).

Table 17. Discontinuing HCV Treatment Based on Lack of Virologic Response

Treatment Monitoring Considerations
• Patients should have an HCV RNA level assessed at week 4 of treatment. (A-lll) • If the HCV RNA is quantifiable* at week 4 or at any time point thereafter, reassess HCV RNA in 2-4 weeks. If the repeated HCV RNA increases (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all treatment should be strongly considered. (A-lll)

* Refer to "Use and Interpretation of HCV RNA Results," below, for details.

Periodic laboratory monitoring of liver enzymes, bilirubin, and hemoglobin (particularly if receiving RBV) is recommended for patients receiving HCV antiviral therapy. Consider checking laboratory tests every 2 weeks for the first month, and then at least monthly thereafter, depending upon patient symptoms and results of prior blood tests. HCV RNA levels at 12 weeks after the completion of treatment need to be obtained to determine whether SVR was achieved. Obtaining HCV RNA levels at the end of treatment and at 24-48 weeks after the completion of treatment are optional.

Among patients receiving EBR/GZR treatment, liver function tests should be performed at baseline, at treatment week 8, and week 12 (if receiving 16 weeks of therapy), and as clinically indicated thereafter. Treatment with EBR/GZR should be discontinued if ALT levels remain persistently >10 times the upper limit of normal (ULN). Discontinue treatment if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, international normalized ratio (INR), or in patients who develop hepatic decompensation (e.g., ascites, jaundice, hepatic encephalopathy, variceal hemorrhage).

Use and Interpretation of HCV RNA Results

The FDA recommends use of a sensitive, real-time, quantitative reverse-transcription polymerase chain reaction (RT-PCR) assay for monitoring HCV RNA levels during treatment with DAA agents. Several FDA-approved assays are available for quantifying HCV RNA, with different lower limits of quantification (LLOQ) and ranges of detection. To assess treatment response, commercial assays that have a lower limit of HCV RNA quantification of ≤25 IU/mL are strongly recommended.[39] Some laboratories that use HCV RNA assays with an LLOQ of ≤25 IU/mL may still report values below 25 IU/mL or may indicate that virus was still "detected" or "not detected" below the LLOQ of ≤25 IU/mL.

Recommendations on treatment discontinuation based on HCV RNA levels have not been established, and the following information is based on expert opinion. If the HCV RNA is quantifiable after 4 or more weeks of DAA-based therapy, HCV RNA should be reassessed in 2-4 weeks. If the repeated HCV RNA level has increased (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all therapy should be strongly considered.

X. Adverse Events

Key Points

- Adverse events are common among patients being treated with DAAs.
- All adverse events, whether appearing to be caused by treatment or not, should be reported to the VA Adverse Event Drug Event Reporting System and the FDA MedWatch program.
- Ethinyl estradiol-containing medications must be discontinued prior to starting GLE/PIB and alternative methods of contraception used.
- Anemia occurring during treatment with RBV-containing regimens should be managed by RBV dosage reduction.

Reporting unexpected or serious adverse events

Clinical trials cannot fully define the range of toxicities associated with a new drug because of the relatively small number of patients enrolled in such trials and exclusion of patients with particular comorbidities or other factors that might confound interpretation of safety or efficacy findings. Thus, recognition and reporting of adverse events occurring during therapy with a new drug, whether or not such events appear to be caused by the drug, are extremely important. Clinicians administering DAA-based regimens should work with clinical pharmacists at their facilities to report such events to the VA Adverse Drug Event Reporting System (VA ADERS) as well as the U.S. Food and Drug Administration's MedWatch program (see www.pbm.va.gov/PBM/vacenterformedicationsafety/tools/VHA_Adverse_Drug_Event_Reporting_System.pdf and www.fda.gov/Safety/MedWatch/).

Elbasvir/grazoprevir ± ribavirin

The most common reported adverse events (>5%) in clinical trials with EBR/GZR were fatigue, headache, and nausea. In patients receiving EBR/GZR + RBV for 16 weeks, the most common adverse events were anemia (8%) and headache (6%).[9]

During clinical trials with EBR/GZR ± RBV, 1% of patients experienced ALT elevations of >5 times the ULN, generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved after completion of therapy. Higher rates of late ALT elevations occurred in the following subgroups: females (2% [10/608]), Asian race (2% [4/164]), and age 65 years or older (2% [3/177]).[9] Refer to Section IX, Laboratory Monitoring, for recommendations on monitoring liver function tests.

Glecaprevir/pibrentasvir

The most common adverse reactions with GLE/PIB for 8, 12, or 16 weeks were headache (13%), fatigue (11%), and nausea (8%); 98-99% of these adverse reactions were Grade 1 or 2 in severity.[40] Adverse reactions in patients with compensated cirrhosis (CTP A) were comparable to those without cirrhosis. In patients with renal insufficiency, the most common adverse reactions were pruritus (17%), fatigue (12%), nausea (9%), asthenia (7%), and headache (6%); 90% had adverse reactions of mild or moderate severity

(Grade 1 or 2). Treatment discontinuation due to adverse reactions in patients with chronic kidney disease occurred in 2% compared with 0.1% in those without. Total bilirubin elevations at least 2 times the ULN occurred in 3.5% of patients. Because GLE/PIB inhibits OATP1B1/3 and is a weak inhibitor of UGT1A1, there is the potential to impact bilirubin transport and metabolism, including direct and indirect bilirubin. No patients experienced jaundice and total bilirubin levels decreased after completing treatment.

Ledipasvir/sofosbuvir

The most common adverse events associated with 8, 12, or 24 weeks of LDV/SOF in clinical trials were fatigue (13-18%) and headache (11-17%). Nausea (6-9%), diarrhea (3-7%), and insomnia (3-6%) also have been reported with LDV/SOF treatment. Rarely, elevated bilirubin levels of >1.5 times the ULN (<1-3%) and transient, asymptomatic lipase elevations of >3 times the ULN (<1-3%) have been observed with LDV/SOF treatment. Post-marketing cases of symptomatic bradycardia, fatal cardiac arrest, and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with LDV/SOF. Refer to DDI table for additional information (Appendix A, Table 23).[27,28]

Sofosbuvir/velpatasvir

The most common adverse reactions with treatment with SOF/VEL for 12 weeks were headache (22%) and fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%).[15] Irritability occurred in 8% of GT3 patients treated with SOF/VEL.[32] In patients with decompensated cirrhosis, the most common adverse reactions with SOF/VEL + RBV for 12 weeks were fatigue (32%), anemia (26%), nausea (15%), headache (11%), insomnia (11%), and diarrhea (10%).[17]

Isolated, asymptomatic lipase elevations of greater than 3 times the ULN occurred in 3-6% vs. 1-3% of patients treated with SOF/VEL and placebo for 12 weeks in ASTRAL-1, ASTRAL-2 and ASTRAL-3, respectively.[15,32] In decompensated cirrhotic patients, this occurred in 2% treated with SOF/VEL + RBV for 12 weeks.[17]

Indirect bilirubin up to 3 mg/dL above baseline occurred among HIV/HCV-coinfected patients treated with SOF/VEL and an atazanavir/RTV-based antiretroviral regimen, which were not associated with clinical adverse events and did not require treatment discontinuation, dosage adjustment or treatment interruption of either SOF/VEL or HIV antiretroviral agents.[57]

Sofosbuvir/velpatasvir/voxilaprevir

The most common adverse reactions with SOF/VEL/VOX for 12 weeks were headache (21-23%), fatigue (17-19%), diarrhea (13-14%), and nausea (10-13%); 99% of these adverse reactions were Grade 1 or 2 in severity.[41] Isolated, asymptomatic lipase elevations of greater than 3 times the ULN were observed in in 2% of patients treated. Increases in total bilirubin less than or equal to 1.5 times the ULN were observed in 4-6% of patients without cirrhosis and 7-13% of patients with compensated cirrhosis. No patients experienced jaundice, and total bilirubin levels decreased after treatment.

XI. Proper Use

Key Points

- DDIs must be considered when selecting a treatment regimen.
- Providers should consult a knowledgeable clinical pharmacist for specific questions regarding DDIs.
- The VA Computerized Patient Record System is updated to alert providers about potential DDIs with all approved HCV antiviral treatment regimens.

Drug-Drug Interactions

All current HCV DAA-based treatment regimens have potentially significant interactions with commonly used drugs.[9,27,40-42] A list of DDIs, summarized from the manufacturer prescribing information, is found in Appendix A, Table 23 and Table 24. Practitioners are strongly encouraged to consult with a knowledgeable clinical pharmacist and to use the web-based resources developed by the University of Liverpool to evaluate DDIs prior to starting DAA treatment (www.hep-druginteractions.org). CPRS is routinely updated to alert providers about potential DDIs with all approved HCV antiviral treatment regimens.

EBR and GZR are substrates of CYP3A and p-glycoprotein (P-gp) and GZR is a substrate of the drug transporter organic anion transporting polypeptide (OATP) 1B1/3 transporters. Co-administration of EBR/GZR with strong CYP3A inducers, including efavirenz, is contraindicated and with moderate CYP3A inducers is not recommended since EBR and GZR concentrations may be decreased, leading to reduced therapeutic effect. Co-administration of strong CYP3A4 inhibitors with EBR/GZR is not recommended since this may increase EBR and GZR concentrations. EBR/GZR is contraindicated with OATP1B1/3 inhibitors including certain HIV protease inhibitors; see Appendix A, Table 23 and Table 24. EBR and GZR are inhibitors of the drug transporter BCRP (breast cancer resistance protein) and may increase plasma concentrations of co-administered BCRP substrates.

GLE and PIB are substrates and inhibitors of P-gp and BCRP and GLE is also a substrate and inhibitor of OATP1B1/3. In addition, GLE and PIB are weak inhibitors of CYP3A, CYP1A2, and UGT1A1. Co-administration of GLE/PIB with drugs that inhibit hepatic P-gp, BCRP, or OATP1B1/3 may increase the plasma concentrations of GLE and/or PIB. Coadministration of GLE/PIB with drugs that induce P-gp/CYP3A may decrease GLE and PIB plasma concentrations.

