Chronic Hepatitis C Virus (HCV) Infection: Treatment Considerations

from the Department of Veterans Affairs National Hepatitis C Resource Center Program and the National Viral Hepatitis Program in the Office of Patient Care Services

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Frequently Used Abbreviations

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

CTP = Child-Turcotte Pugh	PEG-IFN = peginterferon
DAA = direct-acting antiviral	PTV = paritaprevir
DCV = daclatasvir	RAP = resistance-associated polymorphism
DDI = drug-drug interaction	RBV = ribavirin
EBR = elbasvir	RTV = ritonavir
GT= genotype	SVR = sustained virologic response
GZR = grazoprevir	SMV = simeprevir
HCC = hepatocellular carcinoma	SOF = sofosbuvir
LDV = ledipasvir	
OBV = ombitasvir	

I. What's New and Updates/Changes

This revision (March 28, 2016) incorporates updates to treatment regimens for chronic hepatitis C virus (HCV) infection, genotype 1, 2, 3, or 4. The Introduction has been revised to include a new section titled "Interpretation of Resistance Associated Polymorphisms." Additional revisions include updates on drug-drug interactions to provide clinicians with guidance on the concomitant use of HCV drugs and other drugs, including HIV antiretroviral agents (Table 28 and Table 29). Information on HCV resistance genotyping and sample reports have been included (Appendices B and C). The Panel continues to recommend that HIV/HCV-coinfected patients receive the same HCV antiviral regimens as HCV-monoinfected patients.

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 March 28, 2016**. 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.*

HCV GT	Treatment History	Cirrhosis Status	Treatment Option(s) (in alphabetical order)	Alternative Option(s) (in alphabetical order)
GT1	Naïve, HCV RNA <6 million IU/mL, HCV-monoinfected	Non-cirrhotic	• **LDV/SOF** x 8 weeks	
GT1	Naïve or Experienced *(Prior PEG-IFN/RBV only)*	Non-cirrhotic **OR** cirrhotic, CTP A	• **EBR/GZR** o If GT1a, test for NS5A RAPs prior to treatment. ▪ *GT1a **without** baseline NS5A polymorphisms:* 12 weeks treatment ▪ *GT1a **with** baseline NS5A polymorphisms:* Add RBV; 16 weeks treatment ▪ *GT1b:* 12 weeks treatment • **LDV/SOF** x 12 weeks (add RBV for treatment-experienced cirrhotic patients; may consider adding RBV in other situations; refer to Table 6 for details) • **OBV/PTV/RTV + DSV** x 12 weeks; o GT1a: add RBV (may consider 24 weeks in cirrhotics or prior null responders; refer to Table 6 for details); o GT1b: RBV not required	If GT1a, treatment-experienced, cirrhotic and RBV intolerant or contraindicated: LDV/SOF x 24 weeks **
GT1	Naïve or Experienced *(Prior PEG-IFN/RBV only)*	Cirrhotic, CTP B, C	• **LDV/SOF + RBV** (600 mg/day and increase by 200 mg/day every 2 weeks only as tolerated) x 12 weeks	
GT1	Experienced *(Prior NS3/4A inhibitor + PEG-IFN + RBV, or prior SOF + RBV ± PEG-IFN)*	Non-cirrhotic **OR** Cirrhotic, CTP A	• **EBR/GZR + RBV** *NOT FDA approved in prior SOF + RBV ± PEG-IFN treatment failures* o If GT1a, test for NS5A RAPs prior to treatment. ▪ *GT1a **without** baseline NS5A polymorphisms:* 12 weeks treatment ▪ *GT1a **with** baseline NS5A polymorphisms:* 16 weeks treatment ▪ *GT1b:* 12 weeks treatment • **LDV/SOF + RBV** x 12 weeks; *NOT FDA approved in prior SOF + RBV ± PEG-IFN treatment failures*	If GT1a and RBV intolerant or contraindicated: LDV/SOF x 24 weeks **

HCV GT	Treatment History	Cirrhosis Status	Treatment Option(s) (in alphabetical order)	Alternative Option(s) (in alphabetical order)
GT1	Experienced *(Prior NS3/4A inhibitor + PEG-IFN + RBV, or prior SOF + RBV ± PEG-IFN)*	Cirrhotic, CTP B, C	• **LDV/SOF + RBV** (600 mg/day and increase by 200 mg/day every 2 weeks only as tolerated) x 12 weeks; *NOT FDA approved in prior SOF + RBV ± PEG-IFN treatment failures*	
GT1	Experienced *(Prior NS5A-containing regimen)*	Non-cirrhotic or Cirrhotic	• Test for RAPs to NS5A prior to re-treatment (see Section XV, Appendix B). Consult with an expert based on results (see Section XIV, Resources).	
GT2	Naïve	Non-cirrhotic	• **SOF + RBV** x 12 weeks	• DCV + SOF x 12 weeks; *NOT FDA approved* • LDV/SOF x 12 weeks; *NOT FDA approved*
GT2	Naïve	Cirrhotic	• **SOF + RBV** x 16 weeks; *FDA approved for 12 weeks*	Consult an expert (see Section XIV, Resources)
GT2	Experienced *(Prior PEG-IFN/RBV only)*	Non-cirrhotic or Cirrhotic	• **SOF + RBV** x 16 weeks; *FDA approved for 12 weeks*	Non-cirrhotic: • DCV + SOF x 12 weeks; *NOT FDA approved* • LDV/SOF x 12 weeks; *NOT FDA approved* Cirrhotic: Consult an expert (see Section XIV, Resources)
GT3	Naïve	Non-cirrhotic	• **LDV/SOF + RBV** x 12 weeks; *NOT FDA approved*	• DCV + SOF x 12 weeks • SOF + PEG-IFN + RBV x 12 weeks; *NOT FDA approved* • SOF + RBV x 24 weeks
GT3	Naïve	Cirrhotic	• **DCV + SOF + RBV** x 12 weeks in CTP A, or 12-24 weeks in CTP B and C	• SOF + PEG-IFN + RBV x 12 weeks; *NOT FDA approved*
GT3	Experienced *(Prior PEG-IFN/RBV only)*	Non-cirrhotic	• **LDV/SOF + RBV** x 12 weeks; *NOT FDA approved*	• DCV + SOF x 12 weeks • SOF + PEG-IFN + RBV x 12 weeks; *NOT FDA approved* • SOF + RBV x 24 weeks
GT3	Experienced *(Prior PEG-IFN/RBV only)*	Cirrhotic	• **DCV + SOF + RBV** x 12 weeks in CTP A, or 12-24 weeks in CTP B and C patients	If RBV intolerant or contraindicated: DCV + SOF x 24 weeks**
GT4	Naïve	Non-cirrhotic **OR** Cirrhotic, CTP A	• **EBR/GZR** x 12 weeks • **LDV/SOF** x 12 weeks • **OBV/PTV/RTV + RBV** x 12 weeks; *DSV not needed*	
GT4	Experienced *(Prior PEG-IFN/RBV only)*	Non-cirrhotic **OR** Cirrhotic, CTP A	• **EBR/GZR + RBV** x 16 weeks • **LDV/SOF** x 12 weeks • **OBV/PTV/RTV + RBV** x 12 weeks; *DSV not needed*	

HCV GT	Treatment History	Cirrhosis Status	Treatment Option(s) (in alphabetical order)	Alternative Option(s) (in alphabetical order)
GT4	Naïve or Experienced *(Prior PEG-IFN/RBV only)*	Cirrhotic, CTP B, C	• **LDV/SOF** x 12 weeks	

* Testing of HCV resistance-associated polymorphisms 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).

** Contraindication and/or intolerance to RBV: Contraindication is defined as history of significant or unstable cardiac disease, known pregnancy, positive pregnancy test result, and men with a female partner who is pregnant or plans to become pregnant, known hypersensitivity reaction, and/or significant anemia (i.e., symptomatic or baseline hemoglobin <10 g/dL) and/or history of significant adverse events with a previous RBV-containing regimen.

Dosages:

- DCV 60 mg orally daily (Note: 30 mg daily with strong CYP3A inhibitors or 90 mg daily with moderate CYP3A inducers, see Appendix A, Table 28);
- EBR/GZR (50/100 mg): 1 tablet orally daily; LDV/SOF (90/400 mg): 1 tablet orally daily;
- OBV/PTV/RTV (12.5/75/50 mg): 2 tablets once daily in the morning with food + DSV 250 mg orally twice daily in the morning and in the evening with food;
- PEG-IFN alfa-2a 180 mcg subcutaneously weekly or PEG-IFN alfa-2b 1.5 mcg/kg subcutaneously weekly;
- RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food; SOF 400 mg orally daily

Note: EBR/GZR, LDV/SOF, OBV/PTV/RTV + DSV or SOF should not be used in reduced dosages or restarted if discontinued. DCV, DSV, or SOF should not be used as monotherapy.

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 significantly decreases the risk of disease progression and the development of 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 within VHA 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), Infectious Diseases Society of America (IDSA), and International Antiviral Society-USA (IAS-USA) 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).[1] 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 VHA National Viral Hepatitis Program in the VHA Office of Patient Care Services. Additional resources pertaining to the care of the HCV-infected patient are available at the VA 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 December 8, 2015.[1]

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.[2-4] 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 PEG-IFN and RBV 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.[5] 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

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 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 and familiar with 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., omeprazole, 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. 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, telemedicine, or the VHA HIV/HCV Clinical Consultation Service (hepatitis C consultation: 1-844-437-4636; HIV consultation: 1-800-933-3413). Furthermore, trained and supervised advanced practice nurses, nurse practitioners, physician assistants, or clinical pharmacists can independently evaluate and manage patients receiving HCV antiviral therapy under a supervised scope of practice. 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. The supervising physician does not need to be co-located with the mid-level provider or pharmacist but should be available for consultation by phone, email, or the electronic medical record system (i.e., Computerized Patient Record System [CPRS]).

Principles for patient selection for HCV treatment

All patients with chronic HCV who do not have medical contraindications are potential candidates for antiviral treatment. 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) have less urgency for treatment in the short term, but should be informed of current treatments and the potential to cure HCV. Patients with mild liver disease (METAVIR F0-2)

and no extra-hepatic manifestations can be treated in the near term if the patient desires treatment and is otherwise a candidate for HCV treatment.

Ongoing substance use involving alcohol, illicit drugs, and marijuana, or participation in an opioid replacement program, should not be an automatic exclusion criterion for HCV treatment. 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 re-infection, and greater clinical urgency. 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, hepatocellular cancer not amenable to cure) 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 Compensated Cirrhosis for the Purpose of Identifying Treatment Candidates" 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 in whom HCC treatment is potentially curative, 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
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) (vaww.vistau.med.va.gov/VistaU/ccr/default.htm) is available at each VA facility and is accessible to HCV clinicians by request to the facility. Using the CCR, providers can generate facility-specific reports on the numbers and names of patients with HCV stratified by cirrhosis (See Table 16, "Diagnosis of Compensated Cirrhosis for the Purpose of Identifying Treatment Candidates"), genotype, prior treatment experience, and other clinical considerations. The availability and customizability of the information obtained from local CCR reports can optimize identification of patients with the most urgent need for treatment.

Pre-treatment evaluation

Before initiating antiviral therapy in a patient with chronic HCV, the information listed in Table 3 should be obtained.

Table 3. Pre-Treatment Evaluation

Essential pre-treatment information*
• HCV genotype (including subtype, e.g., 1a or 1b) • HCV RNA (quantitative viral load), preferably within the past 6 months • Clinical assessment for cirrhosis (refer to **Table 16**) • If cirrhotic, exclusion of hepatocellular carcinoma based on appropriate imaging study 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 • Documented use of two forms of birth control in patient and sex partners for whom a RBV-containing regimen is chosen

* For further guidance on pre-treatment assessment, refer to the *2012 Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office*. (www.hepatitis.va.gov/provider/guidelines/2012HCV-pretreatment-assessments.asp)[6]

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 treatment with DAA agents. For more information, see Section IX, Laboratory Monitoring on Use and Interpretation of HCV RNA Results.

Definitions of treatment response

- **Rapid virologic response (RVR):** undetectable HCV RNA at 4 weeks during treatment.
- **End-of-treatment response (ETR):** HCV RNA below lower limit of quantification (LLQ) at the end of treatment.
- **SVR_4:** HCV RNA below LLQ at 4 weeks after treatment completion.
- **SVR:** HCV RNA below LLQ at least 12 weeks after treatment completion.
- **Relapse:** HCV RNA below LLQ during treatment and/or at the end of treatment, but subsequent quantifiable HCV RNA following treatment cessation.
- **Partial response:** ≥2 $\log_{10}$ reduction from baseline HCV RNA at week 12, but virus remains detectable through week 24 or treatment end with PEG-IFN and RBV.
- **Non-response:** detectable HCV RNA throughout treatment.
- **Null-response:** <2 $\log_{10}$ reduction from baseline HCV RNA during PEG-IFN and ribavirin treatment.

Interpretation of resistance-associated polymorphisms

DAA efficacy may be affected by the presence of RAPs (also known as resistance-associated variants [RAVs]). RAPs are amino acid substitutions within a particular HCV protein that confer resistance to a DAA. RAPs exist at baseline in a minority of patients and emerge during treatment in most patients who fail to achieve SVR with DAA treatment. In clinical trials enrolling HCV GT1a-infected patients who received EBR/GZR for 12 weeks, SVR

rates were reduced when baseline (i.e., before treatment initiation) HCV NS5A RAPs (at amino acid positions 28, 30, 31, or 93) were present. In individuals with such RAPs, the addition of ribavirin and extending treatment to 16 weeks was required to achieve favorable SVR rates. In clinical trials enrolling HCV GT3-infected patients, SVR rates with DCV and SOF treatment were reduced in the presence of the Y93H NS5A RAP at baseline; in these patients, consider future treatment options unless urgent treatment is required. If needed, consult with an expert to weigh the risks versus benefits of treatment (see Section XIV, Resources).

In general, NS5A RAP 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 who may receive DCV. Patients who virologically fail DAA treatment usually have RAPs to one or more classes of DAAs (i.e., NS3/4A protease inhibitors, NS5A inhibitors, nucleoside and non-nucleoside NS5B polymerase inhibitors) and should undergo RAP testing for each of the drug classes being considered for re-treatment.

Testing for RAPs determines the presence of known drug resistance-conferring mutations in the NS3/4, NS5A, and NS5B genes of HCV and can be obtained by sending a plasma sample to the VHA Public Health Reference Laboratory (PHRL) at VA Palo Alto or a commercial laboratory (see Section XV, Appendix B). The information from these tests can be used to determine the optimal treatment regimen for a given patient. The decision to request RAP testing on one, two, or all three genes 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 4. Recommendations for Performing Pre-treatment RAP Testing

Patient Characteristics	DAA Agent to Be Considered*	Genotype	RAP Test: NS3/4	RAP Test: NS5A	RAP Test: NS5B
Treatment-naïve	**EBR/GZR**	GT1a	No	Yes	No
	DCV	GT3	No	Yes	No
	LDV/SOF	GT3	No	Consider	No
Failed PEG-IFN + RBV ± PI	**EBR/GZR**	GT1a	No	Yes	No
Failed Other DAA-containing Regimens	**LDV/SOF**	GT1a or 1b	No	Yes	Yes
	EBR/GZR	GT1a or 1b	Yes	Yes	No
	OBV/PTV/r + DSV	GT1a or 1b	Yes	Yes	Yes
	SMV + SOF	GT1a or 1b	Yes	No	Yes
	LDV/SOF	GT2	No	Yes	Yes
	DCV + SOF	GT2	No	Yes	Yes
	DCV + SOF	GT3	No	Yes	Yes

* RBV may be required as part of the regimen for patients who have failed prior treatment (see Section IV, Tables 6-7 and Genotype 1-Infected Patients Who Have Failed Treatment with DAA-Based Therapy).

IV. Chronic HCV Genotype 1 Infection

*Including HIV coinfection**

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

Key Points

- Selection of an appropriate regimen and treatment duration for patients with GT1 infection depends on subtype, stage of liver disease, baseline level of HCV viremia, prior treatment history, and concomitant medications.
- EBR/GZR or OBV/PTV/RTV + DSV should not be used in patients with moderate to severe hepatic impairment (CTP B and C).
- Baseline NS5A resistance testing is recommended in GT1a-infected patients prior to initiating EBR/GZR to determine the regimen and treatment duration. Specimens should be sent to the VHA Public Health Reference Laboratory (email V21PHRL@va.gov) or a commercial laboratory (see Section XV, Appendix B).
- Patients experiencing virologic failure with a DAA-containing regimen should have NS3, NS5A and NS5B resistance testing performed prior to re-treatment through the VHA Public Health Reference Laboratory (email V21PHRL@va.gov) or a commercial laboratory (see Section XV, Appendix B).

Table 5. **Treatment Regimens for GT1**

See Table 6 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, HCV-monoinfected non-cirrhotic patients with baseline HCV RNA <6 million IU/mL

- *LDV/SOF (90/400 mg/day): 1 tablet daily for 8 weeks*

Treatment-naïve or -experienced (prior PEG-IFN/RBV) patients without or with cirrhosis (CTP A)

- *EBR/GZR (50/100 mg): 1 tablet orally daily*
  - *GT1a without baseline NS5A polymorphisms: treat for 12 weeks*
  - *GT1a with baseline NS5A polymorphism: add RBV (in divided doses, with food) and treat for 16 weeks*
  - *GT1b: treat for 12 weeks*
- *LDV/SOF (90/400 mg/day) 1 tablet daily for 12 weeks; add RBV (in divided doses, with food) for treatment-experienced cirrhotic patients; may consider adding RBV in other situations (refer to Table 6 for details)*
- *OBV/PTV/RTV (12.5/75/50 mg): 2 tablets once daily in the morning with food + DSV (250 mg): 1 tablet twice daily (in the morning and in the evening with food) for 12 weeks; GT1a: add RBV (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses); may consider 24 weeks in cirrhotics or prior null responders (refer to Table 6 for details), GT1b: RBV not required.*

Table 5. **Treatment Regimens for GT1**

Treatment-experienced (prior NS3/4A inhibitor + PEG-IFN + RBV, or prior SOF + RBV ± PEG-IFN) patients without or with cirrhosis (CTP A)*

- *EBR/GZR (50/100 mg): 1 tablet orally daily and RBV (in divided doses, with food); NOT FDA approved in prior SOF + RBV ± PEG-IFN treatment failures*
  - *GT1a without baseline NS5A polymorphisms: treat for 12 weeks*
  - *GT1a with baseline NS5A polymorphism: treat for 16 weeks*
  - *GT1b: treat for 12 weeks*
- *LDV/SOF + RBV (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks; NOT FDA approved in prior SOF + RBV ± PEG-IFN treatment failures*

Treatment-naïve or -experienced (prior PEG-IFN/RBV, prior NS3/4A inhibitor + PEG-IFN + RBV, or prior SOF + RBV ± PEG-IFN) patients with cirrhosis (CTP B or C)*

- *LDV/SOF + RBV (600 mg/day and increase by 200 mg/day every 2 weeks only as tolerated) for 12 weeks; NOT FDA approved in prior SOF + RBV ± PEG-IFN treatment failures*

Treatment -experienced (prior NS5A-containing regimen) patients with or without cirrhosis*

- *Test for RAPs to NS5A prior to re-treatment (see Section XV, Appendix B); consult with an expert based on results (see Section XIV, Resources)*

*** There are minimal data on re-treatment of patients who failed a regimen containing an NS5A or NS5B inhibitor. Testing of HCV resistance-associated polymorphisms can be performed through the VHA Public Health Reference Laboratory (email V21PHRL@va.gov) or a commercial laboratory (see Section XV, Appendix B). Consult an expert before re-treating (see Section XIV, Resources).**

