Chronic Hepatitis C Virus (HCV) Infection: Treatment Considerations from the Department of Veterans Affairs National Hepatitis C Resource Center Program and National Viral Hepatitis Program

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I. What's New and Updates/Changes

(Last updated: December 15, 2015; last reviewed: December 15, 2015)

This revision (December 15, 2015) incorporates updates to preferred regimens for cirrhotic patients with chronic hepatitis C virus (HCV) genotype 1b infection, and those with genotype 2 or genotype 3 infection. 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 (Appendix A, Tables A4 and A5). Information on HCV resistance genotyping has been included (Appendix B). The Panel continues to recommend that HIV/HCV-coinfected patients receive the same HCV antiviral regimen 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 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 www.hepatitis.va.gov. 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

Preferred regimens for antiviral treatment of patients with chronic hepatitis C are based on the VA PBM criteria for use. Providers should consider the most clinically appropriate option based on patient characteristics.

NOTES: * Ombitasvir/paritaprevir/ritonavir + dasabuvir should be avoided in patients who have the following: Presence of potentially serious drug interactions with ombitasvir/paritaprevir/ritonavir + dasabuvir for which there is no alternative; **OR** HIV/HCV co-infection in patients not receiving antiretroviral therapy **OR** where antiretroviral drug-interactions preclude the use of ombitasvir/paritaprevir/ritonavir + dasabuvir; **OR** decompensated liver disease; **OR** recipient of solid organ transplant; **OR** previous virologic failure to NS3/4A protease inhibitor- or NS5A-based regimen; **OR** patients who cannot receive ribavirin with ombitasvir/ paritaprevir/ritonavir + dasabuvir (if applicable) due to contraindications to ribavirin; **OR** genotype 1a patients with cirrhosis and history of prior null response to peginterferon/ribavirin or those who are known to have the IL-28B T/T polymorphism.

** Contraindication and/or intolerance to ribavirin: 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 ribavirin-containing regimen.

HCV Genotype (GT)	Treatment History	Cirrhosis Status	Preferred Regimen	Alternative Regimen(s)
1	Naïve	Non-cirrhotic	ledipasvir/sofosbuvir x 8 weeks if baseline HCV RNA <6 million IU/mL; 12 weeks if HIV/HCV-coinfected	ledipasvir/sofosbuvir x 12 weeks if baseline HCV RNA ≥6 million IU/mL
			* ombitasvir/paritaprevir/ritonavir + dasabuvir x 12 weeks; GT1a: add ribavirin; GT1b: ribavirin not required	
		Cirrhotic, CTP A	* ombitasvir/paritaprevir/ritonavir + dasabuvir x 12 weeks; GT1a: add ribavirin (may consider 24 weeks; refer to Table 4 for details); GT1b: ribavirin not required	ledipasvir/sofosbuvir x 12 weeks (may consider adding ribavirin; refer to Table 4 for details)
		Cirrhotic, CTP B, C	ledipasvir/sofosbuvir + ribavirin (600 mg/day and increase by 200 mg/day every 2 weeks only as tolerated) x 12 weeks; NOT FDA approved	
	Experienced **(Prior PEG-IFN/RBV only)**	Non-cirrhotic	* ombitasvir/paritaprevir/ritonavir + dasabuvir x 12 weeks; GT1a: add ribavirin; GT1b: ribavirin not required	ledipasvir/sofosbuvir x 12 weeks (may consider adding ribavirin; refer to Table 4 for details)
		Cirrhotic, CTP A	If prior relapser or partial responder: * ombitasvir/paritaprevir/ritonavir + dasabuvir x 12 weeks; GT1a: add ribavirin (may consider 24 weeks; refer to Table 4 for details); GT1b: ribavirin not required	If prior relapser or partial responder: ledipasvir/sofosbuvir + ribavirin x 12 weeks
			If GT1a null responder: ledipasvir/sofosbuvir + ribavirin x 12 weeks	** If ribavirin intolerant or contraindicated: ledipasvir/sofosbuvir x 24 weeks
		Cirrhotic, CTP B, C	ledipasvir/sofosbuvir + ribavirin (600 mg/day and increase by 200 mg/day every 2 weeks only as tolerated) x 12 weeks ; NOT FDA approved	
	Experienced **(Prior NS3/4A**	Non-cirrhotic or	ledipasvir/sofosbuvir + ribavirin x 12 weeks	