LDV, SOF, VEL, and VOX are substrates for P-gp and BCRP, and as such, P-gp inducers may decrease LDV, SOF, VEL, and/or VOX plasma concentrations. LDV also is an inhibitor of intestinal P-gp and BCRP. LDV is subject to slow oxidative metabolism but there is no metabolism by cytochrome P450 (CYP) isoenzymes. SOF is not metabolized by the CYP450 system of enzymes nor is it a CYP450 substrate. VEL is metabolized by CYP2B6, CYP2C8, and CYP3A4; VOX is metabolized by CYP3A4. Thus, potential for drug interaction exists and may be greater with SOF/VEL/VOX.

Moderate to potent inducers of CYP2B6, 2C8, or 3A4 may decrease VEL and/or VOX plasma concentrations. Because VEL and/or VOX is an inhibitor of drug transporters P-gp, BCRP, OATP1B1/3, and OATP2B1, VEL and/or VOX may increase systemic exposure to medications that are substrates of these transporters, which could increase or prolong those medications' therapeutic or adverse effects.

Storage and Stability

LDV, SOF, SOF/VEL, SOF/VEL/VOX can be stored at room temperature (<86°F), but exposure of the medication to direct sunlight should be avoided. GLE/PIB can be stored at room temperature (<86°F). EBR/GZR should be stored at room temperature between 59°F and 86°F and should remain in the original package until use to protect from moisture.[9,27,40-42]

Humidity can alter SOF stability. However, SOF and LDV/SOF were stable for 45 days in an open Petri dish at 77°F with 60-75% relative humidity.[27,43]

SOF, LDV/SOF, or SOF/VEL tablets can be disintegrated in water, juice, or milk with minor stirring and pressure using a spoon; SOF, LDV, or VEL stability in these liquids is unknown. There are no studies evaluating the pharmacokinetic parameters of the disintegrated or crushed SOF, LDV/SOF, or SOF/VEL tablet administered by a PEG (percutaneous endoscopic gastrostomy) tube.[27,42,43]

Missed Doses

Patients should be instructed to take a missed EBR/GZR or SOF plus LDV, VEL or VEL/VOX dose as soon as possible that day and to take the next EBR/GZR or SOF plus LDV, VEL or VEL/VOX dose at the regular time the following day but should not take more than one dose in the same day.[9,27,40-42]

Patients should be instructed to take a missed GLE/PIB dose as soon as possible that day if the missed dose is less than 18 hours from the scheduled dose or skip the dose if the missed dose is more than 18 hours from the scheduled dose, and take the next GLE/PIB dose at the regular time the following day but should not take more than one dose in the same day.[40]

XII. Groups with Special Considerations for Therapy

Key Points

- HIV status should be determined for all patients with HCV.
- DDIs with HIV antiretroviral therapy (ART) should be taken into account when selecting a hepatitis C regimen (see Appendix A, Table 23 and Table 24).
- SOF-containing regimens should not be used in patients with severe renal impairment (eGFR <30 mL/min) or end-stage renal disease requiring dialysis.
- EBR/GZR, GLE/PIB or SOF/VEL/VOX should not be used in patients with moderate to severe hepatic impairment (CTP B and C).

Acute HCV

Approximately 15-50% of patients have been reported to spontaneously clear acute HCV infection within 6 months of acquisition.[44,45] Patients with acute HCV infection should be counseled on the avoidance of needle sharing (including injection equipment) and avoiding high-risk sexual practices. Patients who continue injecting drugs should be referred to an addiction specialist.

If a decision is made to treat the HCV during the acute phase, then the HCV RNA should be monitored for at least 12 weeks to assess for spontaneous recovery before considering HCV antiviral therapy. Historically, antiviral treatment of acute hepatitis C with IFN-based therapy was driven by the potential for preventing chronic infection, and the lower efficacy rates seen once chronic infection had been established.[46,47] There are few data from controlled clinical trials on the benefits and risks of DAA therapy in the general population of patients with acute hepatitis C; thus, it is not clear to what extent the rationale for early treatment of acute disease with IFN-based therapies is applicable in the DAA era, especially given the very high SVRs achieved with current regimens. Some patient populations, e.g., HIV, transplantation, may obtain greater benefits from earlier interventions. Optimal regimens for treatment of acute hepatitis C have not been defined, e.g., DARE-C II, SWIFT-C. There are limited data supporting use of DAAs for pre- or post-exposure prophylaxis. None of the DAA regimens have been approved by the FDA for treatment of acute HCV infection or have acute HCV listed in the PBM Criteria for Use. However, this does not bar VA clinicians from using DAAs in acute infection if they conclude that the potential benefits outweigh the risks of such use. The same regimens that are recommended for chronic HCV are recommended for acute HCV.

Mental Health Disorders

HCV-infected patients with serious mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, post-traumatic stress disorder), as documented by psychiatric evaluation, who are engaged in mental health treatment should be considered for therapy on a case-by-case basis. Patients

should be managed in collaboration with Mental Health providers to determine the risks versus benefits of treatment and potential treatment options.

Substance or Alcohol Use Disorders

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, whereas 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. 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.

HIV/HCV Coinfection

For HCV antiviral treatments options in HIV/HCV coinfection, refer to Tables 6-15.

The Panel recommends that HIV/HCV-coinfected patients receive the same HCV antiviral regimen as HCV-monoinfected patients except for 8 weeks with LDV/SOF, provided the patient is receiving appropriate HIV care and DDIs are addressed appropriately. Consultation with a provider with expertise in HIV and HCV care is advised before initiating HCV treatment in an HIV/HCV-coinfected patient. HCV-related liver disease is a major cause of morbidity and mortality among HIV-infected patients. Thus, HCV antiviral treatment in all HIV-infected patients is encouraged. Refer to Appendix A, Table 23 and Table 24 and the product inserts for a complete list of drug interactions between HCV and HIV agents.

As a corollary, HIV status is essential pre-treatment information, as shown in Table 3, in order to ensure that patients with HIV/HCV coinfection are identified and linked to appropriate HIV care. Thus, patients whose HIV status is unknown, or those who have tested negative for HIV in the past but have had subsequent exposures that could result in HIV infection, should be offered HIV testing before HCV antiviral treatment is started.

Selecting Patients for Treatment

Patients should be managed in collaboration with an ID/HIV specialist. In ART-naïve HIV-infected patients with HCV coinfection, initiation of HIV ART is generally recommended prior to beginning HCV treatment. However, it may be reasonable to defer HIV treatment until HCV treatment is completed in those with an absolute CD4 count of ≥500 cells/mm^3. Studies involving HIV/HCV-coinfected patients have excluded patients with a CD4 count of <200 cells/mm^3; HCV antiviral treatment of a Veteran with a CD4 cell count of <200 cells/mm^3 should be initiated after consultation with an HIV and hepatitis C treatment specialist. In patients who have not initiated HIV therapy and also have a CD4 count of <200 cells/mm^3, initiation of HCV treatment should be delayed until the HIV patient is on a stable HIV antiretroviral regimen (i.e., suppressed HIV RNA for at least 8 weeks).

In selecting an antiretroviral regimen, potential DDIs with HCV antiviral medications (see Appendix A, Table 24) should be taken into account. Changes in HIV therapy may be warranted prior to initiating HCV treatment to avoid known or potential DDIs. In HIV/HCV-coinfected patients who are HIV virally suppressed, HIV RNA level should be checked 4-8 weeks after modification of HIV therapy to ensure HIV viral suppression is maintained before initiating HCV therapy. If a prior HIV regimen is to be reinitiated after HCV treatment is completed, the modified ART should be continued for at least 2 weeks after completion of HCV treatment. Continued use of the modified regimen is necessary because of the prolonged half-life of some HCV drugs and the risk of DDIs if a prior HIV regimen is resumed soon after HCV treatment is completed.[3]

HIV/HCV Coinfection Clinical Trials

A summary of HCV clinical trial results involving DAA therapy in HIV/HCV-coinfected patients follows:

ERADICATE is an open-label, uncontrolled study examining LDV/SOF for 12 weeks in 50 GT1 treatment-naïve, HIV/HCV-coinfected patients without cirrhosis.[48] The majority (74%) of patients were receiving HIV ART; permitted regimens included tenofovir disoproxil fumarate (TDF)/emtricitabine in combination with efavirenz, rilpivirine, or raltegravir. Because LDV/SOF is known to raise TDF levels, kidney function parameters including creatinine level and clearance, glomerular filtration rate, and beta-2 microglobulin levels were examined; no significant abnormalities were noted. SVR rates for patients not on ART and on ART were 100% (13/13) and 97% (36/37), respectively. The sole patient who did not attain an SVR experienced virologic relapse 2 weeks after completing therapy. One other patient also on ART had a detectable HCV RNA level at 36 weeks after completing therapy, but this was thought to be due to HCV reinfection. The most commonly reported side effects were nasal congestion (16%), nasopharyngitis (12%), pain (12%), and fatigue (10%). There were no clinically significant changes in absolute CD4 cell count or HIV viral load. No serious adverse events were reported, but Grade 3/4 changes in serum amylase, lipase, creatine phosphokinase, and neutrophil count were reported.

ASTRAL-5 examined SOF/VEL for 12 weeks in an open-label, single-arm study of 106 HIV/HCV-coinfected GT1-4 patients who were treatment-naïve or treatment-experienced (prior PEG/RBV with or without an HCV PI); 19 (18%) had compensated cirrhosis.[49] The mean CD4 count was 598 cells/mm^3; all were on stable HIV ART. Permitted regimens included a backbone of TDF with or without a boosted agent (RTV or cobicistat or abacavir/lamivudine with rilpilvirine, raltegravir, elvitigravir, darunavir, atazanavir, or lopinavir. SVR was achieved in 95% (99/104) of patients. SVR was achieved in 100% (19/19) of cirrhotics, 100% (12/12) of patients with baseline NS5A RAS, and 97% (28/29) of those with a history of prior HCV treatment. There was little difference in SVR by genotype or subgenotype (92-100%). Adverse events (AEs) were reported in 71% (75/106) of participants. Grade 3/4 AEs occurred in 8% (9/106). There were two serious AEs, which required HCV treatment discontinuation (one due to acute radial nerve palsy; the other due to urinary tract infection/sepsis/toe infection). Fatigue (25%) and headache (13%) were the most commonly reported symptoms; elevated bilirubin levels were the most common lab abnormality in patients taking atazanavir. Patients on TDF with a boosted or unboosted regimen appeared to have some decrease in creatinine clearance.