Table 6. Treatment Regimens and SVR Rates -- Treatment-Naive Patients*

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 any 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 ***HCV RNA <6 million IU/mL, HCV monoinfection***	Non-cirrhotic	**LDV/SOF**	8 weeks	A-I	97% (119/123, – RBV)[7]	Relapse rates were higher with 8 weeks vs. 12 weeks of treatment if baseline HCV RNA ≥6 million IU/mL: 10% (9/92) vs. 1% (1/85), respectively.[7]
Naïve, GT1 ***GT1a without NS5A polymorphisms*** ***GT1a with NS5A polymorphisms*** **GT1b**	Non-cirrhotic	 **EBR/GZR** **EBR/GZR + RBV** **EBR/GZR**	 12 weeks 16 weeks 12 weeks	A-I	 98% (441/450)[8] 100% (6/6)[8] 99% (129/131)[9]	**If GT1a, test for NS5A polymorphisms**** See Section XV, Appendix B for information on testing for NS5A RAPs. GT1a population incudes treatment-experienced cirrhotic patients.[8] 78% were non-cirrhotics, 22% were cirrhotic.[9] See monitoring recommendations below***
Naïve, GT1	Non-cirrhotic	**LDV/SOF**	12 weeks	A-I	96% (82/85, – RBV)[7] 99% (179/180, – RBV)[10] 97% (178/184, + RBV)[10]	
Naïve, GT1 **GT1a** **GT1b**	Non-cirrhotic	 **OBV/ PTV/RTV + DSV + RBV** **OBV/ PTV/RTV + DSV**	 12 weeks 12 weeks	A-I	 91% (182/202, – RBV)[11] 96% (403/420, + RBV)[11] 99% (207/209, – RBV)[12] >99% (209/210, + RBV)[12]	Pooled data for GT1a from SAPPHIRE-I and -II, PEARL IV, TURQUOISE-II[11] Monitor liver function tests and monitor for hepatic decompensation (see Section IX, Laboratory Monitoring).
Naïve, GT1 ***GT1a without NS5A polymorphisms*** ***GT1a with NS5A polymorphisms*** **GT1b**	Cirrhotic, CTP A	 **EBR/GZR** **EBR/GZR + RBV** **EBR/GZR**	 12 weeks 16 weeks 12 weeks	A-I	 98% (441/450)[8] 100% (6/6)[8] 99% (129/131)[9]	**If GT1a, test for NS5A polymorphisms**** See Section XV, Appendix B for information on testing for NS5A RAPs. GT1a population incudes treatment-experienced non-cirrhotic patients.[8] 78% were non-cirrhotics, 22% were cirrhotic.[9] See monitoring

Treatment history & HCV genotype	Cirrhosis status	Regimen	Duration	Evidence grade	SVR% (N/N) in clinical trials	Comments
						recommendations below***
Naïve, GT1	Cirrhotic, CTP A	**LDV/SOF** (may consider adding RBV)	12 weeks	A-I	94% (32/34, – RBV)[10] 100% (33/33, + RBV)[10]	
Naïve, GT1 **GT1a** **GT1b**	Cirrhotic, CTP A	 **OBV/PTV/ RTV + DSV + RBV** **OBV/PTV/ RTV + DSV**	 12 weeks 12 weeks	A-I	 92% (59/64, + RBV)[13] 100% (27/27, – RBV)[14]	GT1a: SVR 95% (53/56) with 24 weeks.[13] Consider extending to 24 weeks for slow on-treatment virologic response on a case-by-case basis. Monitor liver function tests and monitor for hepatic decompensation (see Section IX, Laboratory Monitoring).
Naïve, GT1	Cirrhotic, CTP B,C	**LDV/SOF + RBV**	12 weeks	B-II	CTP B: 87% (26/30)[15] CTP C: 86% (19/22)[15]	LDV/SOF + RBV for 24 weeks: CTP B: 89% (24/27)[15]; CTP C: 87% (20/23)[15] RBV initiated at 600 mg/day, increase by 200 mg/day every 2 weeks only as tolerated.[15] Includes treatment-naïve and -experienced patients.[15]

* SVR rates in patients with HIV/HCV coinfection were similar to those found with HIV monoinfected patients; data are not represented in the above Table. Refer to Section XII, Groups with Special Considerations for Therapy, on HCV treatment in patients with HIV/HCV coinfection and Appendix A, Tables 27 and 28.

** NS5A polymorphisms at amino acid positions 28, 30, 31, or 93. Testing of HCV RAPs can be performed through the VHA Public Health Reference Laboratory (email V21PHRL@va.gov) or a commercial laboratory (see Section XV, Appendix B).

*** 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).

Study references: ION-3[7], SOLAR-1[15], ION-2[17], C-EDGE[9,16], SIRIUS[18], C-SALVAGE,[19] PEARL-III[12], TURQUOISE-II[13], TURQUOISE-III[14]

Dosages:

EBR/GZR (50/100 mg): 1 tablet orally daily

LDV/SOF (90/400 mg): 1 tablet orally daily

OBV/PTV/RTV (12.5/75/50 mg): 2 tablets once daily in the morning with food + DSV 250 mg orally twice daily (in the morning and in the evening with food)

RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food

Note: EBR/GZR, LDV/SOF or OBV/PTV/RTV + DSV should not be used in reduced dosages or restarted if discontinued. Dasabuvir should not be used as monotherapy.

Table 7. Genotype 1: Treatment Regimens and SVR Rates – Treatment-Experienced Patients*

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 any 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 *(Prior PEG-IFN/RBV only)*	Non-cirrhotic			A-II		**If GT1a, test for NS5A polymorphisms**** See Section XV, Appendix B for information on testing for NS5A RAPs.
GT1a without NS5A polymorphisms		**EBR/GZR**	12 weeks		98% (441/450)[8]	GT1a population incudes treatment-experienced and cirrhotic patients.[8]
GT1a with NS5A polymorphisms		**EBR/GZR + RBV**	16 weeks		100% (6/6)[8]	65% were non-cirrhotic; 34% cirrhotic.[16]
GT1b		**EBR/GZR**	12 weeks		100% (35/35)[16]	See monitoring recommendations below***
Experienced, GT1 *(Prior PEG-IFN/RBV only)*	Non-cirrhotic	**LDV/SOF (may consider adding RBV)**	12 weeks	A-I	95% (83/87, – RBV)[17] 100% (89/89, + RBV)[17]	GT1a population includes 46-61% who failed boceprevir- or telaprevir-based therapy.[17]
Experienced, GT1 *(Prior PEG-IFN/RBV only)*	Non-cirrhotic			A-I		Pooled data for GT1a from SAPPHIRE-I and -II, PEARL IV, TURQUOISE-II[11]
GT1a		**OBV/PTV/RTV + DSV + RBV**	12 weeks		94-100% (+ RBV)[11]	Monitor liver function tests and monitor for hepatic decompensation (see Section IX, Laboratory Monitoring).
GT1b		**OBV/PTV/RTV + DSV**	12 weeks		100% (91/91, – RBV)[12] 97% (85/88, + RBV)[12]	
Experienced, GT1 *(Prior PEG-IFN/RBV only)*	Cirrhotic, CTP A			A-II		**If GT1a, test for NS5A polymorphisms**** GT1a population incudes treatment-naïve and non-cirrhotic patients.[8]
GT1a without NS5A polymorphisms		**EBR/GZR**	12 weeks		98% (441/450)[8]	65% were non-cirrhotic; 34% cirrhotic.[16]
GT1a with NS5A polymorphisms		**EBR/GZR + RBV**	16 weeks		100% (6/6)[8]	See monitoring recommendations below***
GT1b		**EBR/GZR**	12 weeks		100% (35/35)[16]	
Experienced, GT1 *(Prior PEG-IFN/RBV only)*	Cirrhotic, CTP A	**LDV/SOF + RBV**	12 weeks	B-II	96% (74/77)[18]	SVR 97% (75/77) with LDV/SOF x 24 weeks.[18]

Treatment history & HCV genotype	Cirrhosis status	Regimen	Duration	Evidence grade	SVR% (N/N) in clinical trials	Comments
Experienced, GT1 *(Prior PEG-IFN/RBV only, if prior relapse or partial responder)* **GT1a** **GT1b**	Cirrhotic, CTP A	**OBV/PTV/RTV + DSV + RBV** **OBV/PTV/RTV + DSV**	12 weeks 12 weeks	A-I	Relapser: 93% (14/15, + RBV)[13] Partial Responder: 100% (11/11, + RBV)[13] 100% (33/33, – RBV)[14]	OBV/PTV/RTV + DSV + RBV for 24 weeks: SVR 100% in relapsers (13/13) and partial responders (10/10)[13] Extend treatment to 24 weeks in prior null responders. Consider extending to 24 weeks for slow on-treatment virologic response. Monitor liver function tests and monitor for hepatic decompensation (see Section IX, Laboratory Monitoring).
Experienced, GT1 *(Prior PEG-IFN/RBV only)*	Cirrhotic, CTP B,C	**LDV/SOF + RBV**	12 weeks	B-II	CTP B: 87% (26/30)[15] CTP C: 86% (19/22)[15]	LDV/SOF + RBV for 24 weeks: CTP B: 89% (24/27)[15] CTP C: 87% (20/23)[15] RBV initiated at 600 mg/day and increased by 200 mg/day every 2 weeks only as tolerated. SVR rates include treatment-naïve and treatment-experienced patients.[15]
Experienced, GT1 *(Prior NS3/4A inhibitor + PEG-IFN + RBV, or SOF + RBV ± PEG-IFN therapy; see comments)* **GT1a without NS5A polymorphisms** **Experienced GT1a with NS5A polymorphisms** **GT1b**	Non-cirrhotic or Cirrhotic, CP A	**EBR/GZR + RBV** *NOT FDA approved in SOF + RBV ± PEG-IFN treatment failures*	12 weeks 16 weeks 12 weeks	B-II/III	96% (76/79)[19]	**If GT1a, test for NS5A polymorphisms**** The FDA label did not include recommendations for patients who failed an NS5B inhibitor-containing regimen. Consult an expert before re-treating (see Section XIV, Resources). See Section XV, Appendix B for information on testing for NS5A RAPs. See monitoring recommendations below***
Experienced, GT1 *(Prior NS3/4A inhibitor + PEG-IFN + RBV, or SOF + RBV ± PEG-IFN therapy; see comments)*	Non-cirrhotic or Cirrhotic, CTP A,B,C	**LDV/SOF + RBV** *NOT FDA approved in SOF + RBV ± PEG-IFN treatment failures*	12 weeks	B-II	• Failed boceprevir or telaprevir + PEG-IFN + RBV: 96% (74/77, cirrhotics)[18] • Failed SOF + PEG-IFN + RBV: 100% (25/25)[20]	The FDA label did not include recommendations for patients who failed an NS5A- or NS5B inhibitor-containing regimen. Consult an expert before re-treating (see Section XIV, Resources). See Section XV, Appendix B for information on testing

Treatment history & HCV genotype	Cirrhosis status	Regimen	Duration	Evidence grade	SVR% (N/N) in clinical trials	Comments
					• Failed SOF + RBV ± PEG-IFN: 97% (62/64)[17] • Failed SOF + RBV: 95% (20/21)[20]	for NS5A RAPs. Among cirrhotics who failed boceprevir or telaprevir + PEG-IFN + RBV: LDV/SOF x 24 weeks: SVR 97% (75/77)[18] 80% were non-cirrhotic; 20% cirrhotic[17] 71% were non-cirrhotic; 29% cirrhotic[20]
Experienced, GT1 *(Other prior DAA-based therapy)*	Non-cirrhotic or Cirrhotic					Test for RAPs to NS3, NS5A, and NS5B (see Section XV, Appendix B for information on RAP testing). Patients who previously failed treatment with an NS5A- or NS5B inhibitor-containing regimen may have RAPs to currently available agents. The optimal DAA-based therapy for this patient population should be determined in consultation with an expert (see Section XIV, Resources).

* SVR rates in patients with HIV/HCV coinfection were similar to those found with HIV monoinfected patients; data are not represented in the above Table. Refer to Section XII, Groups with Special Considerations for Therapy, on HCV treatment in patients with HIV/HCV coinfection and Appendix A, Tables 27 and 28.

** NS5A polymorphisms at amino acid positions 28, 30, 31, or 93. Testing of HCV RAPs can be performed through the VHA Public Health Reference Laboratory (email V21PHRL@va.gov) or a commercial laboratory (see Section XV, Appendix B).

*** 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).

Study references: ION-3[7], SOLAR-1[15], ION-2[17], C-EDGE[9,16], SIRIUS[18], C-SALVAGE,[19] PEARL-III[12], TURQUOISE-II[13], TURQUOISE-III[14]

Dosages:

EBR/GZR (50/100 mg): 1 tablet orally daily

LDV/SOF (90/400 mg): 1 tablet orally daily

OBV/PTV/RTV (12.5/75/50 mg): 2 tablets once daily in the morning with food + DSV 250 mg orally twice daily (in the morning and in the evening with food)

RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food

Note: EBR/GZR, LDV/SOF or OBV/PTV/RTV + DSV should not be used in reduced dosages or restarted if discontinued. Dasabuvir should not be used as monotherapy.

Table 8. Genotype 1: Alternative Regimen and SVR Rates in HCV Monoinfection and HIV/HCV Coinfection*

SVR rates cannot be compared between trials. Within each category, regimens are listed in alphabetical order; this ordering does not imply any 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 **GT1a and RBV-intolerant or contraindicated:**** *(prior PEG-IFN/RBV only)*	Cirrhotic, CTP A	LDV/SOF	24 weeks	A-l	100% (22/22, – RBV)[17]	LDV/SOF for 12 weeks: SVR 82-86%[17] 46-61% failed boceprevir- or telaprevir-based therapy.[17]

* SVR rates in patients with HIV/HCV coinfection were similar to those found in HIV-monoinfected patients; data are not represented in the above Table. Refer to Section XII, Groups with Special Considerations for Therapy, on HCV treatment in patients with HIV/HCV coinfection and Appendix A, Table 28 and Table 29.

** Contraindication and/or intolerance to RBV: Contraindication is defined as history of significant or unstable cardiac disease, known pregnancy, positive pregnancy test, and men with a female partner who is pregnant or plans to become pregnant, known hypersensitivity reaction, and/or significant anemia (i.e., symptomatic or baseline hemoglobin <10 g/dL) and/or a history of significant adverse events with previous RBV-containing regimen.

Study references: ION-2[17]

Dosages:

- LDV/SOF (90/400 mg): 1 tablet orally daily. Note: LDV/SOF should not be used in reduced dosages or restarted if discontinued.

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 Treatment with DAA-Based Therapy

Recommendations on re-treatment of patients who have failed a DAA-containing regimen are based on basic principles of virologic resistance as well as limited data from patients who were re-treated after failing an initial DAA regimen. The recommendations are likely to change as more data become available. If needed, consult with an expert (see Section XIV, Resources).

Patients who have failed treatment with a DAA-containing regimen may have HCV resistance-associated polymorphisms (RAPs) against the class of drugs that was used in the initial regimen. HCV RAP testing should be performed to guide re-treatment options. The VHA Public Health Reference Laboratory (PHRL, email V21PHRL@va.gov) and commercial laboratories offer testing for HCV RAPs for Veterans who have failed regimens containing a DAA and who are being considered for re-treatment (see Section XV, Appendix B).

SOF (SOF), an NS5B inhibitor, appears to have a high genetic barrier to resistance. Thus, RAPs to SOF are uncommon. In patients who failed an SOF- and/or PEG-IFN-containing regimen, but have never been on an NS5A inhibitor, re-treatment with SOF + a DAA that targets an HCV protein that was not included in the prior regimen or EBR/GZR is recommended.

Patients who have failed treatment with an NS5A inhibitor-containing regimen (e.g., OBV, LDV) are likely to have RAPs against the other available NS5A inhibitors (e.g., DCV, EBR). The presence of a RAP against an NS5A inhibitor may reduce the effectiveness of other drugs in this class. Testing for NS5A RAPs should be performed to determine re-treatment options. If re-treatment is considered, RBV should be added to the regimen.

Patients who have failed treatment with peginterferon + ribavirin + an NS3/4A protease inhibitor (i.e., boceprevir, paritaprevir, simeprevir, telaprevir):

For patients who failed PEG-IFN + RBV + an NS3/4A protease inhibitor, LDV/SOF (without RBV) is FDA approved for 12 weeks in those without cirrhosis and 24 weeks in those with cirrhosis, or LDV/SOF + RBV for 12 weeks with cirrhosis.[18,21] 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-containing therapy, 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.[18] Thus, LDV/SOF + RBV for 12 weeks can be considered for cirrhotic patients who failed PEG-IFN + RBV + an NS3/4A protease inhibitor.

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 + a first generation protease inhibitor (i.e., telaprevir [n = 43], boceprevir [n = 28], or SMV [n = 8]).[19] The average patient age was 54 years; 58% of patients were men, 98% were non-CC IL28B genotype, 62% had GT1b, 43% had cirrhosis, and 84% had prior virologic failure. Three patients experienced virologic relapse in the first 12 weeks following treatment completion, resulting in an SVR rate of 96% (76/79). SVR was obtained in 96% (63/66) of patients who experienced virologic failure with the initial treatment, and SVR occurred in 100% (13/13) who failed the initial treatment for non-virologic reasons. SVR was achieved in 91% (31/34) of GT1a and GT1b patients with baseline NS3 RAPs affecting activity of earlier generation protease inhibitors. SVR was 100% (55/55) in subjects without baseline NS3 resistance substitutions. Eight patients had NS5A RAPs at baseline; in 5/8 (63%), the NS5A polymorphism was associated with >5-fold decrease in susceptibility to EBR. SVR was achieved in 75% (6/8) with NS5A RAPs.

Patients who have failed a sofosbuvir-containing regimen:

Among patients who have failed SOF-based therapy, re-treatment with LDV/SOF + RBV for 12 weeks achieved SVR rates of 98-100%.[20,22] In an open-label Phase II study of patients without cirrhosis who virologically relapsed following an SOF + RBV ± DAA regimen (with LDV x 6 weeks [n = 8] or GS-9669 [NS5B non-nucleoside inhibitor; n = 1]), an SVR of 100% (19/19) was achieved when re-treated with LDV/SOF + RBV for 12 weeks.[22] In another 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.[20] 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.

Patients who have failed an NS5A inhibitor-containing regimen:

The optimal treatment for patients who have failed an NS5A inhibitor-containing regimen is not known. In an open-label study of patients who virologically failed LDV/SOF ± RBV (n = 33) or LDV/SOF + GS-9669 (an investigational non-nucleoside HCV polymerase inhibitor; n = 8), 41 patients were re-treated with LDV/SOF (without RBV) for 24 weeks. In this difficult-to-treat cohort, >90% had IL28B non-CC and 46% had cirrhosis (79% among those with NS5A RAPs). SVR rates were reduced if baseline NS5A RAPs were present (SVR 60% [18/30]) compared with those without baseline NS5A RAPs (100% [11/11]).[23] It is unknown whether the addition of RBV would have improved the observed SVR rates in those with baseline NS5A RAPs. In another study, having baseline NS5A RAPs was associated with lower SVR rates in cirrhotic patients treated with LDV/SOF alone compared with treatment arms that received the addition of RBV to LDV/SOF.[24] The efficacy of EBR/GZR has not been established in patients who have previously failed treatment with other regimens that included an NS5A inhibitor. Patients who failed an NS5A inhibitor-containing regimen should be tested for RAPs to NS5A inhibitors to guide re-treatment options. If re-treatment is considered, RBV should be added to the regimen.

Summary of Pivotal Trials in Genotype 1-Infected Patients

The following summarizes the pivotal trials supporting the use of these regimens, including data on specific subgroups of patients with cirrhosis or those with prior DAA treatment experience.

Elbasvir/Grazoprevir (HCV NS5A inhibitor/HCV NS3/4A protease inhibitor) with or without Ribavirin

The following summarizes the pivotal trials supporting the use of EBR/GZR ± weight-based RBV among GT1-infected treatment-naïve and -experienced (previously failed PEG-IFN + RBV) patients.[9,16,25]
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.[9] Of the 288 GT1-infected patients, the mean age was 55 years; 56% were male, 20% were Black, 55% were GT1a, 45% were GT1b, and 24% had cirrhosis. SVR rates with EBR/GZR for 12 weeks were 92% (144/157) in GT1a patients and 98% (129/131) in GT1b patients.[8] SVR rates in GT1-infected patients with cirrhosis were 97% (66/68) and 94% (207/220) in non-cirrhotics; however, responses by genotype subtype were not provided.