HCV Genotype (GT)	Treatment History	Cirrhosis Status	Preferred Regimen	Alternative Regimen(s)
	inhibitor-containing therapy or SOF + RBV ± PEG-IFN therapy)	Cirrhotic		
2	Naïve	Non-cirrhotic	sofosbuvir + ribavirin x 12 weeks	** If ribavirin intolerant or contraindicated: ledipasvir/sofosbuvir x 12 weeks; NOT FDA approved
		Cirrhotic	sofosbuvir + ribavirin x 16 weeks; FDA approved for 12 weeks	** If ribavirin intolerant or contraindicated: Consult an expert (see Section XIV, Resources)
	Experienced **(Prior PEG-IFN/RBV only)**	Non-cirrhotic or Cirrhotic	sofosbuvir + ribavirin x 16 weeks; FDA approved for 12 weeks	** If ribavirin intolerant or contraindicated: <u>Non-cirrhotic:</u> ledipasvir/sofosbuvir x 12 weeks; NOT FDA approved <u>Cirrhotic:</u> Consult an expert (see Section XIV, Resources)
			sofosbuvir + PEG-IFN + ribavirin x 12 weeks; NOT FDA approved	
3	Naïve	Non-cirrhotic	ledipasvir/sofosbuvir + ribavirin x 12 weeks; NOT FDA approved	sofosbuvir + PEG-IFN + ribavirin x 12 weeks; NOT FDA approved sofosbuvir + ribavirin x 24 weeks ** If ribavirin intolerant or contraindicated: daclatasvir + sofosbuvir x 12 weeks
		Cirrhotic	daclatasvir + sofosbuvir + ribavirin x 12 weeks in CTP A, or 24 weeks in CTP B and C; NOT FDA approved with ribavirin	sofosbuvir + PEG-IFN + ribavirin x 12 weeks; NOT FDA approved
	Experienced **(Prior PEG-IFN/RBV only)**	Non-cirrhotic	sofosbuvir + PEG-IFN + ribavirin x 12 weeks; NOT FDA approved	sofosbuvir + ribavirin x 24 weeks ** If ribavirin intolerant or contraindicated: daclatasvir + sofosbuvir x 12 weeks
			ledipasvir/sofosbuvir + ribavirin x 12 weeks; NOT FDA approved	
		Cirrhotic	sofosbuvir + PEG-IFN + ribavirin x 12 weeks; NOT FDA approved	** If ribavirin intolerant or contraindicated: daclatasvir + sofosbuvir x 24 weeks
			daclatasvir + sofosbuvir + ribavirin x 12 weeks in CTP A, or 24 weeks in CTP B and C patients; NOT FDA approved with ribavirin	
4	Naïve or Experienced	Non-cirrhotic or Cirrhotic	* ombitasvir/paritaprevir/ritonavir + ribavirin x 12 weeks; **dasabuvir not needed**. ***DO NOT USE if patient virologically failed DAA-based therapy.***	ledipasvir/sofosbuvir x 12 weeks
				sofosbuvir + PEG-IFN + ribavirin x 12 weeks

Abbreviations: CTP = Child-Turcotte-Pugh; DAA = direct acting antiviral; PEG-IFN = peginterferon; RBV = ribavirin; SOF = sofosbuvir

Dosages: daclatasvir 60 mg orally daily (Note: 30 mg daily with strong CYP3A inhibitors or 90 mg daily with moderate CYP3A inducers); ledipasvir/sofosbuvir (90/400 mg): 1 tablet orally daily; ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg): 2 tablets once daily in the morning with food + dasabuvir 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; ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food; sofosbuvir 400 mg orally daily

Note: ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir + dasabuvir or sofosbuvir should not be used in reduced dosages or restarted if discontinued. Daclatasvir, dasabuvir, or sofosbuvir 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 virological 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 United States Food and Drug Administration (FDA) data, and input from VHA thought leaders involved in the care of Veterans with HCV infection.