C-EDGE is an open-label, single-arm Phase III study of EBR/GZR for 12 weeks in 218 treatment-naïve GT1, 4, or 6 HIV/HCV-coinfected patients.[50] The mean CD4 count was 618 cells/mm^3; a majority of patients (97%) were on HIV ART and virologically suppressed; and 16% (35/218) had compensated cirrhosis. Of the 218 patients, 66% had GT1a, 20% had GT1b, mean age was 49 years, and 17% were African American. Permitted ART regimens were abacavir or tenofovir with lamivudine or emtricitabine plus one of the following: rilpivirine, raltegravir, or dolutegravir. Overall, SVR was 96% (210/218; 95% CI: 93-98). Among GT1a and GT1b patients, SVR rates were similar (139/144 [97%] and 42/44 [96%]), respectively. SVR was achieved in 96% (27/28; 95% CI: 82-100%) of GT4 patients and in 2 patients with GT6. All patients with cirrhosis achieved an SVR (35/35, 100%). Baseline RAS occurred in 7% (10/140) with GT1a and 12% (5/43) with GT1b; 87% (13/15) achieved SVR. In GT1a patients with NS5A RAS conferring a >5-fold resistance to EBR, 75% (3/4) achieved SVR. The most commonly reported side effects were fatigue (13%), headache (12%), and nausea (9%). Grade 3/4 ALT elevations were observed in 5 patients (2%). EBR/GZR for 12 weeks in treatment-naïve HIV/HCV-coinfected patients with GT1, 4, or 6 is effective, although the numbers of patients with GT4, GT6, and cirrhosis were small.

EXPEDITION-2 is a Phase III study of GLE/PIB for 8 or 12 weeks in 153 HIV/HCV GT1-6 coinfected patients.[51] With exception of GT3, patients were permitted to have prior HCV treatment experience. Most patients (82%, n=125) were treatment-naïve. Most HCV treatment-experienced patients were DAA-naïve; 11% (3/28) had prior SOF experience. Included HIV regimens consisted of 2 NRTIs (3TC/FTC + TDF/TAF] or abacavir with rilpivirine or integrase strand transfer inhibitors +/– cobicistat. Patients without cirrhosis (n=137) were treated with 8 weeks of GLE/PIB while those with compensated cirrhosis (n=16) received 12 weeks. Overall SVR rates were 98% (150/153) with 1 discontinuation, 1 lost to follow-up, and 1 on-treatment virologic failure in a GT3 patient with cirrhosis. The high rate of SVR demonstrates 8 weeks of GLE/PIB is effective in noncirrhotic HIV/HCV-coinfected patients without prior DAA treatment experience. Adverse reactions included fatigue (10%), nausea (8%), and headache (5%).

DCV + SOF should be considered if DDI precludes the use of other HCV regimens (see Appendix A, Table 23 and Table 24 for DDIs with recommended regimens).

HIV/HCV Drug-Drug Interactions

SOF/VOX/VEL is the first combination DAA regimen that was FDA approved in the absence of publicly available Phase III clinical trial data in HIV/HCV-coinfected persons. There are specific DDIs that should be considered prior to initiating DAAs. Refer to Appendix A, Table 24, for DDIs. RBV is contraindicated for use with didanosine and can increase the risk of anemia with zidovudine. EBR/GZR and GLE/PIB are contraindicated with certain HIV PIs including atazanavir, darunavir, lopinavir, saquinavir, and tipranavir, as co-administration may increase the risk of ALT elevations due to a significant increase in GZR, GLE, and/or PIB plasma concentrations caused by OATP1B1/3 inhibition.[3,9,27,40-42]

Laboratory Monitoring

In addition to the laboratory tests performed for HCV-monoinfected patients receiving HCV antiviral therapy, HIV RNA and CD4 counts should be measured at baseline and at routine intervals as

recommended by the Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*.[3,9,27,40-42]

Modification of Drug Use in Patients with Renal or Hepatic Impairment

Table 18. Modification of Drug Use in Patients with Renal Insufficiency

Treatment	Comment	Grade
EBR/GZR	No dosage adjustment needed, including use in hemodialysis patients.	A-I
GLE/PIB	No dosage adjustment needed, including use in hemodialysis patients.	A-I
LDV	No dosage adjustment needed.	A-I
RBV	200 mg daily alternating with 400 mg daily for CrCl 30-50 mL/min and 200 mg daily for CrCl <30 mL/min, including hemodialysis.	A-I
SOF	Should not be used if CrCl <30 mL/min or end-stage renal disease.	A-I
VEL	No dosage adjustment needed.	A-I
VOX	No dosage adjustment needed.	A-I

Table 19. Modification of Drug Use in Patients with Hepatic Impairment

Treatment	Comment	Grade
EBR/GZR	No dosage adjustment needed with mild hepatic impairment (CTP A). Contraindicated in moderate or severe hepatic impairment (CTP B or C; CTP score ≥7).	A-I
GLE/PIB	No dosage adjustment needed with mild hepatic impairment (CTP A). Not recommended in patients with moderate hepatic impairment (CTP B, CTP score 7-9). Contraindicated in patients with severe hepatic impairment (CTP C, CTP score 10-15).	A-I
LDV	No dosage adjustment needed.	A-I
RBV	Although RBV is primarily renally cleared, CTP B and C patients may have pre-existing anemia. Thus, RBV 600 mg/day or lower is recommended as an initial dose.	A-II
SOF	No dosage adjustment is required for patients with mild, moderate, or severe hepatic impairment (CTP A, B, or C).	A-I
VEL	No dosage adjustment needed.	A-I
VOX	No dosage adjustment needed with mild hepatic impairment (CTP A). Not recommended in patients with moderate or severe hepatic impairment (CTP B or C; CTP score ≥7).	A-I

Abbreviations: CrCL = creatinine clearance

Elbasvir/grazoprevir

No dosage adjustment of EBR/GZR is required in patients with any degree of renal impairment including patients receiving hemodialysis.[9] If RBV is used concomitantly, RBV dosage should be adjusted based on CrCl <50 mL/min as indicated in Table 18.

A randomized, double-blind, placebo-controlled Phase III study (C-SURFER) evaluated the efficacy and safety of EBR/GZR for 12 weeks in 224 HCV GT1-infected patients with chronic kidney disease (CKD) stage 4 (eGFR 15-29 mL/min) or CKD stage 5 (eGFR <15 mL/min) including those on hemodialysis.[52,53] Of the patients who received EBR/GZR in the immediate- (n=122) or delayed-treatment arm (n=113), 73% were male, 46% were White, 46% were Black, 52% were GT1a, 20% were treatment-experienced, 6% had cirrhosis, 76% were receiving hemodialysis, and 19% were renal transplant recipients. SVR was achieved in 94% (115/122) in the immediate-treatment arm and 95% (97/102) in the delayed-treatment arm. SVR in subgroups were as follows: 99% (172/174) among treatment-naïve, 98% (40/41) among treatment-experienced, 100% (12/12) among cirrhotic patients. Three patients were virologic relapsers; 2 of the 3 were GT1a patients with baseline NS5A RAS. Based on limited data in GT1a patients with CKD, baseline NS5A RAS testing is recommended and, if present, the addition of renally dosed RBV to EBR/GZR and treatment for 16 weeks is recommended. The most commonly reported adverse events (≥10%) were headache, nausea, fatigue, insomnia, and anemia. Anemia occurred in 25% (56/224) of patients (hemoglobin ≤10.0 g/dL). Five patients experienced a cardiac event (infarction and arrest) and 2 patients experienced congestive heart failure. Of 224 patients, 34% experienced an adverse event, 14-17% experienced a serious adverse event, and 4% discontinued treatment owing to adverse events. Anemia along with significant cardiac events highlight the need for close monitoring of stage 4-5 CKD patients while on EBR/GZR therapy, especially those requiring RBV.

EBR/GZR does not require dosage adjustment in patients with mild hepatic impairment (CTP A). EBR/GZR is contraindicated in patients with moderate hepatic impairment (CTP B) due to the lack of clinical safety and efficacy experience in this population. EBR/GZR is contraindicated in patients with severe hepatic impairment (CTP C) due to a 12-fold increase in GZR exposure in non-HCV-infected CTP C subjects.

Glecaprevir/pibrentasvir

GLE/PIB has <1% renal excretion. No dosage adjustment of GLE/PIB is required in patients with any degree of renal impairment including patients receiving hemodialysis.[40]

EXPEDITION-4 is an open-label study of GLE/PIB for 12 weeks in 104 GT1-6 treatment-naïve or treatment-experienced patients (PEG-IFN/RBV or SOF + RBV ± PEG-IFN) with CKD stage 4 (12%; eGFR 15-29 mL/min) or stage 5 (88%; eGFR <15 mL/min or hemodialysis dependent).[54] The majority of patients were male (76%), GT1 (52%), treatment-naïve (58%), and noncirrhotic (81%). Across genotypes, SVR was achieved in 98% (102/104). GLE/PIB generally was well tolerated; 20% (21/104) experienced pruritus, 14% (15/104) fatigue, and 12% (12/104) nausea. Four patients experienced diarrhea, pruritus, pulmonary edema, hypertensive cardiomyopathy with congestive failure, or hypertensive crisis requiring GLE/PIB discontinuation.

In an integrated analysis of 2,238 GT 1-6 treatment-naïve and treatment-experienced (PEG-IFN/RBV or SOF + RBV ± PEG-IFN) patients without and with compensated cirrhosis enrolled in ENDURANCE-1, ENDURANCE-2, ENDURANCE-3, ENDURANCE-4, EXPEDITION-1, EXPEDITION-4, SURVEYOR-1, and SURVEYOR-2I studies, high SVR rates (97-98%) were achieved across all CKD stages.[55] Overall, the mean change in eGFR from baseline was -2.54 ± 12.74. Maximum increases in mean AUC of GLE and PIB were <2-fold and were not considered clinically relevant. Adverse events across CKD stages 1-5 were similar

except for pruritus, which occurred at a higher frequency in CKD stages 4-5 (20% vs. 3-6% with CKD 1-3). Renal function did not appear to impact the efficacy and safety profile of GLE/PIB.