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).[25] Among the four treatment groups, the mean age ranged from 57-59 years; 47-68% of patients were male, 3-16% Black, 65-75% had GT1a, and more than 94% had baseline albumin levels ≥3.5g/dL. 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 prior null responders to PEG-IFN + RBV treatment.[25] The mean age was 55 years and 37% had cirrhosis. 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 RAPs 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.[16] In the GT1-infected cohort, the average age was 57 years, 64% of patients were male, 18% were Black, 60% with GT1a, 39% with GT1b, and 34% had cirrhosis; 43% had prior null response, 21% partial response, and 36% prior relapse. Overall SVR for all genotypes combined 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 RAPs prior to treatment. Three patients who failed to achieve SVR with EBR/GZR + RBV for 16 weeks were either lost to follow up or discontinued treatment early for reasons other than virologic failure. 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.[8] 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.[8]

Impact of Baseline HCV RAPs on SVR Rates with Elbasvir/Grazoprevir in Genotype 1-Infected Patients[8]
SVR rates from pooled data from treatment-naïve patients who received EBR/GZR ± RBV in Phase III clinical trials and those who did not achieve SVR for non-virologic failure were analyzed.

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

NS5A: The presence of one or more HCV NS5A amino acid polymorphisms 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 extending 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 polymorphism (M28, Q30, L31, or Y93) compared with SVR 70% (39/56) with baseline NS5A polymorphism. Although data are limited, among GT1a-infected patients with NS5A polymorphisms who received EBR/GZR + RBV for 16 weeks, 100% (6/6) achieved SVR. The prevalence of polymorphisms 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 RAP testing is recommended in GT1a-infected patients prior to initiating EBR/GZR to determine the regimen (requirement for RBV) and treatment duration.[8]

Genotype 1b
NS3: In GT1b-infected subjects, baseline NS3 polymorphisms 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 polymorphisms at positions 28, 30, 31, or 93.

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

ION-1 was a randomized, open-label Phase III clinical trial examining the safety and efficacy of LDV/SOF in treatment-naïve patients with HCV GT1 infection.[10] Four treatment arms were compared: LDV/SOF for 12 or 24 weeks, with and without RBV. Of the 865 patients who underwent randomization, 67% were GT1a, 12% were Black, 70% were IL-28B non-CC genotype, and 16% met the trial definition of cirrhosis. Clinically significant liver disease was uncommon; only 3% of participants had a platelet count <90K/mm^3 and 4% had albumin <3.5 g/dL. 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 analysis, 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.[7] 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% depending on treatment arm) 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. This trial supports use of LDV/SOF for 8 weeks in non-cirrhotic, treatment-naïve HCV GT1a- or 1b-infected patients with a baseline HCV RNA <6 million IU/mL. However, the effectiveness of 8 weeks of LDV/SOF has not been evaluated in patients with cirrhosis or in previously treated patients.

ION-2 was a Phase III trial of 440 HCV GT1 treatment-experienced patients, each of whom received one of four treatment 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).[17] Across the four 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 protease inhibitor (PI)-based treatment with either boceprevir or telaprevir. In each treatment group, 20% of patients had cirrhosis, defined either histologically or with a FibroTest® score >0.75. 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. SVR rates were similar among subgroups including genotype subtype (i.e., 1a vs. 1b), previous treatment regimen, prior treatment response, IL-28B genotype, and race/ethnicity. 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). In multivariate analysis, the absence of cirrhosis was the only baseline factor associated with an increased rate of response. Of the 62 patients who had an NS5A RAP at baseline, 89% (55/62) achieved SVR; 6 of 11 patients who relapsed after treatment had NS5A RAPs at baseline. Adverse effects were less frequent in the 12-week LDV/SOF arm (67%) than in the other treatment arms (81-90%).

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 LDV/SOF (22/22) or LDV/SOF + RBV (22/22) for 24 weeks. 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 + protease inhibitor.[18] 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) as 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 + protease inhibitor.

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).[22]

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 59 treatment-naïve and -experienced GT1 patients with CPT B (score 7-9) and 49 patients with CPT C (score 10-13) with GT1 (n = 56) or GT4 (n = 3) infection.[15] Inclusion criteria included bilirubin ≤10 mg/dL, hemoglobin ≥10 g/dL, platelets >30,000/mm^3 and eGFR ≥40 mL/min. In the initial report (AASLD 2014), 9 patients were excluded from SVR analysis (6 patients underwent transplant and 3 had yet to reach the SVR time point). 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 each treatment arm (12 and 24 weeks). MELD score improved in most patients. There were 4 treatment-related serious adverse events (anemia [2], hepatic encephalopathy, peritoneal hemorrhage), 2 in CTP B and 2 in CTP C patients. Three patients discontinued treatment due to adverse events. Six patients died (septic shock [2], multi-organ failure and septic shock [2], oliguric renal failure, and cardiac arrest); no death was assessed as being related to study medicines. These preliminary 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. Patients need to be followed closely for adverse events.

Ombitasvir/paritaprevir/ritonavir + dasabuvir (OBV/PTV/r + DSV [HCV NS5A inhibitor/HCV NS3/4A protease inhibitor/CYP3A inhibitor + HCV non-nucleoside NS5B-palm polymerase inhibitor]) with or without ribavirin (RBV)

PEARL III and IV were placebo-controlled Phase III studies of HCV GT1 treatment-naïve non-cirrhotic patients receiving OBV/PTV/RTV + DSV (OBV/PTV/r + DSV) ± RBV for 12 weeks. In patients with GT1b, SVR was achieved in ≥99% of those receiving OBV/PTV/r + DSV with RBV (209/210) or without RBV (207/209).[12] The addition of RBV provided no additional benefit in GT1b patients. In GT1a patients who

received OBV/PTV/r + DSV + RBV, the overall SVR rate was 97% (97/100) and rates ranged from 90-100% among subgroups. In GT1a patients who received OBV/PTV/r + DSV without RBV, the overall SVR rate was 90% (185/205) and rates did not differ among subgroups (SVR range of 82-95%). Anemia and transient asymptomatic hyperbilirubinemia were more common in the OBV/PTV/r + DSV + RBV regimen; however, clinically significant anemia was uncommon and managed with RBV dosage reduction. All patients who received RBV dosage reduction achieved SVR. Overall, higher virologic failure rates were observed in GT1a patients without RBV but not in those with GT1b infection.

SAPPHIRE-I was a double-blind, placebo-controlled Phase III study of HCV GT1a and 1b treatment-naïve non-cirrhotic patients receiving OBV/PTV/r + DSV + RBV for 12 weeks.[26] SVR was achieved in 95% (307/322) of GT1a patients and 98% (148/151) of GT1b patients. Breakthrough and relapse rates were 0.2% (n = 1) and 1.5% (n = 7), respectively. Among subgroups, SVR rates ranged from 92-98%. Hemoglobin reductions between 8-10 g/dL occurred in 5.8% of patients; 31 patients had RBV dosage reductions, and SVR rates in this group were 94% compared with an SVR rate of 96% in those without RBV dosage modification. Only 1 patient received erythropoietin and no patients required transfusion.

PEARL-II was a randomized Phase III trial examining the safety and efficacy of OBV/PTV/r + DSV ± RBV in HCV GT1b treatment-experienced non-cirrhotic patients.[27] The trial was open-label and had two arms that were treated for 12 weeks: OBV/PTV/r + DSV + RBV (n = 91) and OBV/PTV/r + DSV without RBV (n = 95). All patients were previously treated with PEG-IFN + RBV; none had previously received DAA therapy. The majority of patients had METAVIR F0-F2; 13-15% had METAVIR F3. Overall, SVR occurred in 97% (85/88) and 100% (91/91) of those treated with OBV/PTV/r + DSV + RBV and without RBV, respectively. Patients with prior relapse, partial response, and null response achieved SVR 100% in the OBV/PTV/r + DSV without RBV and 93-100% in the OBV/PTV/r + DSV + RBV arms. High SVR rates were achieved using OBV/PTV/r + DSV ± RBV for 12 weeks in treatment-experienced, GT1b non-cirrhotics in all subgroups, including prior null responders. The addition of RBV did not increase SVR rates in any subgroup.

SAPPHIRE-II was a randomized placebo-controlled Phase III trial examining the safety and efficacy of the combination of OBV/PTV/r + DSV + RBV for 12 weeks in treatment-experienced (PEG-IFN + RBV) non-cirrhotic patients.[28] The patients were 58% GT1a and 41% GT1b. The majority of patients had a prior null response (49%); the remainder were categorized as relapsers (29%) or partial responders (22%). The majority of patients had METAVIR F0-F2; 14-15% had METAVIR F3. Results showed high SVR rates in treated patients, regardless of prior treatment history or subtype. SVR occurred in 96% (95% CI: 94-98). SVR was achieved in 96% with GT1a and 97% with GT1b. SVR rates were 95% among prior relapsers (n = 86), 100% (n = 65) among patients with a prior partial response, and 95% (n = 146) among patients with a prior null response. This study demonstrated high SVR rates with a 12-week regimen of OBV/PTV/r + DSV + RBV, in treatment-experienced (PEG-IFN + RBV) GT1a and 1b patients, including prior null responders.

Genotype 1-Infected Patients with Cirrhosis, Compensated

The combination of OBV/PTV/r + DSV + RBV for 12 or 24 weeks was evaluated in a prospective, randomized study of 380 patients with compensated (CTP A) cirrhosis.[13] Inclusion criteria included cirrhosis documented by liver biopsy or FibroScan® (≥14.6 kPa), platelet count ≥60,000/mm^3, serum albumin levels ≥2.8 g/dL, and bilirubin concentrations <3 mg/dL. Approximately 58% of patients were

treatment experienced (36% were null responders); 20% had platelet counts <100,000/mm^3. Overall, SVR rates were 92% (191/208) with 12 weeks of OBV/PTV/r + DSV + RBV and 96% (165/172) with 24 weeks (p = .089). Among GT1a patients, SVR rates with 12 and 24 weeks of treatment were 89% (124/140) and 94% (114/121), respectively. Among GT1b, SVR rates were 99% (67/68) and 100% (51/51) for the two treatment durations. Among treatment-naïve patients with GT1a, SVR rates were 92% (59/64) and 93% (52/56) when treated for 12 and 24 weeks, respectively. In GT1a prior relapsers treated with OBV/PTV/r + DSV + RBV for 12 or 24 weeks, SVR rates were 93% (14/15) and 100% (13/13), respectively. In GT1a prior partial responders, SVR rates were 100% in patients treated for either 12 weeks (11/11) or 24 weeks (10/10). However, among GT1a null responders, SVR rates were 80% (40/50) when treated for 12 weeks and 93% (39/42) among those treated for 24 weeks. All patients who had an RBV dosage reduction achieved SVR (43/43) as compared with 93% (313/337) without RBV dosage reduction. Virologic failure was more common among patients receiving OBV/PTV/r + DSV + RBV for 12 weeks (6%) as compared with those receiving 24 weeks of treatment (3%). Serious adverse events occurred in 6.3% and 4.7% of patients in the 12- and 24-week arms, respectively. Hemoglobin decreased to less than 10 g/dL in 7% of patients in the 12-week arm and 11% in the 24-week arm. There were no deaths. Because of the higher SVR rate, along with the lower incidence of virologic failure among patients receiving 24 weeks of treatment, the FDA recommended that cirrhotic patients receive 24 weeks of OBV/PTV/r + DSV + RBV. However, these data suggest that 12 weeks of OBV/PTV/r + DSV + RBV can be considered among treatment-naïve GT1a patients, GT1a prior relapsers or partial responders to PEG-IFN + RBV, and all patients with GT1b, because there was little difference in SVR between those treated for 12 versus 24 weeks in these subgroups.[13]

TURQUOISE III, a multicenter open-label Phase IIIb study, evaluated the use of OBV/PTV/r + DSV without RBV in 60 GT1b-infected patients with compensated cirrhosis.[14] Participants were mostly White (88%) and male (62%) with a median age of 59.5 years and a median BMI of 27.8 ± 5.4 kg/m^2. The majority (55%) had failed treatment with PEG-IFN + RBV. Cirrhosis was determined by liver biopsy or FibroScan® value ≥12.5 kPa. Median albumin concentration was 4.0 g/dL (range 2.8-4.5 g/dL). All patients (60/60) achieved HCV RNA <25 IU/mL at 4 weeks of treatment, all (60/60) completed the study, and all achieved SVR (60/60). This study offers support to omit RBV from a regimen of OBV/PTV/r + DSV in GT1b patients with compensated cirrhosis.

Sofosbuvir + Simeprevir (NS3/4A protease inhibitor) ± Ribavirin

In open-label Phase III trials (OPTIMIST-1 and -2), the combination of SOF + SMV for 12 weeks was evaluated in GT1-infected patients. In 155 treatment-naïve and -experienced patients without cirrhosis, SVR rates were 97% (112/115) and 95% (38/40), respectively. SVR rates were similar in GT1a patients with and without baseline Q80K mutation; SVR 96% (44/46) and 97% (68/70), respectively. In GT1b patients, SVR was achieved in 97% (38/39).[29] In 103 treatment-naïve and -experienced patients with cirrhosis, SVR rates were 88% (44/50) and 79% (42/53), respectively. In GT1a cirrhotic patients, the presence of NS3 Q80K polymorphism was associated with lower SVR rates compared to those without it; SVR 74% (25/34) vs. 92% (35/38). In GT1b patients, SVR was achieved in 84% (26/31).[30]

In an open-label, Phase IIa trial (COSMOS), the combination of SOF + SMV ± RBV was evaluated in 167 GT1-infected patients.[31] In treatment-naïve patients with cirrhosis, 24 weeks of SOF + SMV ± RBV

achieved SVR in 100% (9/9). In null responders with METAVIR F4, SVR was achieved in 90% (9/10) and 100% (4/4) with 24 weeks of SOF + SMV ± RBV, respectively. The incidence of Grade 3 or 4 adverse events were 17% and 13% with and without RBV, respectively.

V. Chronic HCV Genotype 2 Infection

*Including HIV coinfection**

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

Key Points

- Selection of an appropriate regimen and treatment duration for patients with GT2 infection depends on stage of liver disease, prior treatment history, and concomitant medications.
- The optimal treatment regimen has not been established for cirrhotic GT2 patients who are unable to tolerate RBV or those who have failed DAA therapy; expert consultation is suggested for such patients (see Section XIV, Resources).
- Patients experiencing virologic failure with a DAA-containing regimen should have resistance testing performed through the VHA Public Health Reference Laboratory (email V21PHRL@va.gov) or a commercial laboratory (see Section XV, Appendix B).

Table 9. **Treatment regimens for GT2**

See Table 10 for details

Treatment-naïve patients without cirrhosis

- *SOF (400 mg/day) in combination with RBV (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks.*

Treatment-naïve patients with cirrhosis

- *SOF (400 mg/day) in combination with RBV (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 16 weeks. FDA approved for 12 weeks.*

Treatment-experienced patients with or without cirrhosis

- *SOF (400 mg/day) in combination with RBV (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 16 weeks. FDA approved for 12 weeks.*

Table 10. Genotype 2: Treatment Regimens and SVR Rates in HCV Monoinfection and HIV/HCV Coinfection

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	SOF + RBV	12 weeks	A-I	97% (59/61)[32] 92% (85/92)[33] 97% (29/30)[33,34]	
Naïve GT2	Cirrhotic	SOF + RBV	16 weeks	B-III	Data not available	*FDA approved for 12 weeks* 12 weeks 83% (10/12)[32] 94% (16/17)[33] 100% (2/2)[34]
Experienced GT2 *(Prior PEG-IFN/RBV only)*	Non-cirrhotic	SOF + RBV	16 weeks	A-II	Relapsers: 89% (24/27)[33] Nonresponders: 88% (7/8)[33]	*FDA approved for 12 weeks* 12 weeks 91% (30/33)[34] Relapsers: 86% (25/29)[33] Nonresponders: 70% (7/10)[33] 24 weeks SVR 100% (17/17 in cirrhotics)[35]
Experienced GT2 *(Prior PEG-IFN/RBV only)*	Cirrhotic	SOF + RBV	16 weeks	B-II	78% (7/9)[33] 87% (13/15)[35]	*FDA approved for 12 weeks* 12 weeks SVR 60% (6/10)[33] SVR 88% (7/8)[34] 24 weeks 100% (17/17)[35]
Experienced GT2 (Prior DAA-based therapy)						**The optimal DAA-based therapy for this patient population is not known. Consult with an expert before re-treating (see Section XIV, Resources).**

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

Study references: FISSION[32], POSITRON[33], FUSION[33], VALENCE[34], BOSON[35]

Dosages:

- RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food
- SOF 400 mg orally daily

Note: SOF should not be used as monotherapy or in reduced dosages; it should not be restarted if discontinued.

Table 11. Genotype 2: Alternative Regimens and SVR Rates in HCV Monoinfection and HIV/HCV Coinfection*

SVR rates cannot be compared between trials. Within each category, regimens are listed in alphabetical order; this ordering does not imply any preference for a particular regimen unless otherwise indicated.

Treatment history & HCV genotype	Cirrhosis status	Regimen (in alphabetical order)	Duration	Evidence grade	SVR% (N/N) in clinical trials	Comments
Naïve, GT2	Non-cirrhotic	DCV + SOF *NOT FDA approved*	12 weeks	B-II	100% (11/11)[36]	Regimen studied only in HIV/HCV co-infected patients.
Naïve, GT2	Non-cirrhotic	LDV/SOF *NOT FDA approved*	12 weeks	B-II	96% (25/26)[37]	SVR rates include treatment-experienced and cirrhotic patients.
Experienced, GT2 (Prior PEG-IFN/RBV only)	Non-cirrhotic	DCV + SOF *NOT FDA approved*	12 weeks	B-II	100% (2/2)[36]	Regimen studied only in HIV/HCV co-infected patients.
Experienced, GT2 (Prior PEG-IFN/RBV only)	Non-cirrhotic	LDV/SOF *NOT FDA approved*	12 weeks	B-II	96% (25/26)[37]	SVR rates include treatment-naïve and cirrhotic patients.
Experienced, GT2 (Prior PEG-IFN/RBV only)	Non-cirrhotic	SOF + PEG-IFN + RBV *NOT FDA approved*	12 weeks	B-II	100% (9/9)[38]	If interferon eligible
Experienced, GT2 (Prior PEG-IFN/RBV only)	Cirrhotic, CTP A	SOF + PEG-IFN + RBV *NOT FDA approved*	12 weeks	B-II	93% (13/14)[38] 94% (15/16)[35]	If interferon eligible

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

Study references: ALLY-2[36], LONESTAR-2[38]

Dosages:

- DCV 60 mg orally daily (Note: 30 mg daily with strong CYP3A inhibitors or 90 mg daily with moderate CYP3A inducers)
- LDV/SOF (90/400 mg): 1 tablet orally daily
- PEG-IFN alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly
- RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food
- SOF 400 mg orally daily

Note: LDV/SOF or SOF should not be used in reduced dosages or restarted if discontinued. DCV or SOF should not be used as monotherapy.

Sofosbuvir in Genotype 2

The use of an interferon-free treatment regimen for chronic HCV GT2 infection, SOF (SOF) plus RBV (RBV), is supported by the results of four Phase III studies.[32-34] SVR rates among these four studies were >90% in treatment-naïve and non-cirrhotic populations. Patients with cirrhosis and previous nonresponse to PEG-IFN-containing regimens were less well represented in the studies. Among treatment-experienced patients from the VALENCE study, SVR was achieved in 91% (30/33) of patients without cirrhosis and 88% (7/8) in those with cirrhosis treated with SOF + RBV for 12 weeks.[34] In the FUSION study, SVR rates increased with extending SOF + RBV therapy from 12 to 16 weeks in prior nonresponders without cirrhosis (70% [7/10] vs. 88% [7/8], respectively) and in treatment-experienced patients with cirrhosis (60% [6/10] vs. 78% [7/9], respectively).[33] Among treatment-experienced cirrhotic patients from the Phase III study BOSON, high SVR rates occurred with SOF + RBV for 16 or 24 weeks; SVR 87% (13/15) with 16 weeks and 100% (17/17) with 24 weeks of SOF + RBV.[35] Based on results from these studies, SOF + RBV for 16 weeks should be considered in treatment-experienced patients; however, this 16-week regimen is not FDA approved.