Limitations: There are limitations in the design of most clinical trials of direct-acting antiviral (DAA) agents in the treatment of hepatitis C. These limitations include: 1) small sample sizes and resultant wide confidence intervals for SVR; 2) small number of patients with cirrhosis, especially advanced cirrhosis; 3) lack of a concurrent control arm in some studies; 4) lack of head-to-head trials of DAA regimens; 5) lack of blinding in some trials; 6) exclusion of patients with chronic hepatitis B virus (HBV) infection, human immunodeficiency virus infection (HIV), cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and alcohol or substance use; and 7) lack of follow-up data to determine long-term virological and clinical outcomes of DAA treatment. 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 the 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 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/contentfiles/lvguidelines/adultandadolescentgl.pdf. 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 peginterferon/ribavirin 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.[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 drug-drug interactions (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, drug-drug interactions, 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, advanced fibrosis, selected patients with HCC awaiting liver transplant, post-transplant recipients, patients with serious extra-hepatic manifestations of HCV, and women of child-bearing 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, including alcohol, illicit drugs, and marijuana use, or participating in opioid replacement programs 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 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. 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 noted and adequately 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 10, "Diagnosis of Compensated Cirrhosis for the Purpose of Identifying Treatment Candidates," for guidance on diagnosis of cirrhosis.	A-1
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 10, "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 10) • 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 ribavirin-containing regimen is chosen

* For further guidance on pre-treatment assessment and laboratory monitoring, 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 virological 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.

Sustained virological response (SVR_4): HCV RNA below LLQ at 4 weeks after treatment completion.

Sustained virological response (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 peginterferon and ribavirin.

Non-response: detectable HCV RNA throughout treatment.

Null-response: <2 $\log_{10}$ reduction from baseline HCV RNA during peginterferon and ribavirin treatment.

IV. Chronic HCV Genotype 1 Infection (including HIV coinfection)

Key Points

- Selection of an appropriate regimen and treatment duration for patients with genotype 1 infection depends on subtype, stage of liver disease, baseline level of HCV viremia, prior treatment history, and concomitant medications
- Treatment should be initiated with preferred regimens (see Table 4) unless patient-specific characteristics require an alternative regimen (see Table 5)
- Patients experiencing virologic failure with a DAA-containing regimen should have specimens sent to the VA Public Health Reference Laboratory for resistance testing prior to re-treatment (email V21PHRL@va.gov; see Section XV, Appendix B)

Preferred Regimens (see Table 4 for details)

Treatment-naïve patients without cirrhosis

- *Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily for 8 weeks if baseline HCV RNA <6 million IU/mL; 12 weeks if HIV/HCV-coinfected.*
- ** Ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg): 2 tablets once daily in the morning with food + dasabuvir (250 mg): 1 tablet twice daily (in the morning and in the evening with food) for 12 weeks; GT1a: add ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses), GT1b: ribavirin not required.*

Treatment-naïve patients with cirrhosis

CTP A

- ** Ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg): 2 tablets once daily in the morning with food + dasabuvir (250 mg): 1 tablet twice daily (in the morning and in the evening with food) for 12 weeks; GT1a: add ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses); may consider 24 weeks (refer to Table 4 for details), GT1b: ribavirin not required.*

CTP B and C

- *Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily + ribavirin (600 mg/day with food, and increase by 200 mg/day every 2 weeks only as tolerated if hemoglobin remains above 10 g/dL) for 12 weeks.* ***NOT FDA APPROVED.***

Treatment-experienced patients without cirrhosis (prior peginterferon/ribavirin experienced only)

- ** Ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg): 2 tablets once daily in the morning with food + dasabuvir (250 mg): 1 tablet twice daily (in the morning and in the evening with food) for 12 weeks; GT1a: add ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses), GT1b: ribavirin not required.*

Treatment-experienced patients with cirrhosis (prior peginterferon/ribavirin experienced only)

CTP A

- *In prior partial responders or relapsers: * Ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg): 2 tablets once daily in the morning with food + dasabuvir (250 mg): 1 tablet twice daily (in the morning and in the evening with food) for 12 weeks; GT1a: add ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses); may consider 24 weeks (refer to Table 4 for details), GT1b: ribavirin not required.*
- *In GT1a, prior null responders: Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily + ribavirin (1,000*

mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks.