Ledipasvir

Following administration of a single dose of 90 mg LDV in HCV-negative patients, no clinically relevant differences in LDV pharmacokinetics were observed between healthy patients and those with severe renal impairment (eGFR <30 mL/min by Cockcroft-Gault).[27]

Following administration of a single dose of 90 mg LDV in HCV-negative patients with severe hepatic impairment (CTP C), LDV plasma exposure was similar in patients with severe hepatic impairment and controls with normal hepatic function. In HCV-infected patients with cirrhosis, there was no clinically relevant effect on LDV exposure.[27]

Sofosbuvir

SOF and its major metabolites are eliminated primarily via renal clearance. No dosage adjustment is required for patients with mild or moderate renal impairment (CrCl ≥30 mL/min). However, the safety and efficacy of SOF have not been established in patients with severe renal impairment (CrCl <30 mL/min). A 4-hour hemodialysis session removes 18% of the administered dose. Until additional data are available, SOF should not be used in patients with severe renal impairment (CrCl <30 mL/min) or end-stage renal disease requiring dialysis. Patients with decompensated cirrhosis (CTP B and C) and severe renal impairment (CrCl <30 mL/min) require consultation with an expert (see Section XIV, Resources) to consider the risks versus benefits of SOF-based treatment in this population.[43]

Velpatasvir

VEL does not require dosage adjustment for mild, moderate, or severe renal impairment. No clinically significant differences in pharmacokinetics were observed in HCV-negative volunteers with severe renal impairment (eGFR <30 mL/min).[42]

VEL does not require dosage adjustment in patients with mild hepatic impairment (CTP A) or decompensated cirrhosis (CTP B and C); the AUC of VEL in patients with moderate and severe hepatic impairment was similar to that of patients with normal hepatic function.[42]

Voxilaprevir

VOX does not require dosage adjustment for mild, moderate, or severe renal impairment. No clinically significant differences in pharmacokinetics were observed in HCV-negative volunteers without and with severe renal impairment (eGFR <30 mL/min).[41]

Hepatocellular Carcinoma

The following is based on expert opinion, given the preliminary data that are available. It is reasonable to treat HCV in a patient with HCC or a history of HCC after the HCC has been treated successfully, with follow-up imaging demonstrating locoregional control. Patients with HCC should be assessed for DAA therapy on a case-by-case basis and, ideally, managed with input from a Tumor Board or specialty care. Patients with extensive or progressive HCC (e.g., vascular invasion or metastatic disease) are less likely to benefit from DAA therapy.

Reports that DAA treatment may lead to emergence of aggressive HCC remain controversial. Preliminary reports suggest a higher incidence of HCC occurrence or recurrence and a more aggressive course following successful DAA therapy.[56-59] Based on a large national VA study, DAA therapy does not appear to increase HCC incidence; there was a 60-84% reduction in HCC and 64% reduction in mortality in patients that received DAA therapy.[60] However, patients with chronic HCV and advanced hepatic fibrosis still remain at risk of HCC after achieving SVR, and continued surveillance with imaging studies every 6 months is recommended.

Pre-Liver Transplant Patients

The decision to treat patients undergoing evaluation or currently listed for liver transplantation should be discussed with the transplant center prior to beginning HCV treatment.[61]

Organs from HCV-positive donors are usually given preferentially to HCV-positive recipients. Thus, the state of being HCV positive may improve a patient's access to transplantation in some cases. In patients with compensated cirrhosis referred for liver transplantation, HCV eradication may lead to stabilization and improvement of liver function and eliminate the need for transplantation. Among patients with decompensated cirrhosis, achieving an SVR may lead to a state in which liver function neither improves nor worsens. Since organ allocation in liver transplantation is based on liver disease severity as measured by the MELD score, achieving an SVR may potentially cause patients with a high MELD, but not high enough to receive a liver transplant, to not be eligible to receive a liver transplant. If such an outcome is anticipated, it may be preferable to withhold HCV treatment until after transplantation; DAAs are highly effective after liver transplantation.

Pre-Renal Transplant Patients

The decision to treat patients undergoing evaluation or currently listed for renal transplantation should be discussed with the transplant center prior to beginning HCV treatment.

In an open-label, single study of 10 HCV-infected donor to non-HCV-infected recipients, all recipients received a dose GZR/EBR immediately before transplantation and continued GZR/EBR for 12 weeks following transplantation if GT1 and GZR/EBR + SOF for 12 weeks if GT2 or GT3. All 10 had undetectable HCV RNA at 12 weeks post-DAA therapy and none reported DAA-related adverse effects.[62]

Post-Liver or Post-Renal Transplant Patients

The decision to treat, regimen selection, and management of HCV treatment should be coordinated with the transplant center and/or specialists. In general, DAA treatment in post-transplant patients to eradicate HCV is highly successful, though DDIs with HCV therapy should be thoroughly evaluated (see Appendix A, Table 23). Patients should be informed of the importance of taking their DAAs as directed and of following up with their treating provider as directed.

Table 20. HCV Treatment Recommendations after Liver or Renal Transplant

Consult with the transplant center before initiating hepatitis C treatment.

Refer to Appendix A, Table 23, for DDIs in post-liver or post-renal transplant patients.

Transplant status	HCV GT	Treatment History	Cirrhosis status	Regimen and duration	Evidence grade	SVR % (N/N)	Comments
Post-Liver Transplant	GT1, 4	Naïve, or NS5A- and SOF-naïve	Non-cirrhotic or Cirrhotic, CTP A, B, or C	LDV/SOF + RBV x 12 weeks	A-I	F0-F3: 96% (53/55)[17] CTP A: 96% (25/26)[17] CTP B: 85% (22/26)[17] CTP C: 60% (3/5)[17]	24 weeks F0-F3: 98% (55/56)[17] CTP A: 96% (24/25)[17] CTP B: 88% (23/26)[17] CTP C: 75% (3/4)[17] If CTP B or C, RBV was initiated at 600 mg/day and increased as tolerated.[17]
Post-Liver Transplant	GT1, 2, 3, 4	Naïve, or RBV ± SOF ± PEG-IFN-experienced	Non-cirrhotic or Cirrhotic, CTP A	SOF/VEL x 12 weeks If CTP A: add RBV ***NOT FDA APPROVED in Post-Liver Transplant***	B-II/III	GT1a: 93% (14/15)[63] GT1b: 96% (21/22)[63] GT2: 100% (3/3)[63] GT3: 97% (34/35)[63] GT4: 100% (4/4)[63]	Includes treatment-naïve and treatment-experienced patients.[63] GT1-4, CTP A: 86% (6/7)[63]
Post-Liver or Post-Renal Transplant	GT1, 2, 3, 4	Naïve	Non-cirrhotic or Cirrhotic, CTP A	GLE/PIB x 12 weeks	A-II	98% (98/100)[64]	Includes GT1-6 treatment-naïve and GT1, 2, 4-6 treatment-experienced patients. Patients with cirrhosis were excluded.[64]
Post-Liver or Post-Renal Transplant	GT1 or 3	GT1: NS5A-experienced without an NS3/4 PI GT3: PEG-IFN + RBV ± SOF-experienced	Non-cirrhotic or Cirrhotic, CTP A	GLE/PIB x 16 weeks[40]	B-III	Based on SVR rates in non-transplant studies	SVR rates in non-transplant studies: GT1 (and GT4-6): 94% (17/18)[20] GT3: 96% (21/22) in non-cirrhotics; 96% (45/47) in CTP A[34]

Dosages:

- GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food
- LDV/SOF (90/400 mg, Harvoni®): 1 tablet orally daily
- SOF/VEL (400/100 mg, Epclusa®): 1 tablet orally daily
- RBV 600 mg/day and increase as tolerated in CTP B and C patients

Note: GLE/PIB, LDV/SOF and SOF/VEL should not be used in reduced dosages and should not be restarted if discontinued.

Table 21. Treatment in Post-Liver Transplant Patients

The decision to treat, regimen selection, and management of treatment should be coordinated with the transplant center and/or by specialists with extensive experience in the treatment of pre- or post-transplant patients. *(See Table 20)*

GT1 or 4 without cirrhosis or cirrhosis including CTP A, B, or C who are treatment-naïve or treatment-experienced (NS5A-naive and SOF-naïve)

- *LDV/SOF (90/400 mg/day,* Harvoni®*): 1 tablet daily + RBV 1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food in divided doses in CTP A patients, or RBV 600 mg/day (increase by 200 mg/day every 2 weeks only as tolerated) in CTP B and C patients for 12 weeks*

GT1 without cirrhosis or cirrhosis (CTP A) who are treatment-naïve or treatment-experienced

- *GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food for 12 weeks or 16 weeks if NS5A-experienced without an NS3/4A PI*

GT2 without cirrhosis or cirrhosis (CTP A) who are treatment-naïve

- *GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food for 12 weeks*

GT3 without cirrhosis or cirrhosis (CTP A)

- *GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food for 12 weeks if treatment-naïve or 16 weeks if treatment-experienced with PEG-IFN + RBV ± SOF*

GT4 without cirrhosis or cirrhosis (CTP A) who are treatment-naïve

- *GLE/PIB (100/40 mg, Mavyret™): 3 tablets orally daily with food for 12 weeks*

GT1, 2, 3, or 4 without cirrhosis or cirrhosis (CTP A) who are treatment-naïve or treatment-experienced (RBV ± SOF ± PEG-IFN-experienced)

- *SOF/VEL (400/100 mg, Epclusa®) 1 tablet orally daily for 12 weeks. If CTP A: add RBV, particularly in GT3 SOF-experienced patients. NOT FDA APPROVED*

Treatment in Post-Liver or Post-Renal Transplant Patients

The decision to treat patients with recurrent HCV after a liver or kidney transplant should be discussed with the transplant center prior to starting treatment. DDIs with HCV DAA agents and post-transplant immunosuppressive agents should be thoroughly evaluated; these are listed in Appendix A, Table 23**.**