In interferon-eligible, treatment-experienced patients, SOF + PEG-IFN + RBV for 12 weeks may be considered. Among treatment-experienced patients without and with cirrhosis from the LONESTAR-2 study, SVR was achieved in 100% (9/9) and 93% (13/14), respectively, with the addition of PEG-IFN to SOF + RBV therapy for 12 weeks.[38] Among treatment-experienced cirrhotic patients from the Phase III BOSON study, SVR 94% (15/16) occurred with SOF + PEG-IFN + RBV for 12 weeks.[35] This regimen is not FDA approved.

In patients who have a contraindication or are intolerant to RBV, LDV/SOF for 12 weeks may be an alternative option. An open-label study of GT2 treatment-naïve and -experienced patients (n = 53) evaluated LDV/SOF for 8 or 12 weeks. The majority of patients were male (65-70%) and Caucasian (78-92%). In the 12-week arm, 26% were treatment experienced and 8% had cirrhosis. SVR was achieved in 96% (25/26) with 12 weeks compared with 74% (20/27) with 8 weeks of LDV/SOF.[37]

VI. Chronic HCV Genotype 3 Infection

*Including HIV coinfection**

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

Key Points

- Selection of an appropriate regimen and treatment duration for patients with GT3 infection depends on stage of liver disease, prior treatment history, and concomitant medications.
- Patients with GT3 infection should be considered for NS5A resistance testing if treatment-naïve, particularly prior to starting daclatasvir + SOF, and NS5A resistance testing should be performed in patients who have experienced virologic failure (see Section XV, Appendix B).

Table 12. Treatment regimens for GT3

See Table 13 for details

Treatment-naïve patients without cirrhosis

- *LDV/SOF (90/400 mg/day) plus RBV (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks. NOT FDA APPROVED.*

Treatment-naïve patients with cirrhosis

- *DCV (60 mg/day) plus SOF (400 mg/day) plus RBV (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks in CTP A, or 12-24 weeks in CTP B and C patients.*

Treatment-experienced patients without cirrhosis

- *LDV/SOF (90/400 mg/day) plus RBV (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks. NOT FDA APPROVED.*

Treatment-experienced patients with cirrhosis

- *DCV (60 mg/day) plus SOF (400 mg/day) plus RBV (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks in CTP A, or 12-24 weeks in CTP B and C patients.*

Table 13. Genotype 3: Treatment Regimens and SVR Rates in HCV Monoinfection and HIV/HCV Coinfection*

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)	Comments
Naïve, GT3	Non-cirrhotic	**LDV/ SOF + RBV** *NOT FDA approved*	12 weeks	A-II	100% (20/20)[39] Preliminary VA data for SVR_4: 83% (52/63, ITT)[40] 90% (51/57, completed treatment)[40]	SVR rates include treatment-experienced patients.[40] Consider testing for NS5A RAPs prior to starting treatment. **
Naïve, GT3	Cirrhotic	**DCV + SOF + RBV** *NOT FDA approved with RBV*	12 weeks if CTP A 12-24 weeks if CTP B or C	B-II	83% (15/18,+ RBV)[41] 100% (4/4, + RBV)[42] CTP B or C 70% (7/10, + RBV)[42] 71% (12/17, – RBV)[42] CTP B 86% (6/8, + RBV)[43] 80% (12/15, – RBV)[43] CTP C 100% (2/2, + RBV)[43] 75% (6/8, – RBV)[43]	SVR rates include treatment-experienced patients.[42,43] CTP A 12 weeks: 70% (23/33, – RBV)[42] 16 weeks: 89% (16/18, + RBV)[41] Consider testing for NS5A RAPs prior to starting treatment. **
Experienced, GT3 (Prior PEG-IFN/RBV only)	Non-cirrhotic	**LDV/ SOF + RBV** *NOT FDA approved*	12 weeks	B-II	89% (25/28)[39] Preliminary VA data for SVR_4: 83% (52/63, ITT)[40] 90% (51/57, completed treatment)[40]	SVR rates include includes treatment-naïve patients.[40] Consider testing for NS5A RAPs prior to starting treatment. **
Experienced GT3 (Prior PEG-IFN/RBV only)	Cirrhotic	**DCV + SOF + RBV** *NOT FDA approved with RBV*	12 weeks if CTP A 12-24 weeks if CTP B or C	B-II	88% (14/16,+ RBV)[41] 100% (4/4, + RBV)[42] CTP B or C 70% (7/10, + RBV)[42] 71% (12/17, – RBV)[42]	SVR rates include treatment-naïve patients.[42,43] CTP A 12 weeks: 70% (23/33, – RBV)[42] 16 weeks: 86%

Treatment history & HCV genotype	Cirrhosis status	Regimen	Duration	Evidence grade	SVR% (N/N)	Comments
					CTP B 86% (6/8, + RBV)[43] 80% (12/15, – RBV)[43] CTP C 100% (2/2, + RBV)[43] 75% (6/8, – RBV)[43]	(12/14, + RBV)[41] Consider testing for NS5A RAPs prior to starting treatment. **
Experienced GT3 (Prior DAA-based therapy)						**The optimal DAA-based therapy for this patient population is based on expert opinion. Patients who previously failed treatment with an NS5A inhibitor may have NS5A resistance-associated polymorphisms to currently available NS5A inhibitors. Recommend NS5A resistance testing to determine re-treatment options.**

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

** Testing for NS5A RAPs can be performed by the VA Public Health Reference Laboratory (email V21PHRL@va.gov) or a commercial laboratory (see Section XV, Appendix B). Consult an expert if Y93H RAP in NS5A is found (see Section XIV, Resources).

Abbreviations: ITT = intention to treat

Study references: ELECTRON-2[39], ALLY-3+[41]

Dosages:

- DCV 60 mg orally daily (Note: 30 mg daily with strong CYP3A inhibitors or 90 mg daily with moderate CYP3A inducers, see Appendix A, Table 28);
- LDV/SOF (90/400 mg) orally daily; SOF 400 mg orally daily.

Note: LDV/SOF or SOF should not be used in reduced dosages or restarted if discontinued.
DCV or SOF should not be used as monotherapy.

Table 14. Genotype 3: Alternative Regimens and SVR Rates in HCV Monoinfection and HIV/HCV Coinfection*

Regimens may be effective and tolerable, but have potential disadvantages when compared with other treatment regimens.

SVR rates cannot be compared between trials. ***Within each category, regimens are listed in alphabetical order; this ordering does not imply any preference for a particular regimen unless otherwise indicated.***

Treatment history & HCV genotype	Cirrhosis status	Regimen (in alphabetical order)	Duration	Evidence grade	SVR% (N/N)	Comments
Naïve, GT3	Non-cirrhotic	DCV + SOF	12 weeks	A/B-II	97% (73/75)[44] 96% (24/25)[42] (includes treatment experienced)	Consider future treatment options unless urgent treatment is needed. Test for NS5A RAPs prior to starting treatment. **
Naïve, GT3	Non-cirrhotic	SOF + PEG-IFN + RBV *NOT FDA approved*	12 weeks	A-II	96% (68/71)[35]	If interferon eligible
Naïve, GT3	Non-cirrhotic	SOF + RBV	24 weeks	A-I	94% (86/92)[34] 90% (65/72)[35] Preliminary VA data for SVR_4: 81% (129/159, ITT)[40] 84% (110/131, completed treatment)[40] (includes treatment experienced)	
Naïve, GT3	Cirrhotic	SOF + PEG-IFN + RBV *NOT FDA approved*	12 weeks	A-III	91% (21/23)[35]	If interferon eligible
Experienced, GT3 *(Prior PEG-IFN/RBV only)*	Non-cirrhotic	DCV + SOF	12 weeks	A/B-II	94% (32/34)[44] 96% (24/25)[42] (includes treatment naïve)	Consider future treatment options unless urgent treatment is needed. Test for NS5A RAPs prior to starting treatment. **
Experienced, GT3 *(Prior PEG-IFN/RBV only)*	Non-cirrhotic	SOF + PEG-IFN + RBV *NOT FDA approved*	12 weeks	A-II	94% (49/52)[35] 83% (10/12)[38]	If interferon eligible

Treatment history & HCV genotype	Cirrhosis status	Regimen (in alphabetical order)	Duration	Evidence grade	SVR% (N/N)	Comments
Experienced, GT3 *(Prior PEG-IFN/RBV only)*	Non-cirrhotic	SOF + RBV	24 weeks	A-I	87% (87/100)[34] 82% (44/54)[35]	
Experienced, GT3 *(Prior PEG-IFN/RBV only)*	Cirrhotic	DCV + SOF *(if RBV-intolerant or contraindicated)*** *	24 weeks	B-II	CTP B or C 71% (12/17)[42] CTP B: 80% (12/15)[43] CTP C: 75% (6/8)[43]	SVR rates include treatment-naïve patients.[42,43]

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

** NS5A resistance testing can be performed through the VHA Public Health Reference Laboratory (email at V21PHRL@va.gov) or a commercial laboratory (see Section XV, Appendix B). Consult an expert if Y93H RAP in NS5A is found (see Section XIV, Resources).

*** Contraindication and/or intolerance to RBV: Contraindication is defined as history of significant or unstable cardiac disease, known pregnancy, positive pregnancy test, and men with a female partner who is pregnant or plans to become pregnant, known hypersensitivity reaction, and/or significant anemia (i.e., symptomatic or baseline hemoglobin <10 g/dL) and/or history of significant adverse events with a previous RBV-containing regimen.

Abbreviations: ITT = intention to treat

Study references: ALLY-3[44]; BOSON[35]; VALENCE[34]; LONESTAR[38]

Dosages:

- DCV 60 mg orally daily (Note: 30 mg daily with strong CYP3A inhibitors or 90 mg daily with moderate CYP3A inducers)
- PEG-IFN alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly
- RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food
- SOF 400 mg orally daily

Note: SOF should not be used in reduced dosages. DCV or SOF should not be used as monotherapy or restarted if discontinued.

Treatment of Chronic HCV Genotype 3

The optimal treatment of HCV GT3, especially for patients with cirrhosis, is an area of uncertainty. The primary reason for uncertainty is the limited availability of high-quality studies in an era in which the potential impact of NS5A RAPs is not fully understood. Few randomized, controlled trials have been performed, and many of the available studies had small sample sizes. Open-label, “real world,” compassionate use, and early-access programs usually combine data from patients with multiple characteristics complicating data interpretation. Furthermore, in non-randomized trials, the treating provider often selects the medication, dosage, and treatment duration, making it difficult to discern the effect of the various regimens on SVR.

Based on data currently available, the most effective interferon-free, DAA-containing regimen for GT3 treatment is the combination of an NS5A inhibitor (DCV [DCV] or LDV [LDV]) with SOF and RBV (note: RBV may not be necessary for non-cirrhotic subjects receiving DCV). For combination regimens with either NS5A inhibitor, the SVR among non-cirrhotic patients is between 90-100%, while the SVR among cirrhotic patients range from 60-93%, with the higher SVR rate reflecting 24-week treatment duration. In cirrhotic patients, high SVR rates and similar treatment duration are anticipated with newer therapies. Deferral of HCV treatment may be considered until newer therapies are available that might further optimize the chance of treatment success.

There are several concerns with the use of an NS5A inhibitor + SOF (SOF) + RBV (RBV) to treat GT3-infected patients. First, the combination of LDV/SOF + RBV is not FDA approved for GT3 treatment, although its efficacy among non-cirrhotic patients is comparable to DCV and SOF, which is approved for the treatment of GT3 infection. However, the high cost of DCV and SOF limits its use. Second, only a few small studies have examined the efficacy of LDV/SOF- and DCV + SOF-containing regimens in GT3-infected cirrhotic patients. Finally, the consequences of NS5A RAPs, particularly the Y93H RAP, are not fully understood. At baseline, approximately 10% of GT3-infected patients have the Y93H RAP. The presence of the Y93H RAP has been associated with reduced SVR among patients receiving DCV + SOF; the impact on SVR when RBV is included in the regimen is not well defined.[44] However, Y93H RAP did not appear to reduce SVR rates in a Phase ll open-label study of GT3-infected patients who were treatment naïve (SVR 100% [26/26], 23% with cirrhosis) and treatment experienced (SVR 82% [41/50], 44% with cirrhosis) in which RBV was added to LDV/SOF.[39] Only 1 of 8 patients with baseline Y93H RAP experienced post-treatment relapse; this patient had been assigned to the treatment arm with LDV/SOF alone.

Although this study suggests a beneficial effect of RBV in combination with an NS5A inhibitor + SOF, there are insufficient data to conclusively determine whether the addition of RBV overcomes the effects of NS5A RAPs.[39] Nonetheless, RBV is recommended in all NS5A-containing DAA regimens used to treat GT3. Until more data are available, baseline testing for NS5A RAPs is recommended prior to DCV + SOF treatment, particularly for cirrhotic or treatment-experienced patients.

Another related concern is the potential development of NS5A RAPs among patients who do not achieve an SVR. The Y93H RAP often persists for more than a year in circulating HCV quasi-species after failure of an NS5A-containing regimen and confers cross-resistance to all currently approved NS5A inhibitors. Given the lower SVR rates among GT3 cirrhotic patients with CTP B and C treated with 12 weeks of LDV/SOF + RBV or DCV + SOF ± RBV and concerns about the development of RAPs in those who fail therapy, DCV + SOF + RBV for 24 weeks should be considered. If treatment is not deemed urgent, discussion and shared decision-making with the patient should include the option of waiting for future treatments with shorter treatment durations and higher expected SVR. A practitioner with expertise should be consulted to weigh the risks versus benefits of delaying treatment.

Alternative treatments are available for GT3 patients, but have potential drawbacks. Treatment with SOF + PEG-IFN + RBV for 12 weeks achieves the highest reported SVR among patients with cirrhosis.[35] Although this regimen requires the use of PEG-IFN, patients who fail to respond do not develop NS5A RAPs. SOF + RBV for 24 weeks achieves a high SVR for treatment-naïve, non-cirrhotic GT3-infected

patients. However, SOF + RBV for 24 weeks is less than optimal for cirrhotic patients because of the lower SVR (60-77%).[40]

In summary, an NS5A inhibitor (LDV or DCV) in combination with SOF and RBV is the an interferon-free regimen for GT3 treatment. Among cirrhotic patients, DCV + SOF + RBV should be used for 12 weeks in CTP A patients and 12-24 weeks in CTP B or C patients. It is essential to test for the presence of the Y93H RAP before starting treatment, particularly in any treatment-experienced or cirrhotic patient; if present, potential implications of this RAP should be discussed with the patient. RBV should be used at the recommended dosage (1,000 or 1,200 mg/day); for decompensated cirrhosis, start with 600 mg/day and increase as tolerated. The combination of PEG-IFN + SOF + RBV appears to be the most effective treatment available for cirrhotic patients, but the adverse effects of interferon must be weighed against the benefits. Waiting for newer regimens to treat cirrhotic patients, which are anticipated to become available in the second half of 2016, is reasonable after discussion with the patients.

Summary of Pivotal Trials in Genotype 3-Infected Patients

Ledipasvir/sofosbuvir + ribavirin

Treatment of GT3 with LDV/SOF + RBV for 12 weeks is not approved by the FDA but has been evaluated in a Phase II clinical trial and in preliminary real-world VA data (see Table 13). In the Phase II open-label study, 51 treatment-naïve GT3 patients were randomized to 12 weeks of either LDV/SOF (n = 25) or LDV/SOF + weight-based RBV (n = 26) and 50 treatment-experienced GT3 patients received LDV/SOF + RBV for 12 weeks.[39] More than 80% of patients were Caucasian; compensated cirrhosis was present in 20% (n = 10) of treatment-naïve patients and 44% (n = 22) of treatment-experienced patients. Among treatment-naïve patients, SVR rates were 100% (26/26; 95% CI: 87-100) in the LDV/SOF + RBV arm, including 6 patients with compensated cirrhosis. Only 64% (16/25; 95% CI: 43-82) of patients achieved SVR in the LDV/SOF arm; thus, LDF/SOV use without RBV is not recommended. In treatment-experienced patients, SVR rates were 89% (25/28) and 73% (16/22) among non-cirrhotic and cirrhotic patients, respectively.

In preliminary intention-to-treat analysis of treatment-naïve and -experienced Veterans, SVR_4 rates with LDV/SOF + RBV were 83% (52/63) in those without advanced liver disease (defined as FIB-4 ≤3.25) and 55% (27/49) with advanced liver disease (defined as FIB-4 >3.25). In a subgroup that completed 12 weeks of LDV/SOF + RBV, SVR_4 rates were 90% (51/57) and 59% (27/46) without and with advanced liver disease, respectively.[40]

In GT3 patients without cirrhosis, treatment with LDV/SOF + RBV for 12 weeks is supported based on the high SVR rates observed in a clinical trial (SVR 100% and 89% in treatment-naïve and -experienced non-cirrhotic patients, respectively)[39] along with the high SVR rates from preliminary VA data support. Based on lower SVR rates, high virologic relapse rates in GT3 cirrhotic patients and the potential for increased risk of NS5A RAPs, LDV/SOF + RBV should not be used for GT3 cirrhotic patients.[39]

Daclatasvir + sofosbuvir + ribavirin

Treatment of HCV GT3 infection with DCV + SOF is approved by the FDA; in patients with cirrhosis, this regimen *in combination with RBV for 12 weeks in CTP A, or 12-24 weeks in CTP B and C patients* should be

considered. Data on the use of DCV + SOF ± RBV in patients with cirrhosis are available from Phase lll trials and several early-access programs (EAPs) described below.

ALLY-3 was an open-label, Phase III study of DCV + SOF for 12 weeks in GT3 patients (n = 152) of whom 90% were Caucasian, 57% were men, and 21% had compensated cirrhosis.[44] In treatment-naïve patients, SVR rates were 90% (91/101) overall, and 97% (73/75) and 58% (11/19) in those without and with cirrhosis, respectively. In treatment-experienced patients who failed PEG-IFN + RBV ± DAA, re-treatment with DCV + SOF for 12 weeks resulted in SVR rates of 86% (44/51) overall, 81% (25/31) in prior relapsers, 100% (2/2) in prior partial responders, and 100% (7/7) in prior null responders. SVR rates in treatment-experienced non-cirrhotics were 94% (32/34) and 69% (9/13) in cirrhotics. The Y93H polymorphism was detected in 9% (13/148) of patients at baseline and was associated with reduced SVR rates; SVR rates were 67% (6/9) in non-cirrhotic and 25% (1/4) in cirrhotic patients.[44]

In the UK Early-Access Program, GT3 patients with decompensated cirrhosis received 12 weeks of treatment with DCV + SOF ± RBV (n = 114) or LDV/SOF ± RBV (n = 61) as determined by the provider. In this cohort, 74% were Caucasian, 47% were treatment-experienced, 10% were post-liver transplant, and 94% had current or previous decompensated cirrhosis (CTP B 66%, CTP C 10%, mean MELD score 11.6). The SVR rates for each regimen were as follows: DCV + SOF + RBV, 70% (80/114); DCV + SOF, 71% (5/7); LDV/SOF + RBV, 59% (36/61). In the overall cohort, 9% of patients discontinued treatment and serious adverse events related to liver disease or HCV therapy occurred in 21% of patients.[45]

The Phase lll ALLY-1 study evaluated a 12-week regimen of DCV + SOF + RBV in GT3-infected patients with advanced cirrhosis or recurrent infection after liver transplant. SVR rates were 83% (5/6) in the group with advanced cirrhosis and 91% (10/11) in the post-transplant group.[46]

Suboptimal SVR rates observed in cirrhotic patients receiving DCV + SOF for 12 weeks have prompted investigation of longer treatment duration and/or addition of RBV.