CTP B and C

- *Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily + ribavirin (600 mg/day with food and increase by 200 mg/day every 2 weeks only as tolerated if hemoglobin remains above 10 g/dL) for 12 weeks.* ***NOT FDA APPROVED.***

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

- *Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily + ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks.*

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

* Ombitasvir/paritaprevir/ritonavir + dasabuvir should be avoided in patients who have the following: Presence of potentially serious drug interactions with ombitasvir/paritaprevir/ritonavir + dasabuvir for which there is no alternative; **OR** HIV/HCV co-infection in patients not receiving antiretroviral therapy **OR** where antiretroviral drug-interactions preclude the use of ombitasvir/paritaprevir/ritonavir + dasabuvir; **OR** decompensated liver disease; **OR** recipient of solid organ transplant; **OR** previous virologic failure to NS3/4A protease inhibitor- or NS5A-based regimen; **OR** patients who cannot receive ribavirin with ombitasvir/ paritaprevir/ritonavir + dasabuvir (if applicable) due to contraindications to ribavirin; **OR** genotype 1a patients with cirrhosis and history of prior null responder to peginterferon/ribavirin or who are known to have the IL-28B T/T polymorphism.

**** There are minimal data on re-treatment of patients who failed a regimen containing an NS5A or NS5B inhibitor. VA offers free testing of HCV resistance-associated variants for patients who have failed a DAA regimen through the VHA Public Health Reference Laboratory (email V21PHRL@va.gov, see Section XV, Appendix B). Consult an expert before re-treating (see Section XIV, Resources).

Table 4. Genotype 1: Preferred Regimens and SVR Rates in HCV Monoinfection and HIV/HCV Coinfection*

Preferred regimens for antiviral treatment of patients with chronic hepatitis C are based on the VA PBM Criteria for Use. 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.

Preferred Regimens					Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	**Comments**
Naïve GT1	Non-cirrhotic	ledipasvir/sofosbuvir	8 weeks if baseline HCV RNA <6 million IU/mL; 12 weeks if HIV/HCV-coinfected	A-I	97% (119/123, – RBV)[9]	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.[9]
		** ombitasvir/ paritaprevir/ritonavir + dasabuvir **GT1a: add ribavirin** **GT1b: ribavirin not required**	12 weeks	A-I	GT1a 91% (182/202, – RBV)[7] 96% (403/420, + RBV)[7] GT1b 99% (207/209, – RBV)[8] >99% (209/210, + RBV)[8]	Pooled data for GT1a from SAPPHIRE-I and -II, PEARL IV, TURQUOISE-II[7]
	Cirrhotic, CTP A	** ombitasvir/ paritaprevir/ritonavir + dasabuvir **GT1a: add ribavirin** **GT1b: ribavirin not required**	12 weeks	A-I	GT1a 92% (59/64, + RBV)[10] GT1b 100% (27/27, – RBV)[11]	GT1a: SVR 95% (53/56) with 24 weeks.[10] Consider extending to 24 weeks for slow on-treatment virologic response on a case-by-case basis. Monitor liver function tests including direct bilirubin at baseline, at weeks 2 and 4, and as needed thereafter. Monitor for hepatic decompensation (e.g., ascites, jaundice, encephalopathy) while on treatment.