Glecaprevir/Pibrentasvir after Liver or Renal Transplant

A Phase III, non-randomized, open-label, non-inferiority trial (MAGELLAN-2) evaluated GLE/PIB for 12 weeks in 100 post-renal or post-liver transplant patients, assuming a historical SVR rate of 94%. Patients with cirrhosis were excluded.[64] Patients had either a single kidney (20%) or liver (80%) transplant and were on a stable immunosuppression regimen, including cyclosporine ≤100 mg/day, tacrolimus, sirolimus, everolimus, azathioprine, mycophenolic acid, prednisone up to 10 mg/day, and/or prednisolone. Patients were GT1-6 treatment-naïve (66%), or GT1, 2, 4-6 treatment-experienced (34%; PEG-IFN/IFN ± RBV [32%] or SOF + RBV ± PEG-IFN [1%]). Across both treatment-naïve and treatment-experienced groups, the genotype distribution was GT1 (57%), GT2 (13%), GT3 (24%), GT4 (4%), GT5 (0%), GT6 (2%) with fibrosis stages F0-1 (80%), F2 (6%), F3 (14%). Baseline NS5A RAS were present in 33% (33/100) and none had NS3 RAS. The overall SVR was achieved in 98% (98/100). Of the 2 patients who failed to achieve SVR, 1 was a GT3 virologic relapser and 1 was lost to follow-up. Adverse reactions included headache (17%), fatigue (16%), nausea (8%), and pruritus (7%). There was 1 mild liver transplant rejection at week 10 and GLE/PIB treatment was not interrupted; 1 patient also experienced elevated LFTs post-treatment. Grade ≥3 laboratory abnormalities were ALT (1), total bilirubin (1), and creatinine clearance (2). This study supports the safety and efficacy of GLE/PIB for 12 weeks in post-renal or post-liver transplant patients without cirrhosis, including patients who failed SOF + RBV ± PEG-IFN (except GT3 patients), and patients with baseline NS5A RAS.

Ledipasvir/Sofosbuvir after Liver or Renal Transplant

In a study of post-transplant patients with HCV, 223 patients were randomized to LDV/SOF + RBV for 12 or 24 weeks.[65] RBV dosing was weight-based for patients without cirrhosis and with CTP A; in CTP B and C patients, RBV was initiated at 600 mg/day and increased as tolerated. In this study, 112 patients had F0-F3 fibrosis, while 52, 50, and 9 patients had CTP A, B, and C cirrhosis, respectively. Among patients without cirrhosis (METAVIR F0-F3), SVR was 96-98% with LDV/SOF + RBV for 12 weeks or 24 weeks. Among patients with cirrhosis, the SVR rates were 96% for CTP A, 83-85% for CTP B, and 60- 67% for CTP C with LDV/SOF + RBV for 12 weeks or 24 weeks. Eight patients had serious adverse events that were considered related to study treatment: 4 had anemia, 2 hemolytic anemia, 1 sick sinus syndrome, 1 sinus arrhythmia, and 1 portal vein thrombosis. Five patients with cirrhosis died while in the study due to internal bleeding, multiorgan failure/intestinal perforation, cardiac disease, complications of cirrhosis, and progressive multifocal leukoencephalopathy. Median serum creatinine concentrations and INR remained at baseline levels. Hemoglobin concentration decreased approximately 2-3 g/dL while on treatment, with 33 patients requiring erythropoietin or blood transfusions. Overall, this trial suggests that LDV/SOF + RBV is safe in patients who have received a liver transplant, including those with decompensated cirrhosis. Furthermore, treatment with 12 weeks of LDF/SOF + RBV achieves high SVR rates among patients without cirrhosis. Serious adverse effects occurred in 2-8% of patients, most of

which were related to anemia from RBV. There were no episodes of rejection or renal insufficiency, or significant changes in blood levels of cyclosporine or tacrolimus.

Limited data on SOF-based therapy are available in kidney transplant recipients. SVR rates were 100% (114/114) with LDV/SOF for 12-24 weeks in GT1 and GT4 HCV-infected renal transplant recipients.[65] Close collaboration with the patient's transplant center is encouraged to assess post-transplant treatment candidate selection and type of regimen. No clinically significant DDI was observed with co-administration of LDV or SOF and cyclosporine and tacrolimus, making these two drugs potential treatment options for patients with solid organ transplants other than liver.

Sofosbuvir/Velpatasvir after Liver Transplant

A single-arm, open-label study of 79 liver transplant recipients with recurrent HCV GT1-4 received SOF/VEL for 12 weeks.[63] The majority were White (81%), treatment-experienced (60%; PEG-IFN/IFN ± RBV [54%] or SOF + RBV ± PEG-IFN [5%]), and non-cirrhotic (71%). SVR was achieved in 96% (76/79); SVR occurred in 95% (35/37) with GT1, 100% (2/2) with GT2, 97% (34/35) with GT3, and 100% (4/4) with GT4. SVR occurred in 86% (6/7) of patients with cirrhosis and in 98% (54/55) without baseline NS5A RAS. In patients with baseline NS5A RAS, SVR was achieved in all but two (92%, 22/24). Both had virologic relapse; one had GT1a infection with K24R RAS, the other had GT3b infection with A30K and L31M RAS. No changes in immunosuppression were needed for rejection or suspected DDIs. No deaths, graft loss or rejection were reported.

Limited data are available on the safety and efficacy of SOF/VEL after liver transplantation for cirrhotics. Thus, recommendations for SOF/VEL use in this setting is based on “expert opinion” and should only be considered if other treatment options are not available. The addition of RBV should be included for those with compensated cirrhosis (CTP A), particularly in GT3 SOF-experienced patients; in patients with decompensated cirrhosis, SOF/VEL plus weight-based RBV (600 mg/day for CTP B or C) for 12 weeks can be considered in those who are treatment-naïve or for 24 weeks in those who are treatment-experienced, after approval of the transplant center.

Extra-Hepatic Manifestations of HCV

Table 22. Treatment of Patients with Extra-Hepatic Manifestations of HCV

Treatment Considerations
• Patients with leukocytoclastic vasculitis, symptomatic cryoglobulinemia, membranoproliferative glomerulonephritis, or porphyria cutanea tarda despite mild liver disease should be treated as soon as possible. (A-III)

Pregnancy and Lactation

The safety and efficacy of DAA therapy in pregnant or lactating women have not been established for any of the agents currently approved by the FDA. During pregnancy, these drugs should be used only if the benefits outweigh the risks to the fetus.

RBV-containing regimens are absolutely contraindicated in pregnant women and in the male partners of women who are pregnant; if applicable, the manufacturer product information for RBV should be consulted. The use of two forms of effective contraception is required during RBV therapy and for 6 months after the last dose is taken.[66,67] The Ribavirin Pregnancy Registry (www.ribavirinpregnancyregistry.com) should be contacted if there is direct RBV exposure through the pregnant female taking RBV or indirect exposures through her male sex partner who has taken RBV.

XIII. Panel Members

Panel members who had a financial relationship with a pharmaceutical manufacturer as defined under VHA Handbook 1004.07 were recused from working on sections dealing with any products of that manufacturer. This document was independently reviewed by the VHA Pharmacy Benefits Management Service.

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- VA-specific data:
  vaww.hepatitis.va.gov (VA Only)
- PBM Criteria for Use:
  www.pbm.va.gov/PBM/clinicalguidance/criteriaforuse.asp
- HCV Drug-Drug Interactions:
  www.hep-druginteractions.org

XV. Appendices

Appendix A: Tables

Table 23. Drug-Drug Interactions with HCV Antiviral Agents[9,27,40-42]

✓ = drug that can be used concomitantly ✘ = drug not recommended ? = data limited or not available on pharmacokinetic interactions

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A Inhibitor/NS3/4A Protease Inhibitor: GLE/PIB	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/NS5B Inhibitor: SOF/VEL	Co-formulated NS5A/NS5B inhibitor/NS3/4A Protease Inhibitor: SOF/VEL/VOX
Angiotensin Receptor Blocker					
losartan, valsartan	?	✓	?	?	?
Antacids					
aluminum and magnesium hydroxide	✓	?	Separate dose by 4 hours (↓ LDV concentration)	Separate dose by 4 hours (↓ VEL concentration)	Separate dose by 4 hours (↓ VEL concentration)
Antiarrhythmics					
digoxin	✓	use caution and monitor (may ↑ digoxin concentration) Measure digoxin levels before initiating GLE/PIB. Reduce dose by approximately 50% or by modifying the dosing frequency and continue monitoring.	use caution and monitor (may ↑ digoxin concentration)	use caution and monitor (may ↑ digoxin concentration)	use caution and monitor (may ↑ digoxin concentration)
amiodarone	?	?	✘ (↑ amiodarone concentration; may ↑ risk of bradycardia and	✘ (↑ amiodarone concentration; may ↑ risk of bradycardia and	✘ (↑ amiodarone concentration; may ↑ risk of bradycardia and cardiac

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A Inhibitor/NS3/4A Protease Inhibitor: GLE/PIB	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/NS5B Inhibitor: SOF/VEL	Co-formulated NS5A/NS5B inhibitor/NS3/4A Protease Inhibitor: SOF/VEL/VOX
			cardiac arrest; if amiodarone required, monitor inpatient for first 48 hrs, then daily outpatient for 2 wks)	cardiac arrest; if amiodarone required, monitor inpatient for first 48 hrs, then daily outpatient for 2 wks)	arrest; if amiodarone required, monitor inpatient for first 48 hrs, then daily outpatient for 2 wks)
Anticancer					
topotecan	?	?	?	✘ (↑ topotecan concentration)	?
Anticoagulant					
dabigatran	?	use caution and monitor (may ↑ dabigatran concentration) If coadministered, refer to the dabigatran prescribing information for dabigatran dose modifications in combination with P-gp inhibitors in the setting of renal impairment.	?	?	use caution and monitor (may ↑ dabigatran concentration)
Anticonvulsants					
carbamazepine, phenytoin, phenobarbital, oxcarbazepine	✘ (may ↓ EBR/GZR concentration)	✘ (may ↓ GLE/PIB concentration)	✘ (may ↓ LDV/SOF concentration)	✘ (may ↓ VEL/SOF concentration)	✘ (may ↓ SOF/VEL/VOX concentration)
lamotrigine	?	✓	?	?	?
Antifungals					
ketoconazole	✘ (may ↑ EBR/GZR concentration and	?	?	✓	✓

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A Inhibitor/NS3/4A Protease Inhibitor: GLE/PIB	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/NS5B Inhibitor: SOF/VEL	Co-formulated NS5A/NS5B inhibitor/NS3/4A Protease Inhibitor: SOF/VEL/VOX
	↑ risk of hepatotoxicity)				
Antihyperlipidemic					
gemfibrozil	?	?	✘	✓	✓
Antiinfectives					
nafcillin	✘ (may ↓ EBR/GZR concentration)	?	?	?	?
Antimycobacterials					
rifampin, rifabutin	✘ (may ↓ EBR/GZR concentration)	✘ (may ↓ GLE/PIB concentration)	✘ (may ↓ LDV/SOF concentration)	✘ (may ↓ VEL/SOF concentration)	✘ (may ↓ SOF/VEL/VOX concentration)
rifapentine	?	?	✘ (may ↓ LDV/SOF concentration)	✘ (may ↓ VEL/SOF concentration)	✘ (may ↓ SOF/VEL/VOX concentration)
Calcium channel blockers (CCBs)					
amlodipine	?	✓	?	?	?
felodipine, nicardipine, nifedipine	?	✓	?	?	?
verapamil	?	?	✓	?	?
Corticosteroids					
budesonide, methylprednisone, prednisone	✓	✓	?	?	?
Dual endothelin receptor antagonist					
bosentan	✘ (may ↓ EBR/GZR concentration)	?	?	?	?