In HCV GT3 patients with compensated cirrhosis, treatment with DCV + SOF + RBV achieved SVR in 83% (15/18) in the 12-week arm and 89% (16/18) in the 16-week arm. ALLY-3+ was an open-label, Phase IIIb study of GT3 treatment-naïve and -experienced patients who received DCV + SOF + RBV for 12 or 16 weeks; SVR was achieved in 88% (21/24; 6/6 with advanced fibrosis and 15/18 with cirrhosis) with 12 weeks and 92% (24/26; 8/8 with advanced fibrosis and 16/18 with cirrhosis) with 16 weeks of DCV + SOF + RBV. In treatment-experienced cirrhotic patients, SVR was achieved in 88% (14/16) and 86% (12/14) with 12 weeks and 16 weeks of DCV + SOF + RBV, respectively.[41]

In the French Multicenter Compassionate Use Program, 601 patients received DCV + SOF for 12 or 24 weeks, with RBV added at the provider's discretion. In the cohort, 83%, 14% and 3% were CTP A (F3/F4), B, or C, respectively. Patients were primarily treatment experienced (73%) and cirrhotic (79%); HIV co-infection was present in 14%. RBV was included in the regimen for approximately 20% of patients and 93% of patients received treatment for 24 weeks. In non-cirrhotic patients receiving DCV + SOF for 12 or 24 weeks, interim SVR rates were 96% (24/25) and 100% (29/29), respectively. In cirrhotic patients receiving DCV + SOF for 12 or 24 weeks interim SVR rates were 70% (23/33) and 86% (116/135),

respectively. For cirrhotic patients who received DCV + SOF + RBV for 12 or 24 weeks, interim SVR rates were 100% (4/4) and 81% (39/48), respectively.[42]

The European Multicenter Compassionate Use study (A1444-237), GT3 treatment-naïve and -experienced patients received DCV + SOF ± RBV for 24 weeks as determined by the provider. In cirrhotic patients, interim SVR rates were 88% (37/42) with DCV + SOF and 86% (25/29) with DCV + SOF + RBV. Interim SVR rates were 85% (11/13) in CTP A, 86% in CTP B and 100% (2/2) in CTP C patients treated with DCV + SOF + RBV. Interim SVR rates were 100% (19/19) in CTP A, 80% (12/15) in CTP B and 75% (6/8) in CTP C patients treated with DCV + SOF.[43]

These data indicate GT3 cirrhotic patients may benefit from: 1) an extended 24-week treatment duration in those with CTP B and C; and 2) addition of RBV. However, if a patient cannot tolerate RBV, then DCV + SOF alone can be considered for the remainder of the 24-week course. These recommendations should be interpreted with caution because much of the data are available only from abstracts, non-randomized preliminary studies (e.g., SVR_4 rates), and sub-analyses with small sample sizes.

Sofosbuvir + pegylated interferon + ribavirin

For patients who tolerate interferon, SOF + PEG-IFN + RBV for 12 weeks is an effective regimen, particularly for GT3 cirrhotic patients, although this regimen is not FDA approved. In addition to SOF + PEG-IFN + RBV having the highest SVR rates in GT3 cirrhotics, failure of this regimen is not associated with development of RAPs, potentially allowing treatment with an NS5A inhibitor in the future.

In a Phase II open-label study (LONESTAR-2) of GT3 treatment-experienced patients (n = 24, 50% cirrhotic) who received SOF + PEG + RBV for 12 weeks, SVR was achieved in 83% (10/12) of patients without cirrhosis and 83% (10/12) of those with cirrhosis. [38] The larger, randomized controlled study (BOSON), GT3-infected patients received either SOF + RBV for 16 weeks (n = 196) or 24 weeks (n = 199) or SOF + PEG + RBV for 12 weeks (n = 197).[35] In treatment-naïve patients, SVR of 95% (89/94) was achieved with SOF + PEG + RBV; with SVR 96% (68/71) and 91% (21/23) in those without and with cirrhosis, respectively. In treatment-experienced patients, SVR of 91% (79/87) was achieved with SOF + PEG + RBV for 12 weeks; with SVR 94% (49/52) and 86% (30/35) in those without and with cirrhosis, respectively. The high SVR observed in cirrhotic patients supports the use of this regimen for those who are interferon eligible.

Sofosbuvir + ribavirin

SOF + RBV for 24 weeks is an FDA-approved regimen for HCV GT3 supported by the results of a Phase III randomized study (VALENCE) of 250 European patients.[47] In treatment-naïve patients, SVR was achieved in 94% (86/92) of those without cirrhosis and 92% (12/13) of those with cirrhosis. In treatment-experienced patients, SVR was attained in 87% (87/100) of those without cirrhosis and 60% (27/45) of those with cirrhosis.[24] Another randomized controlled study (BOSON) evaluated patients who received SOF + RBV for either 16 weeks (n = 196) or 24 weeks (n = 199). In treatment-naïve patients, SVR rates in the 24-week SOF + RBV arm were 88% (83/94) overall and 90% (65/72) and 82% (18/22) in those without and with cirrhosis, respectively. In treatment-experienced patients, SVR rates in the the 24-week SOF + RBV arm were 80% (70/88) overall and 82% (44/54) and 77% (26/34) in those without and with cirrhosis,

respectively. In this and other studies, shorter treatment duration (12-16 weeks) with SOF + RBV resulted in lower SVR rates (21-77%).[33-35,48] In preliminary intention-to-treat analysis of VA data of treatment-naïve and -experienced Veterans, SVR_4 rates with SOF + RBV for 24 weeks were 64% (134/210) with advanced liver disease (defined as FIB-4 >3.25). In the VA subgroup that completed 24 weeks of SOF + RBV, SVR_4 rates were 69%. Compared with other treatment options, the treatment duration with SOF + RBV is longer (24 weeks) in non-cirrhotic patients and results in sub-optimal SVR in cirrhotic patients.

VII. Chronic HCV Genotype 4 Infection

Including HIV coinfection*

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

Key Points

- Selection of an appropriate regimen and treatment duration for patients with GT4 infection depends on stage of liver disease, prior treatment history, and concomitant medications.
- EBR/GZR or OBV/PTV/RTV + DSV should not be used in patients with moderate to severe hepatic impairment (CTP B and C).
- Patients experiencing virologic failure with a DAA-based regimen should have resistance testing prior to re-treatment performed through the VHA Public Health Reference Laboratory (email V21PHRL@va.gov) or a commercial laboratory (see Section XV, Appendix B).

Table 15. **Treatment Regimens for GT4**

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 patients with or without cirrhosis:

- *EBR/GZR (50/100 mg): 1 tablet orally daily for 12 weeks*
- *LDV/SOF (90/400 mg/day): 1 tablet daily for 12 weeks*

Treatment-experienced (prior PEG-IFN + RBV) patients with or without cirrhosis:

- *EBR/GZR (50/100 mg): 1 tablet orally daily + RBV for 16 weeks*
- *LDV/SOF (90/400 mg/day): 1 tablet daily for 12 weeks*
- *OBV/PTV/RTV (12.5/75/50 mg): 2 tablets once daily in the morning with food + RBV (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks; DSV not needed.*

Alternative regimens

Treatment-naïve patients with or without cirrhosis:

- *OBV/PTV/RTV (12.5/75/50 mg): 2 tablets once daily in the morning with food + RBV (1,000*

Table 15. **Treatment Regimens for GT4**
mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks; DSV not needed.

The following summarizes the main trials supporting treatment in GT4 patients. For details regarding HIV/HCV-coinfected patients, see Section XII, Groups with Special Considerations for Therapy, on HCV treatment in patients with HIV/HCV coinfection.

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).[9] 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.[16] 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.

Ledipasvir/sofosbuvir

LDV/SOF for 12 weeks was evaluated in 21 patients with GT4 infection in the NIAID SYNERGY study.[49] 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).

Ombitasvir/paritaprevir/ritonavir

In an open-label Phase IIb study (PEARL-1) of 86 treatment-naïve GT4-infected patients who received OBV/PTV/r (without DSV) ± RBV for 12 weeks, SVR was achieved in 100% (42/42) and 91% (40/44) of those who received treatment with and without RBV, respectively.[50] In the same study, 49 treatment-experienced GT4-infected patients who previously failed PEG-IFN + RBV were re-treated with OBV/PTV/r + RBV for 12 weeks; 10% had METAVIR ≥F3 fibrosis and 47% were prior null responders. SVR was achieved in 100% (49/49).[50]

A Phase III study (AGATE-1) evaluated the safety and efficacy of OBV/PTV/r (without DSV) + RBV in GT4-infected treatment-naïve and treatment-experienced patients (previously treated with PEG-IFN/RBV, SOF/PEG-IFN/RBV or SOF/RBV), all with compensated cirrhosis.[51] Patients who were treatment-naïve or previously treated with PEG-IFN + RBV (n = 120) were randomized to 12 weeks or 16 weeks of OBV/PTV/r

+ RBV. Preliminary results found SVR 96% (52/54) in the 12-week arm and SVR 100% (49/49) in the 16-week arm.

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 course of treatment.

Table 16. Diagnosis of Compensated Cirrhosis for the Purpose of Identifying Treatment Candidates

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	• Both elastography and ARFI are FDA-approved, ultrasound-based techniques for estimating the extent of liver fibrosis. • FibroScan® value of >12.5 kilopascals has been associated with histologic cirrhosis. • ARFI value of >1.75 meters/second has been associated with histologic cirrhosis.
Serum Markers of Fibrosis/Cirrhosis • Platelet count • APRI • FIB-4 • HALT-C cirrhosis score • 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. • HALT-C cirrhosis score predicts likelihood of having cirrhosis based on standard clinical data. • 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$^{1/2}$; HALT-C cirrhosis score (see http://archives.niddk.nih.gov/haltctrial/displaypage.aspx?pagename=haltctrial/cirrhosis.html)

* 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 Compensated Cirrhosis for the Purpose of Identifying Treatment Candidates

See Table 16. Noninvasive and invasive methods to determine the presence and stage of cirrhosis are continually evolving.

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 one in 500 cases) and mortality (approximately 1 in 2,000-3,000 cases).

Serum markers

Routine blood tests can assist in identifying patients with advanced liver disease and, in some instances, predict the likelihood of developing decompensated disease or HCC. Serum markers of fibrosis (e.g., APRI, FIB-4, FibroSure®) may suggest the presence of advanced fibrosis or cirrhosis (Table 10). Similarly, the Ghany HALT-C score uses standard clinical data to predict the likelihood of a patient having cirrhosis. (see archives.niddk.nih.gov/haltctrial/displaypage.aspx?pagename=haltctrial/cirrhosis.html). A score of >0.6 (i.e., >60%) generally is considered as an indication of cirrhosis. A Lok HALT-C HCC score of >3.25 is associated with increased risk of developing HCC in the subsequent 3-5 years (see archives.niddk.nih.gov/haltctrial/displaypage.aspx?pagename=haltctrial/hccform.html).

Platelet counts are an additional noninvasive tool to identify cirrhotic patients with more advanced cirrhosis. 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, whereas patients with platelet counts of <100,000/mm^3 have an even higher risk of developing HCC.

Radiological studies

Findings of 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 fibrosis assessment

The FDA has approved two specialized ultrasound-based evaluations, vibration-controlled transient elastography (FibroScan®) and acoustic radiation force impulse (ARFI) imaging, to monitor liver fibrosis progression. These modalities have been correlated with stage of histologic fibrosis; cutoffs that

correspond to histologic cirrhosis have been developed, but may vary by population studied. However, not all VA facilities offer these studies.

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 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 **12 weeks after completion of treatment** to determine whether SVR was achieved.

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-III) • If the HCV RNA is quantifiable* at week 4 or at any time point thereafter, reassess HCV RNA in 2 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-III) • HCV RNA levels should be assessed at 12 weeks after completion of treatment to determine whether SVR was achieved. (A-I)

*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 should be considered at the end of treatment. 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 24 weeks after the completion of treatment is 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. Among patients receiving OBV/PTV/r + DSV therapy, liver function tests including direct bilirubin levels should be performed at baseline, at weeks 2 and 4 of starting treatment, and as clinically indicated thereafter. Treatment with EBR/GZR or OBV/PTV/r + DSV should be discontinued if ALT levels remain persistently >10 times the 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.[52] Some laboratories that use HCV RNA assays with a 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 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 therapy with OBV/PTV/r + DSV ± RBV and alternative methods of contraception used.
- Anemia occurring during treatment with RBV-containing regimens should be managed by RBV dosage reduction rather than use of erythropoiesis-stimulating agents.

Reporting unexpected or serious adverse events

As discussed in the "Introduction under Limitations," 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/).

Daclatasvir + sofosbuvir[53]

The most common adverse events associated with DCV + SOF in clinical trials were headache (14%), fatigue (14%), nausea (8%), and diarrhea (5%). Rarely, transient and asymptomatic lipase elevations of >3 times the upper limit of normal (ULN) have been observed (2%). During post-marketing, serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with DCV + SOF. Refer to DDI table for additional information (Appendix A, Table 28).

Elbasvir/grazoprevir ± ribavirin[8]

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%).

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 with ongoing or 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]). Refer to Section IX, Laboratory Monitoring, for recommendations on monitoring liver function tests.

Ledipasvir/sofosbuvir[20,21]

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. Postmarketing 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 28).

Ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin[54]

The most common reported adverse events (>10%) in clinical trials with OBV/PTV/r + DSV + RBV were fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. Without RBV, the most commonly reported adverse events (≥5% of patients) with OBV/PTV/r + DSV were nausea, pruritus, and insomnia.

During clinical trials with OBV/PTV/r + DSV ± RBV, ALT elevations of >5 times the ULN occurred in approximately 1% of patients. ALT elevations were typically asymptomatic, occurred during the first 4 weeks of treatment, and declined within 2-8 weeks of onset with continued use. Refer to Section IX, Laboratory Monitoring, for recommendations on monitoring liver function tests.

ALT elevations were significantly more frequent in female patients using ethinyl estradiol-containing medications such as combined oral contraceptives, contraceptive patches, and contraceptive vaginal rings. Ethinyl estradiol-containing medications must be discontinued prior to starting therapy with OBV/PTV/r + DSV ± RBV. Alternative methods of contraception (e.g., progestin-only contraception or

non-hormonal methods) are recommended during therapy. Ethinyl estradiol-containing medications can be restarted approximately 2 weeks following completion of OBV/PTV/r + DSV ± RBV treatment.

Sofosbuvir + simeprevir ± ribavirin[31,55]

The most common adverse events associated with SOF + SMV ± RBV for 12 weeks in clinical trials were fatigue (25%), headache (21%), nausea (21%), insomnia (14%), and pruritus (11%). A higher incidence of rash occurred in the RBV-containing arm (11% vs. 7%). Grade 3 or 4 adverse events were higher in the 24-week regimens (17% and 13% with and without RBV, respectively) compared with the 12-week regimens (4% and 7% with and without RBV, respectively). In the 24-week arms, dizziness (16%) and diarrhea (16%) also were reported. Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with SOF + SMV. Refer to the DDI table for additional information (Appendix A, Table 28).

Rash and photosensitivity

In clinical trials with SMV + PEG-IFN + RBV, rash including photosensitivity occurred most frequently in the first 4 weeks of treatment, but can occur at any time during treatment. The majority (99%, 215/218) of rash and photosensitivity events were of mild (Grade 1) or moderate (Grade 2) severity. There were no reports of life-threatening (Grade 4) rash. Two SMV-treated patients experienced photosensitivity reactions that resulted in hospitalization. Rash and photosensitivity reactions were more likely to occur in patients with higher SMV exposures.

Patients should be counseled to use sun-protective measures, limit sun exposure, and avoid tanning devices during treatment with an SMV-based regimen. Patients with mild or moderate rash should be followed for possible progression of rash, including the development of mucosal signs (e.g., oral lesions, conjunctivitis) or systemic symptoms. If the rash becomes severe, SMV should be discontinued. Consider urgent medical care and dermatological consultation if needed. Patients should be monitored until the rash has resolved.

Sulfa allergy

SMV contains a sulfonamide moiety. Based on limited data, patients with a history of sulfa allergy enrolled in clinical trials (n = 16) did not appear to have an increased incidence of rash or photosensitivity reactions.

Dyspnea

In clinical trials of SMV + PEG-IFN + RBV, increased dyspnea occurred in patients treated with SMV-based therapy compared with placebo-treated patients (12% and 8%, respectively); the majority of events occurred in the first 4 weeks of treatment. The dyspnea events were of mild or moderate severity (Grade 1 or 2). No patients discontinued SMV treatment due to dyspnea.

Hyperbilirubinemia

Approximately 50% of SMV-treated patients in clinical trials experienced elevated bilirubin levels compared with 26% of placebo-treated patients. Elevations of both direct and indirect bilirubin were predominately mild (Grade 1; >1.1 to ≤ 1.5 times the ULN) to moderate (Grade 2; >1.5 to ≤2.5 times the ULN) in severity. Bilirubin elevations occurred early after treatment initiation, peaking by week 2, and

were rapidly reversible upon SMV discontinuation. Bilirubin elevations generally were not associated with elevations in liver transaminases.

Sofosbuvir + ribavirin[56]

The most common adverse events observed with SOF + RBV for 12-24 weeks were fatigue (30-38%), headache (24-30%), nausea (13-22%), insomnia (15-16%), and pruritus (11-27%). Approximately 10% of patients treated with SOF + RBV experienced a hemoglobin of <10 g/dL and <1% developed a hemoglobin level of <8.5 g/dL. Neutropenia (absolute neutrophil count [ANC] <750/mm^3) and thrombocytopenia (platelet counts of <50,000/mm^3) were not observed. Rarely, total bilirubin elevation of more than 2.5 times the ULN was observed with SOF + RBV treatment (3% with 12 weeks and 3% with 24 weeks). Bilirubin levels peaked during the first 1 to 2 weeks of treatment and subsequently decreased and returned to baseline levels by post-treatment week 4. These bilirubin elevations were not associated with transaminase elevations.

Sofosbuvir + peginterferon + ribavirin[56]

The most common adverse events with SOF + PEG-IFN + RBV were fatigue (59%), headache (36%), nausea (34%), and insomnia (25%). Anemia occurred in 22% of patients (hemoglobin <10 g/dL). Neutropenia developed in approximately 20% of cases and thrombocytopenia in <1% of cases. Anemia was managed by RBV dosage reduction in all studies, and <1% of patients received a blood transfusion.

Erythropoiesis-stimulating agents (ESAs) are not FDA approved for the treatment of anemia occurring during HCV treatment. In a controlled clinical trial comparing ESA use with RBV dosage reduction for treatment of anemia occurring during HCV treatment, patients receiving an ESA had an increased risk of thromboembolic events, including pulmonary embolism, acute myocardial infarction, cerebrovascular accidents, and deep venous thrombosis when compared with patients managed by RBV dosage reduction. In addition, SVR rates were similar in the two arms. Because of the risks associated with ESAs, anemia occurring during hepatitis C treatment with RBV-containing regimens should be managed by RBV dosage reduction. ESA use should comply with PBM Criteria for Use of these agents (available at www.pbm.va.gov/PBM/clinicalguidance/criteriaforuse/Erythropoiesis_Stimulating_Agent_CFU_for_Hepatitis_C_treatment_related_anemia.doc).

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 has been updated to alert providers about potential DDIs with all approved HCV antiviral treatment regimens.

Drug-Drug Interactions[8,20,21,54-56]

Refer to the Appendix A, Table 28 and Table 29 for summary of DDIs.

All current HCV DAA-based treatment regimens have potentially significant interactions with commonly used drugs. A list of DDIs, summarized from the product inserts, is found in Appendix A, Table 28 and Table 29. Practitioners are strongly encouraged to consult with a knowledgeable clinical pharmacist and to use the web-based resources developed by Liverpool University to evaluate DDI prior to starting DAA treatment (www.hep-druginteractions.org/). CPRS has been updated to alert providers about potential DDIs with all approved HCV antiviral treatment regimens.

Both LDV and SOF are substrates for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and as such, P-gp inducers may decrease LDV and/or SOF 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. Hence, the overall potential for clinically significant drug interactions is low.

EBR and GZR are substrates of CYP3A and P-gp and GZR is a substrate of OATP1B1/3 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 are 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 29. EBR/GZR are inhibitors of the drug transporter BCRP and may increase plasma concentrations of co-administered BCRP substrates.