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A Inhibitor/NS3/4A Protease Inhibitor: GLE/PIB	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/NS5B Inhibitor: SOF/VEL	Co-formulated NS5A/NS5B inhibitor/NS3/4A Protease Inhibitor: SOF/VEL/VOX
H_2-Receptor Antagonists	✓	✓	do not exceed 40 mg BID equivalent of famotidine; administer simultaneously or 12 hours apart	do not exceed 40 mg BID equivalent of famotidine; administer simultaneously or 12 hours apart	do not exceed 40 mg BID equivalent of famotidine; administer simultaneously or 12 hours apart
HCV drug					
SOF	✓	✓			
Herbal supplements					
St. John's wort (Hypericum perforatum)	✘ (may ↓ EBR/GZR concentration)	✘ (may ↓ GLE/PIB concentration)	✘ (may ↓ LDV/SOF concentration)	✘ (may ↓ VEL/SOF concentration)	✘ (may ↓ SOF/VEL/VOX concentration)
HIV ARVs (See **Table 24**: Drug-Drug Interactions with HIV Antiretrovirals)					
HMG Co-A reductase inhibitors					
rosuvastatin	✓ (may ↑ statin concentration) dose ≤10 mg once daily	✓ (may ↑ statin concentration) dose ≤10 mg once daily	✘ (may ↑ statin concentration; potential for myopathy and rhabdomyolysis)	✓ dose ≤10 mg daily (may ↑ statin concentration; potential for myopathy and rhabdomyolysis)	✘ (may ↑ statin concentration; potential for myopathy and rhabdomyolysis)
atorvastatin	✓ (may ↑ statin concentration) dose ≤20 mg once daily	✘ (may ↑ statin concentration; potential for myopathy and rhabdomyolysis)	✓ (may ↑ statin concentration; potential for myopathy and rhabdomyolysis)	✓ (may ↑ statin concentration; potential for myopathy and rhabdomyolysis)	✓ (may ↑ statin concentration) Use lowest approved statin dose
simvastatin, lovastatin	✓ use lowest necessary dosage, titrate	✘ (may ↑ statin concentration; potential	?	?	✓ (may ↑ statin concentration)

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A Inhibitor/NS3/4A Protease Inhibitor: GLE/PIB	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/NS5B Inhibitor: SOF/VEL	Co-formulated NS5A/NS5B inhibitor/NS3/4A Protease Inhibitor: SOF/VEL/VOX
	carefully; monitor closely, may ↑ statin concentration	for myopathy and rhabdomyolysis)			Use lowest approved statin dose
pitavastatin	✓	✓ use lowest necessary dosage, titrate carefully; monitor closely, may ↑ statin concentration	?	?	✘ (may ↑ statin concentration; potential for myopathy and rhabdomyolysis)
pravastatin	✓	✓ Reduce statin dose by 50% (may ↑ statin concentration; potential for myopathy and rhabdomyolysis)	✓	✓	✓ dose ≤40 mg daily (may ↑ statin concentration; potential for myopathy and rhabdomyolysis)
fluvastatin	✓ use lowest necessary dosage, titrate carefully; monitor closely, may ↑ statin concentration	✓ use lowest necessary dosage, titrate carefully; monitor closely, may ↑ statin concentration	?	?	✓ (may ↑ statin concentration) Use lowest approved statin dose
Immunosuppressants					
cyclosporine (CSA)	✘ (may ↑ GZR concentration and increased ALT)	✓ (may ↑ GLE/PIB concentration) Not recommended in patients requiring cyclosporine dose >100mg/day	✓	✓	✘ (↑ VOX concentration)
tacrolimus	no dosage adjustment; use caution (potential ↑	✓	✓	✓	✓

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A Inhibitor/NS3/4A Protease Inhibitor: GLE/PIB	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/NS5B Inhibitor: SOF/VEL	Co-formulated NS5A/NS5B inhibitor/NS3/4A Protease Inhibitor: SOF/VEL/VOX
	tacrolimus concentrations) and monitor tacrolimus concentrations and renal function				
mycophenolate mofetil	✓	?	?	?	?
Narcotic analgesic					
buprenorphine, naloxone	✓	✓	?	?	?
methadone	✓	✓	✓	✓	✓
Opioid antagonist					
naloxone	?	✓	?	?	?
Oral contraceptive					
ethinyl estradiol	✓	✘ Coadministration may increase risk of ALT elevations	✓	✓	✓
norgestimate products, norethindrone	✓	✓	✓	✓	✓
progestin-only contraceptives	✓	✓	✓	?	?
Proton Pump Inhibitors (PPIs)					
omeprazole	✓	✓[a]	✓ dose ≤20 mg/day; administer simultaneously under fasting conditions	✘ If medically necessary; administer with food 4 hours before omeprazole 20 mg/day	✓ dose ≤20 mg/day
other PPI	✓	✓	✓ PPI doses comparable to omeprazole ≤20 mg/day	✘ Use with other PPIs have not been studied	? Use with other PPIs have not been studied

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A Inhibitor/NS3/4A Protease Inhibitor: GLE/PIB	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/NS5B Inhibitor: SOF/VEL	Co-formulated NS5A/NS5B inhibitor/NS3/4A Protease Inhibitor: SOF/VEL/VOX
			can be administered simultaneously, fasting		
Sedatives/ Anxiolytics					
oral midazolam, triazolam	?	✓	?	?	?
Stimulants					
modafinil	✘ (may ↓ EBR/GZR concentration)	?	?	?	?

[a] Glecaprevir AUC may be reduced when co-administered with omeprazole, however, SVR rates were 100% (64/64) with concomitant use of GLE/PIB and high doses of PPIs including omeprazole 40 mg/day.[40,68]

Table 24. Drug-Drug Interactions with HIV Antiretrovirals[9,27,40-42]

Adapted from U.S. Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents[1] and product prescribing information. ***Note:*** *Fosamprenavir (FPV), Indinavir (IDV), Nelfinavir (NFV), and Saquinavir (SQV) are* ***not*** *included in this table. Refer to the FDA product labels for FPV, IDV, NFV, and SQV for information regarding drug interactions with these PIs.*

✓ = drug that can be used concomitantly ✘ = drug not recommended **?** = data limited or not available on pharmacokinetic interactions

Selected HIV Drug Classes and Drugs	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: GLE/PIB	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/NS5B Inhibitor: SOF/VEL	Co-formulated NS5A/NS5B inhibitor/NS3/4A Protease Inhibitor: SOF/VEL/VOX
Nucleoside Reverse Transcriptase Inhibitors					
FTC	✓	✓	✓	✓	✓
3TC	✓	✓	✓	✓	✓
ABC	✓	✓	✓	✓	✓
TDF	✓	✓	✓ Monitor for TDF toxicity	✓ Monitor for TDF toxicity	✓ Monitor for TDF toxicity
TAF	✓	✓	✓	✓	✓
ZDV[a]	✓	✓	✓	✓	✓
HIV Protease Inhibitors					
ATV (unboosted)	✘	✘ (may ↑ GLE/PIB concentration and ↑ risk of ALT elevations)	✓	✓	✓
ATV/r or ATV/c	✘ (may ↑ GZR concentration and ↑ risk of ALT elevations)	✘ (may ↑ GLE/PIB concentration and ↑ risk of ALT elevations)	✓[b]	✓[b]	✘
DRV/r or DRV/c	✘	✘	✓[b]	✓[b]	✓[b] Consider monitoring for hepatotoxicity.[c]

Selected HIV Drug Classes and Drugs	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: GLE/PIB	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/NS5B Inhibitor: SOF/VEL	Co-formulated NS5A/NS5B inhibitor/NS3/4A Protease Inhibitor: SOF/VEL/VOX
LPV/r	✘	✘	✓[b]	✓[b]	✘
TPV/r	✘	✘	✘	✘	✘
Nonnucleoside Reverse Transcriptase Inhibitors					
EFV	✘ (may ↓ EBR/GZR concentration)	✘ (may ↓ GLE/PIB concentration)	✓ If EFV used with TDF/FTC, monitor for TDF toxicity due to ↑ TDF concentrations	✘ (may ↓ VEL concentration)	✘
ETR	✘ (may ↓ EBR/GZR concentration)	✘ (may ↓ GLE/PIB concentration)	✓	✘	✘
NVP	✘	?	✓	✘	✘
RPV	✓	✓	✓	✓	✓
Integrase Strand Transfer Inhibitors					
DTG	✓	✓	✓	✓	✓
EVG/c/TDF/FTC	✘ (may ↑ EBR/GZR concentration)	✓ Consider monitoring for hepatotoxicity.[d]	✘	✓ If used with TDF, monitor for TDF toxicity	✓ If used with TDF, monitor for TDF toxicity. Consider monitoring for hepatotoxicity.[c]
EVG/c/TAF/FTC	✘ (may ↑ EBR/GZR concentration)	✓ Consider monitoring for hepatotoxicity.[d]	✓	✓	✓ Consider monitoring for hepatotoxicity.[c]
EVG + (PI/r without COBI)	Refer to recommendations for individual PI/r	Refer to recommendations for individual PI/r	Refer to recommendations for individual PI/r	✓	Refer to recommendations for individual PI/r
RAL	✓	✓	✓	✓	✓

Selected HIV Drug Classes and Drugs	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: GLE/PIB	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/NS5B Inhibitor: SOF/VEL	Co-formulated NS5A/NS5B inhibitor/NS3/4A Protease Inhibitor: SOF/VEL/VOX
CCR5 Antagonist					
MVC	?	?	✓	✓	✓

✓ = can be used concomitantly ✘ = not recommended ? = data limited or not available on PK interactions with antiretroviral drug

Abbreviations: 3TC = lamivudine; ABC = abacavir; ATV/r = atazanavir/ritonavir; ATV/c = atazanavir/cobicistat; COBI = cobicistat; DAA = direct-acting antiviral agents; DRV/r = darunavir/ritonavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

[a] Concomitant use of ZDV with RBV is not recommended due to potential for worsening anemia; concomitant use with PEG-IFN is not recommended due to potential for worsening neutropenia.