DCV is a substrate of CYP3A and an inhibitor of P-gp, OATP 1B1 and 1B3, and BCRP. Moderate or strong inducers of CYP3A may decrease the plasma levels and therapeutic effect of DCV. Since strong CYP3A inhibitors may increase the plasma levels of DCV, the DCV dosage should be reduced to 30 mg once daily. DCV is contraindicated with strong CYP3A inducers as this may lead to lower exposure and loss of efficacy of DCV. When administered with a moderate CYP3A inducer, the DCV dosage should be increased to 90 mg once daily. Because DCV also is an inhibitor of P-gp, OATP 1B1 and 1B3, and BCRP, administration of DCV may increase systemic exposure to medications that are substrates of these transporters and proteins, which could increase or prolong that medication's therapeutic or adverse effects.

SMV is metabolized by the CYP enzyme, CYP3A; coadministration with moderate or strong inducers or inhibitors of CYP3A is not recommended as this may decrease or increase SMV concentrations, respectively. SMV is an inhibitor of P-gp and the drug transporter organic anion transporting polypeptide (OATP) 1B1/3. SMV mildly inhibits CYP1A2 activity and intestinal CYP3A4 activity, but does not affect hepatic CYP3A4 activity. Coadministration of SMV with drugs that are primarily metabolized by CYP3A4 may result in increased plasma concentrations of those drugs.

PTV and RTV are primarily metabolized by CYP3A enzymes; coadministration with strong inhibitors of CYP3A may increase PTV and RTV concentrations. Dasabuvir is primarily metabolized by CYP2C8

enzymes; coadministration with drugs that inhibit CYP2C8 may increase DSV plasma concentrations. OBV, PTV, and DSV are inhibitors of UGT1A1, and RTV is an inhibitor of CYP3A4. PTV is an inhibitor of OATP1B1 and OATP1B3 and PTV, RTV, and DSV are inhibitors of BCRP. Coadministration with drugs that are substrates of CYP3A, UGT1A1, BCRP, OATP1B1, or OATP1B3 may result in increased plasma concentrations of such drugs. OBV, PTV, DSV, and RTV are substrates of P-gp. OBV, PTV, and DSV are substrates of BCRP. PTV is a substrate of OATP1B1 and OATP1B3; inhibition of P-gp, BCRP, OATP1B1, or OATP1B3 may increase the plasma concentrations of HCV drugs.

Storage and Stability[8,21,54-56]

LDV, SOF, and SMV can be stored at room temperature (<86°F), but exposure of the medication to direct sunlight should be avoided. OBV/PTV/RTV plus DSV can be stored at room temperature (<86°F). DCV and EBR/GZR should be stored at room temperature between 59°F and 86°F. EBR/GZR should be in the original package until use to protect from moisture.

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.

Missed Doses[8,21,54-56]

Patients should be instructed to take a missed DCV dose as soon as possible that day and to take the next DCV dose at the regular time the following day.

Patients should be instructed to take a missed EBR/GZR dose as soon as possible that day and to take the next EBR/GZR dose at the regular time the following day.

Patients should be instructed to take a missed SOF ± LDV dose as soon as possible that day and to take the next SOF ± LDV dose at the regular time the following day.

Patients should be instructed to take the missed dose of OBV/PTV/RTV within 12 hours of the scheduled dose and to take the missed dose of DSV within 6 hours of the scheduled dose. If more than 12 hours has passed since OBV/PTV/RTV is usually taken or more than 6 hours has passed since DSV is usually taken, the missed dose should NOT be taken and the patient should take the next dose at the usual scheduled time.

Patients should be instructed to take a missed SMV dose if it is less than 12 hours from the next scheduled SMV dose and to take the next SMV dose at the regular time the following day.

XII. Groups with Special Considerations for Therapy

Key Points

- HIV status should be determined for all patients with HCV.
- DDIs with HIV antiretroviral therapy should be taken into account when selecting a hepatitis C regimen.
- Sofosbuvir-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 or OBV/PTV/RTV + DSV should not be used in patients with moderate to severe hepatic impairment (CTP B and C).
- OBV/PTV/RTV + DSV should not be used in patients who are not suppressed on HIV antiretroviral therapy.

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. The use of interferon-containing regimens is associated with worsening of these conditions. 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, while multiple studies show successful treatment of patients who have short durations of abstinence or infrequent use of alcohol. Thus, automatic disqualification of patients as treatment candidates based on length of abstinence is unwarranted and strongly discouraged.

The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once a month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. Patients with active substance or alcohol use disorders may be considered for therapy on a case-by-case basis, and care should be coordinated with substance use treatment specialists.

HIV/HCV Coinfection

For HCV antiviral treatments options in HIV/HCV coinfection, refer to Tables 6-10.

The Panel recommends that HIV/HCV-coinfected patients receive the same HCV antiviral regimen as HCV-monoinfected patients, 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.

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.

LDV/SOF ± RBV can be used in HIV/HCV-coinfected patients who are not receiving HIV antiretroviral therapy **OR** have experienced DDIs that would preclude use of other HCV DAA agents. If an OBV/PTV/RTV + DSV (OBV/PTV/r + DSV) regimen is being considered, the patient should be on a suppressive HIV antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance due to the inclusion of RTV in the OBV/PTV/r + DSV regimen. HIV antiretroviral regimens that are acceptable for use with OBV/PTV/r + DSV include tenofovir/emtricitabine in combination with either atazanavir 300 mg (without RTV) once daily or raltegravir 400 mg twice daily Refer to the Appendix A, Table 28 and Table 29, and the product prescribing inserts for a complete list of drug interactions between HCV and HIV agents.

Selecting Patients for Treatment

Patients should be managed in collaboration with an ID/HIV specialist. In antiretroviral therapy-naïve HIV-infected patients with HCV coinfection, initiation of HIV antiretroviral therapy 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, provided that OBV/PTV/r + DSV is not used in HIV treatment-naïve patients. 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 29) 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 antiretroviral therapy (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.[1]

HIV/HCV Coinfection Clinical Trials

A summary of results from HCV clinical trials involving interferon-free regimens 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.[57] The majority (74%) of patients was receiving HIV ART; permitted regimens included tenofovir/emtricitabine in combination with efavirenz, rilpivirine, or raltegravir. Because LDV/SOF is known to raise tenofovir 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 was found to have a detectable HCV RNA level 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.

ALLY-2 is an open-label study that examined the efficacy and safety of DCV (dose adjusted for the concomitant antiretroviral regimen) plus SOF given for: 1) either 12 weeks or 8 weeks in 151 treatment-naïve HIV/HCV-coinfected patients and 2) 12 weeks in 52 treatment-experienced HIV/HCV-coinfected patients.[36] Among the 203 enrolled GT1-4 patients, 83% had GT1; 14% compensated cirrhosis; 94% had an HIV RNA level of <50 copies/mL, and the median CD4 count was >500 cells/mm^3. Patients were on HIV regimens that included boosted darunavir, atazanavir, and lopinavir, efavirenz, nevirapine, rilpivirine, raltegravir, and dolutegravir. Among HCV treatment-naïve GT1 patients, SVR was reported in 96% (95% CI: 90-99) treated for 12 weeks and 76% (95% CI: 60, 80) treated for 8 weeks. Among HCV treatment-experienced GT1 patients (71% with IFN or PEG-IFN plus RBV; 21% with prior PEG-IFN/RBV/NS3/4A inhibitor; and 6% prior SOF/RBV) treated for 12 weeks, SVR was 98% (95% CI: 88, 100). Among the 26 patients with GT2-4, SVR was 100% in the two 12-week arms and 78% in the 8-week arm. Among the 24 patients with cirrhosis in the combined 12-week groups, SVR was 92% (22/24). The most commonly reported side effects were fatigue (17%), nausea (13%), and headache (11%). These findings show that DCV + SOF for 12 weeks are associated with a high SVR rate in HIV/HCV-coinfected patients with HCV GT1-4, regardless of prior HCV therapy or the presence of cirrhosis. DCV + SOF should be considered if DDI precludes the use of other HCV regimens (see Appendix A, Table 28 and Table 29, for DDIs).

C-EDGE is an open-label, single-arm Phase III study examining the efficacy and safety of EBR/GZR for 12 weeks in 218 treatment-naïve GT1, 4, or 6 HIV/HCV-coinfected patients.[58] 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 the GT4-infected patients and in the 2 patients with GT6 infection. All patients with cirrhosis achieved an SVR (35/35, 100%). Baseline RAPs occurred in 7% (10/140) of those with GT1a and 12% (5/43) of those with GT1b; 87% (13/15) achieved SVR. In GT1a patients with NS5A RAPs conferring a greater than 5-fold resistance to EBR, 75% (3/4) achieved SVR. There were no serious adverse events. The most commonly reported side effects were fatigue (13%), headache (12%), and nausea (9%). Grade 3 and Grade 4 ALT elevations were observed in 5 patients (2%). The data suggest that 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.

The multicenter, open-label Phase II/III clinical trial TURQUOISE-I examined the safety and efficacy of 12 and 24 weeks of the fixed-drug combination of OBV/PTV/r + DSV + weight-based RBV (1,000 or 1,200 mg daily according to body weight <75 kg and ≥75 kg, respectively) in HIV/HCV-coinfected patients with HCV GT1 infection (treatment naïve and experienced, including those with cirrhosis).[59] The mean CD4 count of study participants was >500 cells/mm^3; cirrhosis was present in 19% of participants in both the 12-week and the 24-week arms; >65% were HCV treatment naïve, 16% were null responders, and the remainder were either relapsers or partial responders. ART regimens consisted of tenofovir/emtricitabine combined with atazanavir or raltegravir. Overall, SVR rates were 94% (29/31) in the 12-week arm and 91% (29/32) in the 24-week arm. In the 12-week arm, 1 patient withdrew prior to study completion and 1 patient relapsed at post-treatment week 4. In the 24-week arm, 1 patient experienced on-treatment virologic failure and 2 patients appeared to be reinfected with HCV. No serious adverse events or adverse events resulting in treatment discontinuations were reported. The most commonly reported side effects were fatigue, headache, nausea, and insomnia.[59]

PHOTON-1 and PHOTON-2 examined the use of SOF + RBV (1,000 mg or 1,200 mg daily) in HIV/HCV-coinfected patients.[60,61] PHOTON-1 included 223 treatment-naïve GT1 patients, and both treatment-naïve and -experienced GT2 and GT3 patients from the United States and Puerto Rico. PHOTON-2 included 274 HIV/HCV-coinfected patients with GT1, 2, 3, or 4 infection from Europe and Australia. SOF + RBV should not be used for GT1 and 4 patients due to suboptimal SVR rates (81-88%). In pooled analysis of PHOTON-1 and PHOTON-2 data, a similar SVR (89%) was observed for treatment-naïve GT2 patients treated for 12 weeks and treatment-experienced GT2 patients treated for 24 weeks. In treatment-naïve GT3 patients, SVR was attained in 67% vs. 91% in those treated for 12 vs. 24 weeks, respectively; in treatment-experienced GT3 patients, SVR was attained in 88% after 24 weeks of therapy. In GT2 patients with and without cirrhosis, SVR occurred in 100% and 88%, respectively. In GT3 patients with and without cirrhosis, SVR was achieved in 100% and 91%, respectively, in treatment-naïve patients and SVR occurred in 79% and 95%, respectively, in treatment-experienced patients. In both PHOTON-1 and PHOTON-2, no significant change in HIV RNA or CD4 percentages was observed. However, 4 patients (1.5%) in PHOTON-2 experienced low-level HIV viral breakthrough that resolved without a change in the HIV regimen. The data suggest that, regardless of treatment history, 12 weeks of SOF + RBV therapy in GT2 patients can

achieve SVR in 89-90%, but 24 weeks of therapy is needed in GT3 patients to achieve SVR in 88-91%. However, SOF + RBV is not recommended in treatment-experienced GT3 patients with cirrhosis given the low SVR rates seen in HIV negative studies.

The most commonly reported adverse effects in HIV/HCV-coinfected patients treated with SOF + RBV were fatigue (30-38%), headache (24-30%), nausea (13-22%), and insomnia (15-16%).[56] Hyperbilirubinemia (total bilirubin >2.5 mg/dL) was observed in 22/114 (20%) of HIV/HCV-coinfected patients treated with SOF + RBV for 24 weeks. Of these patients, 20 (95%) also were prescribed atazanavir-containing regimens. About 20% of HIV/HCV-coinfected patients developed Grade 2 anemia (hemoglobin level of <10 g/dL); only 2% developed a Grade 3 anemia (hemoglobin level of <8.5 g/dL). One-fourth of HIV/HCV-coinfected patients required RBV dosage reduction for management of anemia. For additional information, refer to Sofosbuvir (NDA 204671). Presentation to: FDA Antiviral Drugs Advisory Committee; October 25, 2013.[62]

Although there are few data on the use of SMV (SMV) in HIV/HCV-coinfected patients, the use of SOF + SMV (±RBV) for 12 weeks can be considered in GT1-infected patients who have NS5A RAPs, but do not appear resistant to SMV. SMV use in HIV/HCV-coinfected patients is not addressed in the FDA labeling.

HIV/HCV Drug-Drug Interactions[1,8,21,53-56,63-67]

Refer to Appendix A, Table 29 for DDIs. RBV is contraindicated for use with didanosine and can increase the risk of anemia with zidovudine (AZT). Although SOF in combination with RBV was well-tolerated in studies of HIV/HCV-coinfected patients, LDV/SOF in combination with RBV has not been studied in HIV/HCV-coinfected patients. EBR/GZR is contraindicated with certain HIV protease inhibitors including atazanavir, darunavir, lopinavir, saquinavir, and tipranavir, as coadministration may increase the risk of ALT elevations due to a significant increase in GZR plasma concentrations caused by OATP1B1/3 inhibition.

Laboratory Monitoring[1,6,8,21,53-56,64-67]

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*.[1]

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
DCV	No dosage adjustment needed.	A-I
EBR/GZR	No dosage adjustment needed, including use in hemodialysis patients.	A-I
LDV	No dosage adjustment needed.	A-I
OBV/PTV/ RTV + DSV	No dosage adjustment needed.	A-II
PEG-IFN alfa-2a	Dosage reduce to 135 mcg/week subcutaneously once weekly for CrCl <30 mL/min, including hemodialysis.	A-I
PEG-IFN alfa-2b	Dosage reduce by 25% for CrCl 30-50 mL/min and by 50% for CrCl <30 mL/min, including hemodialysis.	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
SMV	Has not been studied in HCV-infected patients with CrCl <30 mL/min.	A-I
SOF	Should not be used if CrCl <30 mL/min or end-stage renal disease.	A-I

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

Treatment	Comment	Grade
DCV	No dosage adjustment needed.	A-I
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
LDV	No dosage adjustment needed.	A-I
OBV/PTV/ RTV + DSV	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
PEG-IFN	Should not be used in patients with moderate or severe hepatic impairment (CTP B or C; CTP score ≥7).	A-l
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
SMV	Should not be used in patients with moderate or severe hepatic impairment (CTP B or C; CTP score ≥7) due to higher SMV exposures.	A-I
SOF	No dosage adjustment is required for patients with mild, moderate, or severe hepatic impairment (CTP A, B, or C).	A-l

Abbreviations: CrCL = creatinine clearance

Daclatasvir[53]

DCV 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 mild, moderate, or severe renal impairment. Patients with end-stage renal disease requiring hemodialysis had a 27% increase in DCV AUC and a 20% increase in unbound AUC compared with patients with normal renal function.

DCV does not require dosage adjustment for patients with mild, moderate, or severe hepatic impairment (CTP A, B, or C). No clinically significant differences in pharmacokinetics were observed in HCV-negative volunteers with CTP A, B, or C compared with a corresponding matched control group.

Elbasvir/grazoprevir[8]

No dosage adjustment of EBR/GZR is required in patients with any degree of renal impairment including patients receiving hemodialysis**.** 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.[68,69] 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 RAPs. Based on limited data in GT1a patients with CKD, baseline NS5A RAP 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 two 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.

Ledipasvir[21]

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).

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.

Ombitasvir/paritaprevir/ritonavir + dasabuvir[54,70]

Pharmacokinetic data suggest that the elimination of the OBV/PTV/RTV + DSV is not altered in patients with mild (CrCl 60-89 mL/min), moderate (CrCl 30-59 mL/min), or severe (CrCl 15-29 mL/min) renal insufficiency. This regimen with or without RBV was studied in 20 patients with chronic renal insufficiency (eGFR <30 mL/min), including 13 patients on hemodialysis. The trough levels of OBV/PTV/RTV + DSV appear similar compared with historical Phase III clinical trials. All 13 GT1a patients received RBV 200 mg daily; 8 patients required RBV dose interruption because of anemia. SVR was achieved in 90% (18/20).[70]

This regimen does not require dosage adjustment in patients with mild hepatic impairment (CTP A). This regimen is not recommended in patients with moderate hepatic impairment (CTP B), and is contraindicated in patients with severe hepatic impairment (CTP C).

Simeprevir[55]

SMV 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 mild, moderate, or severe renal impairment. Creatinine clearance was not identified as a significant covariate of SMV population pharmacokinetics in HCV-infected patients.

SMV is primarily cleared by the liver through biliary excretion. However, SMV does not require dosage adjustment in patients with mild hepatic impairment (CTP A). In HCV-negative patients, the mean steady-state AUC of SMV was 2.4-fold higher with moderate hepatic impairment (CTP B) and 5.2-fold higher with severe hepatic impairment (CTP C). The safety and efficacy of SMV have not been established in HCV-infected patients with CTP B or C. Due to higher SMV exposure and potentially increased adverse reactions, no dosage recommendation can be given for SMV in patients with moderate or severe hepatic impairment (CTP B or C).

Sofosbuvir[56]

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. CTP B and C patients with severe renal impairment (CrCl <30 mL/min) require consultation with an expert (see Section XIV, Resources).

Because PEG-IFN is not recommended and no dosage recommendation can be given for SMV in patients with decompensated cirrhosis (CTP B or C; CTP score ≥7), the safety and efficacy of SOF in combination with these agents have not been established. Collaboration with an experienced hepatologist is necessary to carefully consider the risks versus benefits of SOF-based treatment in patients with decompensated cirrhosis.

Hepatocellular Carcinoma

The following is based on expert opinion, given that minimal data are available. It is reasonable to treat HCV in any patient with HCC or other malignancy if there is a high likelihood that the cancer will be or has been cured. Curative treatments for solitary or early-stage HCC within Milan criteria include resection and thermal ablation as well as liver transplantation. For those receiving resection or thermal ablation, staging studies should indicate a high likelihood of success (e.g., absence of macrovascular invasion, clear margins). Among patients in whom HCC treatment is noncurative (i.e., palliative), treatment of HCV is unlikely to provide significant prolongation of life or improvement in symptoms, and is not recommended until evidence of survival benefit is available.

Pre-Liver Transplant and Post-Liver or -Other Solid Organ Transplant Patients

Close collaboration with the patient's transplant center is necessary to determine the timing of HCV treatment initiation (e.g., treat once patient is listed for transplant), and DDIs should be thoroughly evaluated in post-transplant patients (See Appendix A, Table 28).

The decision to treat, regimen selection, and management of treatment should be coordinated with the transplant center and/or specialists.

Table 20. Treatment Considerations for Patients Who Will or Have Received a Solid Organ Transplant (after consultation with Transplant Center)

Transplant status	HCV genotype	Regimen	Duration	Evidence grade	SVR % (N/N)	Comments
Pre-Liver Transplant (including CTP A, B, and C, as well as HCC)	GT1	LDV/SOF + RBV	12 weeks	B-II	CTP B: 87% (26/30)[15] CTP C: 86% (19/22)[15]	24 weeks CTP B: 89% (24/27)[15] CTP C: 87% (20/23)[15]
Pre-Liver Transplant (including HCC)	GT2	SOF + RBV *(combination with PEG-IFN may be considered but is not FDA approved)*	24-48 weeks	B-II	No data available	SVR 64% (25/39) for GT1, 2, 3, and 4.[71] Patients had HCC with compensated liver disease (CTP score <7).[71]
Post-Liver Transplant	GT1	LDV/SOF + RBV	12 weeks	B-II	F0-F3: 96% (53/55)[15] CTP A: 96% (25/26)[15] CTP B: 85% (22/26)[15] CTP C: 60% (3/5)[15]	24 weeks F0-F3: 98% (55/56)[15] CTP A: 96% (24/25)[15] CTP B: 88% (23/26)[15] CTP C: 75% (3/4)[15] RBV dosage was weight-based for patients without cirrhosis and CPT A; in CPT B and C patients, RBV was initiated at 600 mg/day and increased as tolerated.[72] Refer to Appendix A, Table 28, for DDIs.
Post-Liver Transplant	GT1	*In patients who cannot tolerate RBV*: LDV/SOF	24 weeks	B-III	Data not available	Effectiveness is presumed, based on use in non-transplant, treatment-experienced patients with cirrhosis.
Post-Liver Transplant	GT2	SOF + RBV (PEG-IFN may be considered) **NOT FDA APPROVED**	24 weeks	B-lll	77% (31/40)[73] 60% (19/32)[74] 50% (6/12)[74] with PEG-IFN	SVR rates included GT1, 3 and 4 patients. Refer to Appendix A, Table 28, for DDIs.