[b] Regimens containing TDF and an HIV protease inhibitor/RTV or cobicistat (ATV/r or ATV/c, DRV/r or DRV/c, LPV/r): ↑TDF concentrations are expected; consider alternative HCV or antiretroviral therapy to avoid increases in TDF exposures. If co-administration is necessary, monitor for TDF-associated adverse reactions.

[c] Due to increased voxilaprevir exposures when given with pharmacologically boosted DRV or EVG, monitoring for hepatotoxicity is recommended until more safety data in clinical settings becomes available.

[d] Due to increased glecaprevir exposures when given with EVG/c, monitoring for hepatotoxicity is recommended until more safety data in clinical settings becomes available.

Refer to full prescribing information for a complete list of potential DDIs and dosage adjustments of concomitantly prescribed medications.[9,27,40-42]

- Elbasvir/grazoprevir prescribing information
- Glecaprevir/pibrentasvir prescribing information
- Ledipasvir/sofosbuvir prescribing information
- Sofosbuvir/velpatasvir prescribing information
- Sofosbuvir/velpatasvir/voxilaprevir prescribing information

Appendix B: HCV Resistance Genotyping

The Public Health Reference Laboratory (PHRL) at the VA Palo Alto and commercial laboratories provide resistance genotyping of the HCV NS3/4A and NS5A genes for Veteran patients. These tests determine the presence of known drug resistance-conferring mutations in the NS3/4A and/or NS5A genes of plasma-derived virus by RT-PCR and population-based sequencing methods. The information from these tests can be used to determine the best drug choices for selecting a treatment regimen for a given patient. The decision to request resistance genotyping on one or both genes depends on genotype, the known prevalence of baseline (naturally occurring) resistance mutations, treatment history, and projected drug options for a given patient (see Table 5, "Recommendations for Performing Pre-Treatment RAS Testing").

Please note that PHRL will perform resistance genotyping only on gene-genotype combinations for which there are FDA-approved drug classes (e.g., there are no NS3/4A PIs that are FDA approved for GT3, thus, NS3/4A resistance genotyping for HCV GT3 will not be performed). In addition, resistance interpretations will be provided only for drugs that are FDA approved for a given genotype (e.g., resistance genotyping of the NS5A gene will be performed in HCV GT3 patients for DCV and VEL [FDA-approved indications]).

Ordering the Test(s)

Electronic ordering and reporting through VISTA (with LEDI connections) are the ideal ordering and reporting methods of choice. This method places the resistance genotyping results directly in the patient's medical record. It is understood that it takes time to generate this pathway, and while PHRL prefers the VISTA/LEDI method, a backup manual option is available for those sites that wish to have specimens tested but have not yet completed VISTA/LEDI setup. Regardless of which method for ordering will be used, an HCV team member from the local site will need to contact that site's lab supervisor to initiate the process and collaborate. CLIA and CAP certifications can be sent upon request.

1. **For VISTA/LEDI Ordering/Reporting:** The requesting site's Laboratory Information Manager (LIM) should contact PHRL's LIM to exchange File 60s and validate the LEDI connections. Once connected, VISTA-generated Shipping Manifests will be sent along with the specimens. When ordering in CPRS, there should be a pop-up window asking for "Relevant Clinical Information" – here is where the patient's HCV genotype/subtype must be entered. **This is important for HCV resistance testing since each HCV genotype/subtype requires different reagents**. **Failure to provide genotype/subtype information will result in delay of testing until the information is provided.** Resistance genotyping results will be entered into VISTA, transferred by LEDI, and will then be viewable at the requesting site's VISTA or CPRS.
2. **For Manual Ordering/Reporting:** Specimens can be submitted to PHRL with a paper manifest. Attached is PHRL's Shipping Manifest, which contains the shipping/contact information and fields to enter patient/sample information. Specify the HCV resistance test (i.e., NS3/4A and/or NS5A) needed. **The "genotype/subtype" field is important for HCV resistance testing since each HCV genotype/subtype requires different reagents. Failure to provide genotype/subtype information**

will result in delay of testing until the information is provided. Result reports will be sent to the site designee(s) by encrypted email.

3. **Specimens can be submitted to commercial laboratories.** Check with your facility's Laboratory Service to determine which laboratories provide resistance testing.

Specimens

1. The requesting site should provide 2 x 2 mL frozen EDTA plasma (lavender top) on dry ice or frozen ice packs for each patient (regardless of whether NS3 and/or NS5A is being requested) by overnight shipping. After collection, the plasma specimens can be held indefinitely, when frozen, until shipping.
2. If File 60 is not in place, the local site's HCV team will need to work with the site's lab supervisor to determine how the CPRS order should be entered by providers (e.g., "miscellaneous" with requested tests specified in comments section, versus specific test entry).
3. HCV RNA levels for submitted specimens must be >1,000 IU/mL.
4. Results should be available approximately 10-14 working days after the specimen is received at PHRL.

Laboratory Procedures for Isolation and Storage of Plasma for NS3 or NS5A Resistance Genotyping

Materials and Reagents

1. Vacutainer Tubes with EDTA, with or without gel plug, at least 6 mL draw volume. **NOTE**: Vacutainers containing heparin are NOT suitable for molecular testing; heparin interferes with DNA polymerases used in molecular tests.
2. Polypropylene **screw-capped** freezer vials (e.g., Nunc 1.8 mL cryovials, VWR cat #66021-987, or equivalent). **Please do not use slip-top (unthreaded) tubes.**
3. Sterile serological pipets or transfer pipets.

Procedure

1. Collect blood into the Vacutainer using standard venipuncture techniques.
2. After collection, invert the tubes 8-10 times to ensure proper mixing of the anticoagulant and blood sample.
3. Centrifuge the Vacutainer at 800-1,000 x g for 10 minutes at room temperature. Tubes with gel barriers should be centrifuged at 1,000-1,300 x g for 10 minutes at room temperature. **WARNING:** Excessive centrifuge speed (over 1,300 x g) may cause tube breakage, injury, and exposure to blood.
4. After centrifugation, collect the plasma with a pipet, taking care to avoid aspirating any part of the cell layer, and transfer plasma into AT LEAST TWO appropriately labeled cryovials (1.0-1.8 mL per vial).
5. Store at –20°C to –80°C.
6. Ship overnight with specimen shipment manifest to PHRL on dry ice or frozen ice packs.

Figure 2. Sample Specimen Shipment Manifest

U.S. Department of Veterans Affairs

VA Palo Alto Public Health Reference Laboratory
Specimen Shipment Manifest

From:	Institution/Site:	**SHIP TO:**	Public Health Reference Laboratory
	Ordering Physician:		VA Palo Alto Health Care System
	Name of person completing form:		Bldg MB4 Room 418
	Address:		3801 Miranda Ave
	Location (city, state, zipcode):		Palo Alto, CA 94304
	Phone:		650-493-5000 x69294
	Fax:		650-858-3978 (FAX)
	E-mail:		V21PHRL@va.gov

DATE SHIPPED	TOTAL NUMBER OF SPECIMENS	TRACKING NUMBER

Sample ID	Patient Name	SSN or Patient ID	Date of Birth	Date & Time Collected	Sample Type	Subtype/Genotype (if applicable)	Test Requested

E-MAIL or FAX THESE PAGES ON THE DAY OF SHIPMENT. Please include a copy of these pages with specimens.

For questions or problems, please contact Mark Winters (650) 493-5000 x69294; mark.winters@va.gov

Appendix C: Sample Resistance Test Reports

Figure 3. Sample Test Report for HCV NS3 Resistance

Laboratory Test Report

Patient: **SSN:**
DOB: **Ordering Physician:**
Collection Date: **Ordering Site:**
Site Accession No: PHRL 16 97 **Local Lab ID:**

Received Date/Time: Dec 30,2016@13:11 **Sample Type:** plasma
Test Performed: HCV NS3 Resistance Genotype[a] **Test Date:** Jan 3,2017
Results File Name: P16-8022_1aNS3 nucleo.fasta **Report Date:** Jan 9,2017@10:01
Results:

HCV Protease Inhibitor:	Resistance Mutation(s)[b]:	Resistance Predicted[c]:
boceprevir	none detected	no
simeprevir	none detected	no
paritaprevir	none detected	no
grazoprevir	none detected	no

All amino acid differences between patient strain and reference strain[d]: I18V, T40A, S91A, L153I, N174S

Comments: genotype 1a; codons 1 to 182 analyzed **Reference Range:** none detected

Note:

[a] The test uses RT-PCR and population-based sequencing to determine the consensus nucleotide and resulting amino acid sequence of the NS3 gene. This test was developed and its performance characteristics determined by PHRL. The U.S. FDA has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions.

[b] Known resistance associated mutations include:
boceprevir: V36A/M, T54A/S, V55A, R155K/T, A156S/T/V (Victrelis package insert)
simeprevir: Q80K, S122R, R155K, D168A/V/E (Olysio package insert)
paritaprevir: F43L, Q80K, R155G/S/K, A156T, D168A/F/E/H/N/V/Y
grazoprevir: V36L/M, Y56H, V107I, R155I/K, A156G/T/V, V158A, D168A/G/N/V/Y

[c] Predicted resistance is determined from codon changes that are known to confer a loss of susceptibility in vitro, or from treatment emergent codon changes in clinical trials, as described in each drug's package insert.

Figure 4. Sample Test Report for HCV NS5A Resistance

U.S. Department of Veterans Affairs

Page 1 of 2

Laboratory Test Report

Patient: **SSN:**
DOB: **Ordering Physician:**
Collection Date: **Ordering Site:**
Site Accession No: MOL 1220 82 **Local Lab ID:**

Received Date/Time: Dec 30,2016@13:12 **Sample Type:** plasma
Test Performed: HCV NS5A Resistance Genotype[a] **Test Date:** Jan 3,2017
Results File Name: P16-8037_1b5A nucleo.fasta **Report Date:** Jan 9,2017@10:33
Results:

NS5A Inhibitor:	Resistance Mutation(s)[b]:	Resistance Predicted[c]:
daclatasvir	Y93H	YES
ledipasvir	L31M, Y93H	YES
ombitasvir	Y93H	YES
elbasvir	Y93H	YES
velpatasvir	L31M, Y93H	YES

All amino acid differences between patient strain and reference strain[d]: T17S, L31M, F37L, T56V, T64A, Y93H, V119A, M133I, V138L, L176Q, A197T, R246H

Comments: genotype 1b; codons 1 to 260 analyzed **Reference Range:** none detected

Note:

Appendix D: Recommendations for Hepatitis B Viral Infection Testing and Monitoring

Recommendations for Hepatitis B Viral Infection Testing and Monitoring among HCV-Infected Veterans Being Considered for DAA Treatment

October 2016 - VA HIV, Hepatitis, and Public Health Pathogens Program

Background:

1. Reactivation of hepatitis B virus (HBV) is defined as an increase in hepatitis B viral replication (HBV DNA) associated with an increase in liver damage. Reactivation is detected by an increase in HBV DNA level or HBsAg detection (in someone previously HBsAg (-) and anti-HBc (+)), and is usually associated with an increase in ALT, with or without an increase in bilirubin.
2. In HCV-infected patients who are ready to start DAA treatment, those who are also HBsAg (+) are at the **highest risk** for HBV reactivation and should be initiated on HBV treatment prior to starting DAA therapy. Consideration can also be given to initiating HBV treatment in Childs-Pugh B and C cirrhotics who are anti-HBc positive only, but HBsAg negative.
3. HBV reactivation is very rare among HBsAg (-) and anti-HBc (+)patients who are not immunocompromised. Only three cases have been reported to date, although one of them developed fulminant hepatic failure requiring a liver transplantation.
4. Reactivation of HBV usually **occurs within 4-8 weeks** after starting DAAs (mean = 52 days) but can occur at any time, even after DAA treatment has completed.

Baseline assessment for HBV

1. History
    a. Is patient known to have documented HBV or documented immunity from prior vaccination? If unknown, check HBV serology and immunize if necessary. Each patient should have documented HBV serology prior to HCV treatment.
    b. Assessment for cirrhosis; patients with cirrhosis are at a higher risk for decompensation if a flare occurs.
2. HBV serologic tests
    a. **HBsAg** (hepatitis B surface antigen)
    b. **anti-HBc total** (hepatitis B core antibody, also known as HBcAb)
    c. **anti-HBs** (hepatitis B surface antibody, also known as HBsAb)
    d. HBV DNA (not required in those with anti-HBs)
3. Other baseline laboratory tests
    a. Liver Panel (albumin, total protein, total bilirubin, direct bilirubin, alkaline phosphatase, ALT, AST)
    b. CBC/platelets
    c. INR
    d. hepatitis A antibody (total)
    e. HIV

Table 1: Interpretation of HBV Serologic Tests and Recommendations for Monitoring and Treatment during DAA Treatment

Tests	Results	Interpretation	Next Steps/ Monitoring	Treatment
HBsAg **anti-HBc** **anti-HBs**	Negative Negative Negative	Susceptible to HBV infection	Immunize* for HBV	**HCV:** Start DAA treatment. **HBV:** Immunize*; DAA treatment can be given concurrently with immunization.
HBsAg **anti-HBc** **anti-HBs**	Negative Negative Positive	Immune due to HBV vaccination	No additional HBV monitoring	**HCV:** Start DAA treatment. **HBV:** No HBV treatment.
HBsAg **anti-HBc** **anti-HBs**	Negative Positive Positive	Recovered from HBV; immune due to natural infection	Monitor **ALT** while on DAA treatment at weeks 4, 8, and 12 and at 12 weeks post-treatment; if ALT does not normalize or rises on therapy, check HBV DNA and HBsAg	**HCV:** Start DAA treatment. **HBV:** No HBV treatment. If HBV DNA detectable, treat with entecavir or tenofovir**
HBsAg **anti-HBc** **anti-HBs**	Positive Positive Negative	Chronic HBV	Check HBV DNA, HBeAg and anti-HBe Monitor ALT while on DAA at weeks 4, 8, and 12, and at 12 weeks post-treatment. Monitor HBV DNA every 3 months.	**HCV and HBV:** Start DAA concurrently with or after starting HBV treatment** After completing DAA treatment, reassess need for continued HBV therapy per AASLD HBV guidelines*** or consult with an expert.
HBsAg **anti-HBc** **anti-HBs**	Negative Positive Negative	Possible interpretations: 1. Distantly immune and test not sensitive enough to detect very low level of anti-HBs in serum 2. Susceptible, with a false positive anti-HBc 3. Recovering from acute HBV infection 4. Undetectable level of HBsAg present in the serum but is actually chronically infected	Check HBsAg or HBV DNA (one or both of these should be performed within the prior 12 months); note: this should ***not*** delay start of DAA treatment and can be ordered at start of DAA treatment. Monitor ALT at weeks 4, 8, and 12 and at 12 weeks post-treatment; if ALT does not normalize or rises on therapy, check HBV DNA and HBsAg. Strongly consider checking HBV DNA between weeks 4-8 of DAA treatment (**particularly in cirrhotics**). If HBV DNA is detectable, check HBsAg and HBeAg	**HCV:** Start DAA treatment **HBV:** HBV treatment not routinely recommended ***However:*** a) If HBV DNA is detectable or HBsAg is positive prior to DAA treatment ***or*** becomes detectable during DAA treatment, initiate HBV treatment**. b) Consider HBV prophylaxis in patients with decompensated cirrhosis (CTP class B and C) regardless of HBV DNA or HBsAg status c) For patients on an immunosuppressant agent HBV treatment may be indicated. After completing DAA treatment, reassess need for continued HBV therapy per AASLD HBV guidelines*** or consult with an expert.
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	Positive Positive Positive Negative	Acute hepatitis B infection	Recheck HBsAg, anti-HBc and anti-HBs in six months. Recheck liver panel in 6 months	**HCV:** If possible, wait 6 months for HBV to recover. **HBV:** Symptomatic support (no specific HBV treatment). Monitor for at least 6 months to determine recovery (vs. chronic infection).

* Hepatitis B vaccine (e.g., Engerix-B, Recombivax HB or TwinRx), series of 3 doses; recheck anti-HBs ≥1 month after the third vaccination

**HBV treatment: entecavir 0.5mg-1mg/day or tenofovir 300 mg/day. In HIV/HBV/HCV-coinfected patients, the antiretroviral regimen should include tenofovir, or if not tolerated, entecavir should be added during DAA therapy.

*** AASLD Guidelines for Treatment of Chronic Hepatitis B

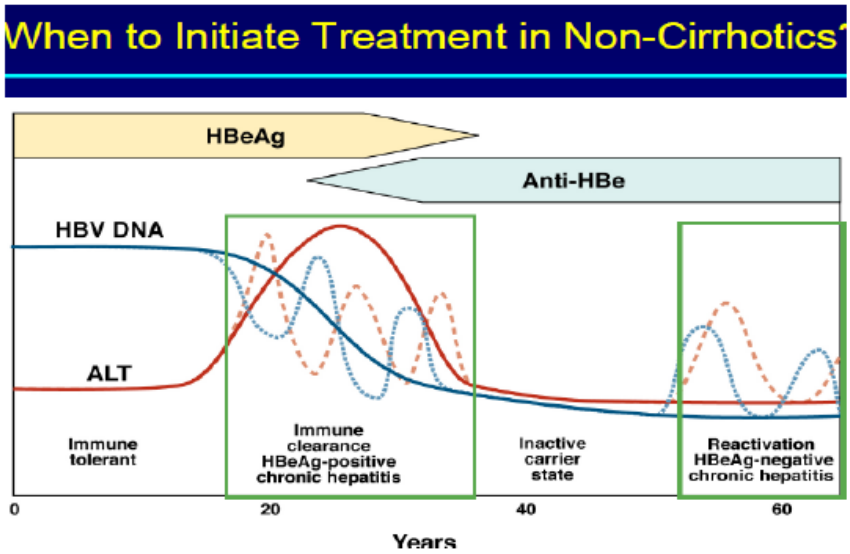
Table 2. Summary of AASLD HBV Treatment Criteria

ALT*	HBV DNA (IU/mL)	HBeAg	Other factors which should be present	Treatment Recommended per AASLD HBV Guideline**
≥ 2x ULN	>2,000	negative		yes
≥ 2x ULN	>20,000	positive		yes
>ULN but <2x ULN	>2,000	negative	Evidence of histological disease	yes
>ULN but <2x ULN	>20,000	positive	Evidence of histological disease	yes
>ULN but <2x ULN	<2,000 <20,000	negative positive	Any one of the following: Age>40 Family history of HCC Previous HBV therapy Extrahepatic manifestations	yes
Normal or elevated	>2,000	negative or positive	Cirrhosis	yes
Normal or elevated	>100,000	positive or negative	Age>40	yes
Normal or elevated	positive or negative	positive or negative	Immunosuppressants	yes
Normal	Any detectable	positive or negative		No (Immune Tolerant)

*ULN for men = 30 U/L; ULN for women = 19 U/L

**HBV treatment: entecavir 0.5mg-1mg/day or tenofovir 300 mg/day

AASLD HBV guidelines available at: www.aasld.org/sites/default/files/guideline_documents/hep28156.pdf



Source: Anna Lok, DDW 2016 (Yapali S, et al. Clin Gastro Hepatol 2014)

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