Transplant status	HCV genotype	Regimen	Duration	Evidence grade	SVR % (N/N)	Comments
Pre- or Post-Liver Transplant	GT3, GT4					Consult with a transplant center prior to starting treatment. In general, treatment options are the same as is recommended for treatment-naïve or treatment-experienced (as appropriate) patients with close attention to DDIs. **LDV/SOF + RBV and SOF + RBV + PEG-IFN have not been well studied in GT3 or GT4 pre- or post-liver transplant patients.**
Post-Other Solid Organ Transplant (kidney, heart, or lung)	GT1, 2, 3, or 4					Discuss with transplant center. **DO NOT USE regimens containing PEG-IFN in these populations. SOF has not been studied in non-liver transplant recipients.**

Dosages:

- PEG-IFN alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly
- RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food
- SOF 400 mg orally daily

Note: SOF should not be used as monotherapy or in reduced dosages; it should not be restarted if discontinued.

The decision to treat, regimen selection, and management of treatment should be coordinated with the transplant center and/or specialists.

Table 21. Alternative Treatments for Patients Who Will or Have Received a Solid Organ Transplant (after consultation with Transplant Center)

Transplant status	HCV genotype	Regimen	Duration	Evidence grade	SVR % (N/N)	Comments
Post-Liver Transplant	GT1	SOF + SMV *NOT FDA APPROVED*	12-24 weeks	B-II	12 weeks: 91% (-RBV)[75] 89% (+RBV)[75] F0-2: 97%[75] F3-4: 64%[75]	**AVOID USE in patients receiving cyclosporine**; refer to Appendix A, Table 28, for DDIs. Can be considered for patients who cannot tolerate RBV.
Post-Liver Transplant	GT1	OBV/PTV/RTV + DSV + RBV	12 weeks	B-II	F0-2: 97% (33/34)[76]	Dosage of tacrolimus or cyclosporine needs to be reduced because of DDIs. Refer to Appendix A, Table 28, for DDIs.

Table 22. **Treatment in Pre-Liver Transplant Patients**

GT1, including patients with CTP A, B, or C and suitable patients with HCC

- *LDV/SOF (90/400 mg/day): 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 (increased by 200 mg/day every 2 weeks only as tolerated if hemoglobin remains above 10 g/dL) in CTP B and C patients for 12 weeks. NOT FDA APPROVED.*

GT2, including patients including suitable patients with HCC

- *SOF (400 mg/day): 1 tablet daily + RBV (1,000 mg/day if <75 kg or 1,200 mg if ≥75 kg with food, in divided doses) for 24 to 48 weeks or until the time of transplantation, whichever occurs first.*

GT 3 or GT 4

- *Consult with a transplant center prior to starting treatment. In general, the treatment options are the same as is recommended for treatment-naïve or treatment-experienced (as appropriate) patients.*

The decision to treat patients undergoing evaluation or currently listed for liver transplantation should be discussed with the transplant center prior to beginning treatment. In general, patients awaiting liver transplantation can receive HCV antiviral therapy as described for patients with cirrhosis in the prior treatment sections (See Tables 6-10).

For GT1-infected patients with compensated cirrhosis, the FDA has approved the use of LDV/SOF for 12 weeks if treatment naïve and for 24 weeks if treatment experienced (see Section IV, "Chronic HCV

Genotype 1 Infection"). Treatment-experienced GT1-infected patients with compensated cirrhosis may also be treated with 12 weeks of LDV/SOF + RBV, with reported SVR of >95%. As described previously (see Section IV, "Genotype 1-Infected Patients with Cirrhosis, Decompensated"), LDV/SOF + RBV for 12 weeks achieves an SVR of 87-89% among GT1-infected patients with decompensated cirrhosis. Studies of the treatment efficacy in decompensated cirrhosis among non-GT1 patients are not available.

If HCV treatment is undertaken, it is preferable to achieve SVR prior to transplant. If this is not possible, studies suggest that having undetectable HCV RNA for more than 30 days prior to transplant reduces the risk of virologic recurrence post-transplant. Among 61 patients with HCC awaiting liver transplant (median MELD score of 8, CTP score of <7) who were treated with SOF + RBV for up to 48 weeks, 41 had undetectable HCV RNA at the time of transplant.[74] In the 39 evaluable post-transplant patients, the 12-week post-transplant virologic response (pTVR) was 64% (25/39). The longest duration for which this regimen has been studied is 48 weeks, thus the timing of treatment initiation should be considered carefully and in coordination with the patient's transplant center.[74]

Table 23. Treatment Regimens for Post-Liver or -Other Solid Organ Transplant Patients
*(See **Table 20**)*
GT1
• *LDV/SOF (90/400 mg/day): 1 tablet daily + RBV (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks.*
• *If RBV intolerant: LDV/SOF (90/400 mg/day): 1 tablet daily for 24 weeks.*
GT2
• *SOF (400 mg/day): 1 tablet daily + RBV (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 24 weeks. NOT FDA APPROVED.*
GT3
• *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.*
GT4
• *LDV/SOF (90/400 mg/day): 1 tablet daily + RBV (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks.*
• *If RBV intolerant: LDV/SOF (90/400 mg/day): 1 tablet daily for 24 weeks.*

Treatment in Post-Liver or -Other Solid Organ Transplant Patients

The decision to treat patients with recurrent HCV after a liver 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 and are listed in Appendix A, Table 28.

Ledipasvir/Sofosbuvir in the Post-Liver Transplant Setting

In a study of post-transplant patients with HCV, 223 patients were randomized to LDV/SOF + RBV for 12 or 24 weeks.[72] 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 level of cyclosporine or tacrolimus.

SOF + RBV have been evaluated in two Phase II trials of post-transplant HCV. In one study, 40 patients with post-transplant HCV recurrence were treated with SOF + RBV for 24 weeks. The majority of patients were HCV GT1-infected (73%); 40% had cirrhosis, and 23% had bridging fibrosis. In this study, the SVR rate was 77%. There were no deaths, graft loss, or rejection.[73] In a compassionate-use program, 44 patients with severe recurrence of HCV following liver transplantation, including fibrosing cholestatic hepatitis, were treated with SOF + RBV either with (n = 12) or without (n = 32) PEG-IFN for 24 weeks. The decision to use PEG-IFN was left to the treating physician. The reported SVR rates were 60% for SOF + RBV and 50% for SOF + PEG-IFN + RBV. Because of the severity of the HCV disease in patients at the time of treatment initiation, 15 patients died of progressive liver disease during the treatment period. No deaths were attributed to SOF + RBV treatment. Liver function tests (e.g., bilirubin, INR) improved with treatment.[73] Although these trials are small, they are consistent in suggesting that SOF + RBV is safe and effective in the treatment of HCV post-transplant.

Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir + Ribavirin in the Post-Liver Transplant Setting

CORAL-1 was a Phase II, open-label study of OBV/PTV/r + DSV + RBV for 12 weeks in 34 patients with recurrent HCV GT1 after liver transplantation.76 All patients had stage F0-F2 fibrosis and had received a

liver transplantation more than 1 year prior to starting the study medicines. Because of DDIs with calcineurin inhibitors, the starting dosage of tacrolimus was 0.5 mg/week or 0.2 mg every other day and the starting dosage of cyclosporine was one fifth of the pre-treatment total daily dosage, administered once a day. Use of mTor inhibitors (e.g., rapamycin, everolimus) was not permitted. The dosage of calcineurin inhibitors was adjusted during treatment based on trough levels. The average eGFR at baseline was 90 mL/min and was never less than 50 mL/min during treatment. SVR12 and SVR24 were achieved in 97% (33/34) of patients. One patient relapsed at post-treatment day 3. One patient stopped treatment because of an adverse event but achieved SVR. 17% (5/29) of patients had tacrolimus levels >15 ng/mL during treatment (mostly dosing errors) and 28% (8/29) had one or more tacrolimus levels below the reference range after stopping treatment. There were no episodes of rejection. Neither tacrolimus nor cyclosporine changed the trough levels of OBV, PTV, DSV, or RBV. Although OBV/PTV/r + DSV is FDA approved for use in post-transplant patients, because of the greater likelihood of DDIs with calcineurin inhibitors as well as lack of safety and efficacy data among patients with fibrosis levels METAVIR >F2, OBV/PTV/r + DSV is not recommended for treatment of patients with recurrent hepatitis C after liver transplantation.

Sofosbuvir and Simeprevir in the Post-Liver Transplant Setting

SOF + SMV ± RBV for 12 weeks has been evaluated in a non-randomized study of 109 post-transplant patients with GT1 infection (the majority of whom received therapy without RBV). In this study, the median age was 61 ± 6 years, the median time after transplant was 29 months, and 82% of patients were treatment experienced.[75] Post-transplant immunosuppressive regimens included tacrolimus (n = 98), cyclosporine (n = 9), and sirolimus (n = 1). Overall, SVR was 89% with SOF + SMV + RBV and 91% with SOF + SMV. SVR occurred in 97% of patients with METAVIR F0-2 fibrosis and in 64% of patients with METAVIR F3-4 fibrosis. In patients who received an RBV-containing regimen, all required RBV dosage reduction, and 50% received erythropoiesis-stimulating agents. Tacrolimus levels were not significantly altered, and no episodes of rejection occurred. This study suggests that the combination of SOF + SMV for 12 weeks may be considered as treatment for GT1-infected patients who cannot tolerate RBV. However, concomitant use of SMV with cyclosporine results in significantly increased SMV concentrations (approximately 6-fold) due to inhibition of OATP1B1, P-gp, and CYP3A; SMV should not be coadministered with cyclosporine. Although concomitant use of SMV with tacrolimus resulted in increased SMV concentrations (approximately 2-fold) due to inhibition of OATP1B1, no dosage adjustment is required for either drug. Given the potential DDI between SMV and cyclosporine (see Appendix A, Table 28), SMV use is contraindicated for use in patients receiving cyclosporine.

HCV Treatment in Patients Receiving Solid Organ Transplants Other Than Liver

SOF has not been studied in the setting of solid organ transplantation other than liver. Close collaboration with the patient's transplant center is encouraged to assess post-transplant treatment candidate selection and type of regimen. Patients without urgent need for HCV antiviral therapy would likely benefit from receiving future therapies that are more evidence based. No clinically significant DDI was observed with coadministration of LDV or SOF and cyclosporine and tacrolimus, making these two drugs potential treatment options for patients with solid organ transplants other than liver.

Extra-Hepatic Manifestations of HCV

Table 24. 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)

East Asian Ancestry

Higher SMV exposure occurred among individuals of East Asian ancestry and has been associated with increased adverse reactions, including rash and photosensitivity.[55]

Pregnancy and Lactation

The safety and efficacy of DAA therapy in pregnant or lactating women have not been established for any of the currently FDA-approved agents. Embryofetal toxicity has been observed in rats and rabbits administered with very high doses of DCV. In general 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. Two forms of effective contraception is required during RBV therapy and for 6 months after the last dose.[64,65]

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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XIV. Resources

Patient Related-Questions

- VHA HIV/HCV Clinical Consultation Service - hepatitis C consultation: 1-844-437-4636; HIV consultation: 1-800-933-3413

For Further Information

- VA National Hepatitis C Resource Program: Timothy.Morgan@va.gov
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- HCV Resistance Testing: V21PHRL@va.gov
- Current VA policies and information: www.hepatitis.va.gov
- 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 25. Summary of SVR Results from Phase II/III Studies of Sofosbuvir-Based Therapy in Genotype 1-Infected, Treatment-Naïve Patients

Trial	Regimen and Duration	Treatment Category	Non-Cirrhotic (SVR, %)	Cirrhotic (SVR, %)
ION-1[10]	LDV/SOF ± RBV x 12 weeks	Naïve	179/180 (99, – RBV) 178/184 (97, + RBV)	32/34 (94, – RBV) 33/33 (100, + RBV)
ION-1[10]	LDV/SOF ± RBV x 24 weeks	Naïve	181/184 (98, – RBV) 179/181 (99, + RBV)	31/33 (94, – RBV) 36/36 (100, + RBV)
ION-3[7]	LDV/SOF ± RBV x 8 weeks	Naïve	202/215 (94, – RBV) 201/216 (93, + RBV)	Not studied
ION-3[7]	LDV/SOF x 12 weeks	Naïve	206/216 (95)	Not studied
ELECTRON-2[22]	LDV/SOF x 12 weeks	Naïve	Not studied	13/20 (65) (all were CTP B)
ERADICATE[57]	LDV/SOF x 12 weeks	Naïve, HCV/HIV coinfected	10/10 (100, ARV untreated) SVR_4: 22/22 (100, ARV treated)	Not studied
COSMOS[31]	SOF + SMV ± RBV x 12 weeks	Naïve	Not studied	2/3 (67, – RBV) 6/6 (100, + RBV)
COSMOS[31]	SOF + SMV ± RBV x 24 weeks	Naïve	Not studied	5/5 (100, – RBV) 3/3 (100, + RBV)

Table 26. Summary of SVR Results from Phase II/III Studies of Sofosbuvir-based Therapy in Genotype 1-infected, Treatment-experienced Patients

Trial	Regimen	Treatment Category	Non-Cirrhotic (SVR, %)	Cirrhotic (SVR, %)
ION-2[17]	LDV/SOF ± RBV x 12 weeks	Experienced (PEG-IFN + RBV ± BOC or TVR)	83/87 (95, – RBV) 89/89 (100, + RBV)	19/22 (86, – RBV) 18/22 (82, + RBV)
ION-2[17]	LDV/SOF ± RBV x 24 weeks	Experienced (PEG-IFN + RBV ± BOC or TVR)	86/87 (99, – RBV) 88/89 (99, + RBV)	22/22 (100, – RBV) 22/22 (100, + RBV)
SYNERGY[49]	LDV/SOF x 12 weeks	Experienced (SOF + RBV relapsers)	7/7 (100)	7/7 (100)
ELECTRON-2[22]	LDV/SOF + RBV x 12 weeks	Experienced (SOF + RBV ± DAA)	19/19 (100)	Not studied
COSMOS[31]	SOF + SMV ± RBV x 12 weeks	Experienced (PEG-IFN + RBV)	13/14 (93, – RBV) 26/27 (93, + RBV)	4/4 (100, – RBV) 4/5 (80, + RBV)
COSMOS[31]	SOF + SMV ± RBV x 24 weeks	Experienced (PEG-IFN + RBV)	14/15 (93, – RBV) 19/24 (79, + RBV)	4/4 (100, – RBV) 9/9 (100, + RBV)

Table 27. Summary of SVR Results from Phase III Studies of Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir (OBV/PTV/r + DSV)-Based Therapy in Genotype 1-Infected Patients

Trial	Regimen	Treatment Category	Cirrhotic	SVR, %
SAPPHIRE-I,[26] n = 631	OBV/PTV/r + DSV + RBV x 12 weeks	GT1, Naïve	No	96% (455/473)
SAPPHIRE-II,[28] n = 394	OBV/PTV/r + DSV + RBV x 12 weeks	GT1, Experienced	No	96% (285/297) (95% in prior null responders)
PEARL-II,[27] n = 186	OBV/PTV/r + DSV ± RBV x 12 weeks	GT1b, Experienced	No	100% (91/91, – RBV) 97% (85/88, + RBV)
PEARL-III,[12] n = 419	OBV/PTV/r + DSV ± RBV x 12 weeks	GT1b, Naïve	No	99% (207/209, – RBV) >99% (209/210, + RBV)
PEARL-IV,[12] n = 305	OBV/PTV/r + DSV ± RBV x 12 weeks	GT1a, Naïve	No	90% (185/205, – RBV) 97% (97/100, + RBV)
TURQUOISE-II,[13] n = 380	OBV/PTV/r + DSV + RBV x 12 weeks	GT1, Naïve and Experienced	Yes	92% (191/208) GT1a: 89% (124/140) GT1a, relapser: 93% (14/15) GT1a, partial responder: 100% (11/11) GT1a, prior null responder: 80% (40/50) GT1b: 99% (67/68) GT1b, relapser: 100% (14/14) GT1b, partial responder: 86% (6/7) GT1b, prior null responder: 100% (25/25)
TURQUOISE-II,[13] n = 380	OBV/PTV/r + DSV + RBV x 24 weeks	GT1, Naïve and Experienced	Yes	96% (165/172) GT1a: 94% (114/221) GT1a, relapser: 100% (13/13) GT1a, partial responder: 100% (10/10) GT1a, prior null responder: 93% (39/42) GT1b: 100% (51/51) GT1b, relapser: 100% (10/10) GT1b, partial responder: 100% (3/3) GT1b, prior null responder: 100% (20/20)
TURQUOISE-III,[14] n = 380	OBV/PTV/r + DSV x 12 weeks	GT1b Naïve and Experienced	Yes	100% (60/60) Treatment-naïve: 100% (27/27) Treatment-experienced: 100% (33/33)

Table 28. Drug-Drug Interactions with HCV Antiviral Agents[8,21,53-56,77]

✓ = 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/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
Alpha1-adrenoreceptor antagonist						
alfuzosin HCL	?	?	✘	?	?	?
Beta-adrenoreceptor agonist						
salmeterol	?	?	✘ (may ↑ risk of cardiovascular events)	?	?	?
Antacids						
aluminum and magnesium hydroxide	✓	Separate dose by 4 hours (↓ LDV concentration)	?	✓	?	?
Antiarrhythmics						
digoxin	✓	use caution and monitor (may ↑ digoxin concentration)	✓	use caution and monitor (may ↑ digoxin concentration; *Patients already receiving DCV initiating digoxin*: Initiate digoxin at lowest appropriate dose. Monitor digoxin concentrations; adjust	?	use caution and monitor (may ↑ digoxin concentration)

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
				digoxin doses as necessary. *Patients already receiving digoxin prior to initiating DCV*: Measure serum digoxin concentrations before initiating DCV. Reduce digoxin dose by 30-50% or modify dose frequency and closely monitor.		
amiodarone	**?**	✘ (↑ amiodarone concentration; may ↑ risk of bradycardia and cardiac arrest; if amiodarone required, monitor inpatient for first 48 hrs, then daily outpatient for 2 wks)	use caution and monitor (may ↑ amiodarone concentration)	✘ (if given with SOF) (↑ amiodarone concentration; may ↑ risk of bradycardia and cardiac arrest; if amiodarone required, monitor inpatient for first 48 hrs, then daily outpatient for 2 wks)	✘ (if given with SMV or DCV) (↑ amiodarone concentration-- may ↑risk bradycardia and cardiac arrest; if amiodarone required, monitor inpatient for first 48 hrs, then daily outpatient for 2 wks)	use caution and monitor (may ↑ amiodarone concentration) ✘ (if given with SOF)
bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine,	**?**	**?**	use caution and monitor (may ↑ antiarrhythmic concentration)	**?**	**?**	use caution and monitor (may ↑

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
propafenone, quinidine						antiarrhythmic concentration)
Anticoagulant						
dabigatran	?	?	?	✘ (↑ dabigatran concentration in specific renal impairment groups)	?	?
Anticonvulsants						
carbamazepine, phenytoin, phenobarbital, oxcarbazepine	✘ (may ↓ EBR/GZR concentration)	✘ (may ↓ LDV/SOF concentration)	✘ (may ↓ OBV/PTV/r + DSV concentrations)	✘ (may ↓ DCV concentration)	✘ (may ↓ SOF concentration)	✘ (may ↓ SMV concentration)
Antifungals						
fluconazole	?	?	?	✓ (monitor for DCV adverse events)	?	✘ (may ↑ SMV concentration)
itraconazole, posaconazole	?	?	?	✓ (↓ DCV dose to 30mg/day)	?	✘ (may ↑ SMV concentration)
ketoconazole	✘ (may ↑ EBR/GZR concentration and ↑ risk of hepatotoxicity)	?	use caution and monitor (↑ ketoconazole concentration, dose ≤200 mg per day)	✓ (↓ DCV dose to 30mg/day)	?	✘ (may ↑ SMV concentration)
voriconazole	?	?	✘ (↓ voriconazole concentration)	✓ (↓ DCV dose to 30mg/day)	?	✘ (may ↑ SMV concentration)

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
Anti-gout						
Colchicine	?	?	?	✘	?	?
Antihyperlipidemic						
gemfibrozil	?	✘	✘ (↑ DSV concentration -- may increase risk of QT prolongation)	?	?	?
Antiinfectives						
clarithromycin, telithromycin	?	?	?	✓ (↓ DCV dose to 30mg/day)	?	✘ (may ↑ SMV concentration)
erythromycin	?	?	?	✓ (monitor for DCV adverse events)	?	✘ (may ↑ SMV concentration)
nafcillin	✘ (may ↓ EBR/GZR concentration)	?	?	✓ (↑ DCV dose to 90 mg/day)	?	?
Antimycobacterials						
rifampin, rifabutin	✘ (may ↓ EBR/GZR concentration)	✘ (may ↓ LDV/SOF concentration)	✘ (rifampin may ↓ OBV/PTV/r + DSV concentrations)	✘ (may ↓ DCV concentration)	✘ (may ↓ SOF concentration)	✘ (may ↓ SMV concentration)
rifapentine	?	✘ (may ↓ LDV/SOF concentration)	✘	✓ (↑ DCV dose to 90 mg/day)	✘ (may ↓ SOF concentration)	✘ (may ↓ SMV concentration)
Antipsychotics						
quetiapine	?	?	consider alternative anti-HCV therapy; if	?	?	?

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
			co-administration is necessary, reduce quetiapine dose to 1/6th of the current dose and monitor (↑ quetiapine concentration)			
Calcium Channel Blockers (CCB)						
amlodipine	?	?	monitor blood pressure (may ↑ amlodipine concentration, consider amlodipine dose reduction)	?	?	use caution and monitor (may ↑ CCB concentration)
diltiazem	?	?	?	✓ (monitor for DCV adverse events)	?	use caution and monitor (may ↑ CCB concentration)
felodipine, nicardipine, nifedipine	?	?	?	?	?	use caution and monitor (may ↑ CCB concentration)
verapamil	?	✓	?	✓ (monitor for DCV adverse events)	?	use caution and monitor (may ↑ CCB concentration)
Corticosteroids						
dexamethasone *(systemic)*	?	?	?	✓ (↑ DCV dose to 90 mg/day)	?	✗ (may ↓ SMV concentration)
budesonide, methylprednisone, prednisone	✓	?	?	?	?	✓

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
fluticasone	?	?	monitor closely (may ↑ fluticasone concentration; may ↓ serum cortisol concentrations. Consider alternative corticosteroid, particularly for long term use)	?	?	✓
Diuretics						
furosemide	?	?	use caution and monitor – adjust dose based on response (may ↑ furosemide concentration)	?	?	?
Dual endothelin receptor antagonist						
bosentan	✘ (may ↓ EBR/GZR concentration)	?	?	✓ (↑ DCV dose to 90 mg/day)	?	?
Ergot derivatives						
ergotamine, dihydroergotamine, ergonovine, methylergonovine	?	?	✘ (acute ergot toxicity)	?	?	?

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
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	✓
HCV drug						
SMV	?	✘ (↑ LDV/SOF concentration)	?	?	✓	
SOF	✓		?	✓		✓
Herbal supplements						
St. John's wort (Hypericum perforatum)	✘ (may ↓ EBR/GZR concentration)	✘ (may ↓ LDV/SOF concentration)	✘ (may ↓ OBV/PTV/r +DSV concentrations)	✘ (may ↓ DCV concentration)	✘	✘ (may ↓ SMV concentration)
milk thistle	?	?	?	?	?	✘ (may ↑ SMV concentration)
HIV ARVs (See Appendix Table A5: Drug-Drug Interactions with HIV Antiretrovirals)						
HMG Co-A Reductase Inhibitors						
rosuvastatin	✓ (may ↑ statin concentration) dose ≤10 mg once daily	✘ (may ↑ statin concentration; potential for myopathy and rhabdomyolysis)	✓ dose ≤10 mg daily (↑ statin concentration)	? (may ↑ statin concentration; potential for myopathy)	?	✓ initiate at 5 mg once daily; dose ≤10 mg daily

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
atorvastatin	✓ (may ↑ statin concentration) dose ≤20 mg once daily	?	?	? (may ↑ statin concentration; potential for myopathy)	?	✓ dose ≤40 mg once daily
simvastatin, lovastatin	✓ use lowest necessary dosage, titrate carefully; monitor closely, may ↑ statin concentration	?	✗ (potential for myopathy and rhabdomyolysis)	? (may ↑ statin concentration; potential for myopathy)	?	✓ use lowest necessary dosage, titrate carefully; monitor closely, may ↑ statin concentration
pitavastatin	✓	?	?	? (may ↑ statin concentration; potential for myopathy)	?	✓ use lowest necessary dosage, titrate carefully; monitor closely, may ↑ statin concentration
pravastatin	✓	✓	✓ dose ≤40 mg once daily (↑ statin concentration)	? (may ↑ statin concentration; potential for myopathy)	?	✓ use lowest necessary dosage, titrate carefully; monitor closely, may ↑ statin concentration
fluvastatin	✓ use lowest necessary dosage, titrate	?	?	? (may ↑ statin concentration; potential for	?	✓

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
	carefully; monitor closely, may ↑ statin concentration			myopathy)		
Immunosuppressants						
cyclosporine (CSA)	✘ (may ↑ GZR concentration and increased ALT)	✓	✓ (↑ CSA concentrations, reduce CSA dosage to 1/5th current dosage; measure CSA levels to determine dosage modifications; Recommend frequent assessment of renal function and CSA-related side effects)	✓	✓	✘ (may ↑ SMV and cyclosporine concentrations)
tacrolimus	no dosage adjustment; use caution (potential ↑ tacrolimus concentrations) and monitor tacrolimus concentrations and renal function	✓	✓ (↑ tacrolimus concentrations; decrease tacrolimus dosage based on blood concentrations; typical dose is 0.5 mg every 7 days; monitor renal function)	✓	✓	no dosage adjustment; use caution and monitor (potential ↑ SMV and/or ↓ tacrolimus concentrations)
sirolimus	?	?	?	?	?	use caution and monitor (potential ↑ SMV and/or ↓/↑ sirolimus

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
						concentrations)
mycophenolate mofetil	✓	?	?	?	?	?
Narcotic analgesic						
buprenorphine, naloxone	✓	?	✓ (↑ buprenorphine or naloxone concentrations, monitor for sedation and cognitive effects)	?	?	?
methadone	✓	✓	✓	✓	✓	✓
Neuroleptic						
pimozide	?	?	✗ (potential for cardiac arrhythmias)	?	?	?
Opioid Antagonist						
naloxone		?	?	?	?	✓
Oral Contraceptive						
ethinyl estradiol	✓	✓	✗ (ethinyl estradiol-containing medications may ↑ ALT)	✓	?	?
norgestimate products, norethindrone	✓	✓	?	✓	?	?
progestin-only contraceptives	✓	✓	✓	?	?	?
PDE-5 Inhibitors						
tadalafil, vardenafil	?	?	?	?	?	use caution and

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
						monitor (may ↑ concentration of PDE-5 inhibitor)
sildenafil	?	?	✘ (potential for sildenafil-associated AEs in doses taken for pulmonary artery hypertension)	?	?	use caution and monitor (may ↑ concentration of PDE-5 inhibitor)
Proton Pump Inhibitors (PPI)						
omeprazole	✓	✓ dose ≤20 mg/day; administer simultaneously under fasting conditions	✓ ↓ omeprazole concentrations, monitor for decreased omeprazole efficacy; avoid dose >40 mg per day	✓	?	✓
Other PPI	✓	✓ PPI doses comparable to omeprazole ≤20 mg/day can be administered simultaneously, fasting	?	✓	?	✓
Propulsive						
cisapride	?	?	?	?	?	✘
Quinolone						
ciprofloxacin	?	?	?	✓	?	?

Drug Classes and Drugs (grouped by class)	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
				(monitor for DCV adverse events)		
Sedatives/Anxiolytics						
oral midazolam, triazolam	?	?	✗ (may ↑ concentration of sedative)	✓	?	use caution and monitor (may ↑ concentration of sedative)
alprazolam	?	?	✓ monitor closely (↑ alprazolam concentration)	?	?	?
zolpidem	?	?	✓	?	?	?
Stimulants						
methylphenidate	?	?	?	?	?	✓
modafinil	✗ (may ↓ EBR/GZR concentration)			✓ (↑ DCV dose to 90mg/day)		
SSRI/SNRI						
escitalopram	?	?	✓	✓	?	✓
duloxetine	?	?	✓	?	?	?
nefazodone	?	?	?	✓ (↓ DCV dose to 30 mg/day)	?	?

Table 29. Drug-Drug Interactions with HIV Antiretrovirals[8,21,53-56,63,77]

(Adapted from U.S. Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and product prescribing information[1])

✓ = 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/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
Nucleoside Reverse Transcriptase Inhibitors						
FTC	✓	✓	✓	✓	✓	✓
3TC	✓	✓	✓	✓	✓	✓
ABC	✓	✓	✓	✓	✓	✓
TDF	✓	✓ Monitor for TDF toxicity	✓	✓	✓	✓
TAF	✓	✓	✓	✓	✓	✓
ZDV [a]	✓	✓	✓	✓	✓	✓
HIV Protease Inhibitors		If PI/r [or ATV/c, DRV/c] is used with TDF, ↑TDF concentrations are expected. If coadministration is necessary, monitor for TDF-associated toxicities (see footnote[b])				
ATV (unboosted)	✘	✓	✓ reduce ATV dose to 300	✓ (monitor for DCV	✓	✘

Selected HIV Drug Classes and Drugs	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
			mg in the morning at the same time as OBV/PTV/r + DSV; if RTV cannot be used, choose an alternative HCV regimen	adverse events)		
ATV/r or ATV/c	✘ (may ↑ GZR concentration and ↑ risk of ALT elevations)	✓[b]	✓ take ATV 300 mg in the morning at same time as OBV/PTV/r + DSV; discontinue RTV or COBI in HIV regimen until HCV therapy completed	✓ (↓ DCV dose to 30 mg/day)	✓	✘
DRV/r or DRV/c	✘	✓[b]	✘ (↓ DRV trough concentrations)	✓ (monitor for DCV adverse events)	✓	✘
FPV or FPV/r	✘	✓[b]	✘	✓ (monitor for DCV adverse events)	✓	✘
IDV/r	?	✓[b]	?	?	✓	
LPV/r	✘	✓[b]	✘ (may ↑ PTV concentrations)	✓ (monitor for DCV adverse events)	✓	✘
SQV/r	✘	✓[b]	✘	✓ ↓ DCV dose to 30 mg/day	✓	✘
TPV/r	✘	✘	✘	?	✘	✘
Nonnucleoside Reverse						

Selected HIV Drug Classes and Drugs	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
Transcriptase Inhibitors						
EFV	✘ (may ↓ EBR/GZR concentration)	✓ If EFV used with TDF/FTC, monitor for TDF toxicity due to ↑ TDF concentrations	✘ (poorly tolerated and liver enzyme elevations)	✓ (↑ DCV dose to 90 mg/day)	✓	✘
RPV	✓	✓	✘ (may ↑ RPV concentrations; potential QT prolongation)	✓	✓	✓
ETR	✘ (may ↓ EBR/GZR concentration)	✓	✘	✓ (↑ DCV dose to 90 mg/day)	✓	✘
NVP	✘	✓	✘	✓ (↑ DCV dose to 90 mg/day)	✓	✘
Integrase Strand Transfer Inhibitors						
DTG	✓	✓	?	✓	✓	✓
EVG/c/TDF/FTC	✘ (may ↑ EBR/GZR concentration)	✘	✘	✓ (↓ DCV dose to 30 mg/day)	✓	✘
EVG/c/TAF/FTC	✘ (may ↑ EBR/GZR concentration)	✓	✘	✓ (↓ DCV dose to 30 mg/day)	✓	✘
EVG + (PI/r without COBI)	Refer to recommendations for	Refer to recommendations for	Refer to recommendations for	✓ ↓ DCV dose to 30	Refer to recommen	Refer to recommendatio

Selected HIV Drug Classes and Drugs	Co-formulated NS5A Inhibitor/ NS3/4A Protease Inhibitor: EBR/GZR	Co-formulated NS5A/NS5B Inhibitor: LDV/SOF	Co-formulated NS5A/Protease Inhibitor/ NS5B Inhibitor: OBV/PTV/r + DSV	NS5A Inhibitor: DCV	NS5B Inhibitor: SOF	NS3/4A Protease Inhibitor: SMV
	individual PI/r	individual PI/r	individual PI/r	mg/day, regardless of which PI/r is used, except TPV/r - do not coadminister	dations for individual PI/r	ns for individual PI/r
RAL	✓	✓	✓	✓	✓	✓
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; DCV = DCV; DRV/r = darunavir/ritonavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FPV/r = fosamprenavir/ritonavir; 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; SQV/r = saquinavir/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 coadministration is necessary, monitor for TDF-associated adverse reactions.

Refer to full prescribing information for a complete list of potential DDIs and dosage adjustments of concomitantly prescribed medications.[8,21,53-56]

- Daclatasvir product prescribing information (http://packageinserts.bms.com/pi/pi_daklinza.pdf)
- Elbasvir/grazoprevir prescribing information (https://www.merck.com/product/usa/pi_circulars/z/zepatier/zepatier_pi.pdf)
- Ledipasvir/sofosbuvir prescribing information (www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf)
- Ombitasvir/paritaprevir/ritonavir+ dasabuvir prescribing information (www.accessdata.fda.gov/drugsatfda_docs/label/2014/206619lbl.pdf)
- Sofosbuvir prescribing information (www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf)
- Simeprevir prescribing information (www.olysio.com/shared/product/olysio/prescribing-information.pdf)

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, NS5A, and NS5B genes for Veteran patients. These tests determine the presence of known drug resistance-conferring mutations in the NS3/4A, NS5A, and/or NS5B 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, two, or all three genes lies with the provider, and depends on genotype, the known prevalence of baseline (naturally occurring) resistance mutations, treatment history, and projected drug options for a given patient.

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 protease inhibitors 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 [FDA-approved indication], however, a resistance interpretation for LDV [non FDA-approved indication for HCV GT3] will not be provided but the amino acid changes from the reference sequence will be listed to enable a provider to interpret the likelihood of resistance).

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 VISTA, there will 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, NS5A, and/or NS5B) 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, NS5A, and/or NS5B 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 7-10 working days after the specimen is received at PHRL.

Laboratory Procedures for Isolation and Storage of Plasma for NS3, NS5A, or NS5B Resistance Genotyping

Materials and Reagents

1. Vacutainer Tubes with EDTA, sodium citrate, or acid citrate dextrose (ACD), 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).
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 to –80°C.
6. Ship overnight with specimen shipment manifest to PHRL on dry ice or frozen ice packs.

Figure 1. Sample Specimen Shipment Manifest

VA Palo Alto Public Health Reference Laboratory
Specimen Shipment Manifest

From:
Institution/Site: _____
Ordering Physician: _____
Name of person completing form: _____
Address: _____
Location (city, state, zipcode): _____
Phone: _____
Fax: _____
E-mail: _____

SHIP TO:
Public Health Reference Laboratory
VA Palo Alto Health Care System
Bldg MB4 Room 418
3801 Miranda Ave
Palo Alto, CA 94304
650-493-5000 x69294
650-858-3978 (FAX)
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 2. Sample Test Report for HCV NS3 Resistance

VA | U.S. Department of Veterans Affairs

Laboratory Test Report

Patient: Example
SSN:
DOB: Feb 10, 2016
Ordering Physician: unknown
Collection Date/Time: Jan 18, 2016@22:16
Ordering Site: Palo Alto HCS
Site Accession No: PHRL 16 457
PHRL Accession No: P16-0096

Received Date/Time: Jan 19, 2016@22:16
Sample Type: plasma
Test Performed: HCV NS3 Resistance Genotype {a}
Test Date: Jan 22, 2016
Results File Name: P16-0096_1aNS3 nucleo.fasta
Report Date/Time: Feb 10, 2016@22:18

Results:

HCV Protease Inhibitor	Resistance Mutation(s){b}:	Resistance Predicted:
paritaprevir	Q80K, D168Y	YES
simeprevir	Q80K	YES
grazoprevir	Y56H, D168Y	YES
boceprevir	none detected	no

All amino acid differences between patient strain and reference strain {c}: V29A, T40A, Y56H, Q80K, S91T, L153I, D168Y, K224K/R

Comments: genotype 1a; codons 1 to 236 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: genotype 1a: F43L, Q80K, R155G/S/K, A156T, D168A/F/E/H/N/V/Y;
genotype 1b: A156T, D168A/H/V (Viekira Pak package insert);
grazoprevir: genotype 1a: V36L/M, Y56H, V107I, R155I/K, A156G/T/V, V158A, D168A/G/N/V/Y;
genotype 1b: Y56F, V107I, A156T;
genotype 4: A156M/T/V, D168A/G, V170I

{c} Reference sequence is Genbank NC004102 (HCV genotype 1a, strain H77)

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Figure 3. Sample Test Report for HCV NS5A Resistance

Laboratory Test Report

Patient: SSN:

DOB: Ordering Physician: unknown

Collection Date/Time: Ordering Site: Palo Alto HCS

Site Accession No: FB 16 40 PHRL Accession No: P16-0250

Received Date/Time: Jan 22, 2016@14:00 Sample Type: plasma

Test Performed: HCV NS5A Resistance Genotype {a} Test Date: Jan 22, 2016

Results File Name: P16-0250_1a5A nucleo.fasta Report Date/Time: Feb 9, 2016@18:19

Results:

NS5A Inhibitor	Resistance Mutation(s){b}:	Resistance Predicted:
elbasvir	M28T, Q30H	YES
ombitasvir	M28T	YES
daclatasvir	M28T, Q30H	YES
ledipasvir	M28T, Q30H	YES

All amino acid differences between patient strain and reference strain {c}: M28T, Q30H, R44K, R78K, S85S/N, K107T, R123Q, S131T, I144V, S174T, M226V, V296I, R311Q, E365E/D, L368V, T389A, G390A, T393M, P401S, V410A

Comments: genotype 1a; codons 1 to 448 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 NS5A 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:

ledipasvir: genotype 1a: K24R, M28A/G/T/V, Q30E/G/R/H/K/L, L31M/V, P32L, H58D, Y93H/N/S/C/T;
genotype 1b: L31M/V/I, P58D, A92K, Y93H (US and EMEA Harvoni package inserts).

ombitasvir: genotype 1a: M28T/V, Q30E/R, L31V, H58D, Y93H/L/N/C;
genotype 1b: L28T, L31F/V, Y93H (Viekira Pak package insert)

elbasvir: genotype 1a: M28A/G/T, Q30H/K/R/Y, L31F/M/V, H58D, Y93H/N/S/C;
genotype 1b: L28M, L31F/V, Y93H;
genotype 4: L28S/T, M31I/V, P58D, Y93H

daclatasvir: genotype 1a: M28T, Q30E/H/R/K, L31M/V, H54R, H58D/P, Y93C/H/N;
genotype 1b: L31V, P32del, Y93H

{c} Reference sequence is Genbank NC004102 (HCV genotype 1a, strain H77)

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XVI. References

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