Preferred Regimens					Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	**Comments**
Naïve GT1	Cirrhotic, CTP B,C	ledipasvir/sofosbuvir + ribavirin **NOT FDA approved**	12 weeks	B-II	CTP B: 87% (26/30) [12] CTP C: 86% (19/22) [12]	<u>ledipasvir/sofosbuvir + ribavirin for 24 weeks:</u> CTP B: 89% (24/27)[12] CTP C: 87% (20/23)[12] Ribavirin initiated at 600 mg/day and increase by 200 mg/day every 2 weeks only as tolerated. [12] SVR rates include treatment-naïve and treatment-experienced patients.[12]
Experienced GT1 ***(Prior PEG-IFN/RBV only)***	Non-cirrhotic	** ombitasvir/ paritaprevir/ritonavir + dasabuvir **GT1a: add ribavirin** **GT1b: ribavirin not required**	12 weeks	A-I	<u>GT1a</u> 94-100% (+ RBV)[7] <u>GT1b</u> 100% (91/91, – RBV)[8] 97% (85/88, + RBV)[8]	Pooled data for GT1a from SAPPHIRE-I and -II, PEARL IV, TURQUOISE-II[7]
	Cirrhotic, CTP A	If prior relapser or partial responder: ** ombitasvir/ paritaprevir/ritonavir + dasabuvir **GT1a: add ribavirin** **GT1b: ribavirin not required**	12 weeks	A-I	<u>GT1a</u> Relapser: 93% (14/15, +RBV)[10] Partial Responder: 100% (11/11, + RBV)[10] <u>GT1b</u> 100% (33/33, – RBV)[11]	<u>ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin for 24 weeks:</u> SVR 100% in relapsers (13/13) and partial responders (10/10)[10] Consider extending to 24 weeks for slow on-treatment virologic response. Monitor liver function tests including direct bilirubin at baseline, at weeks 2 and 4, and as needed thereafter. Monitor for hepatic decompensation (e.g., ascites, jaundice, encephalopathy) while on treatment.

Preferred Regimens					Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	**Comments**
Experienced GT1 ***(Prior PEG-IFN/RBV only)***	Cirrhotic, CTP A	If GT1a, prior null responder: ledipasvir/sofosbuvir + ribavirin	12 weeks	B-II	96% (74/77)[13]	<u>ledipasvir/sofosbuvir for 24 weeks:</u> SVR 97% (75/77)[13]
		ledipasvir/sofosbuvir **(If ribavirin-intolerant or contraindicated)*****	24 weeks	A-I	100% (22/22, – RBV)[14] 100% (22/22, + RBV)[14]	<u>ledipasvir/sofosbuvir for 12 weeks:</u> SVR 82-86%[14] Population includes 46-61% who failed boceprevir- or telaprevir-based therapy.[14]
	Cirrhotic, CTP B,C	ledipasvir/sofosbuvir + ribavirin **NOT FDA approved**	12 weeks	B-II	CTP B: 87% (26/30) [12] CTP C: 86% (19/22) [12]	<u>ledipasvir/sofosbuvir + ribavirin for 24 weeks:</u> CTP B: 89% (24/27)[12] CTP C: 87% (20/23)[12] Ribavirin 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.[12]
Experienced GT1 ***(Prior NS3/4A inhibitor-based therapy or SOF + RBV ± PEG-IFN therapy; see comments)***	Non-cirrhotic or Cirrhotic	ledipasvir/sofosbuvir + ribavirin	12 weeks	B-II	<u>Failed boceprevir or telaprevir + PEG-IFN + RBV:</u> 96% (74/77, cirrhotics)[13] <u>Failed SOF + PEG-IFN + RBV:</u> 100% (25/25)[15] <u>Failed SOF + RBV ± PEG-IFN:</u> 97% (62/64)[14] <u>Failed SOF + RBV:</u> 95% (20/21)[15]	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). The VA offers testing of HCV resistance-associated variants for patients who have failed a DAA regimen. <u>Among cirrhotics who failed boceprevir or telaprevir + PEG-IFN + RBV:</u> ledipasvir/sofosbuvir x 24 weeks: SVR 97% (75/77)[13] 80% were non-cirrhotic; 20% cirrhotic.[14] 71% were non-cirrhotic; 29% cirrhotic.[15]

Preferred Regimens				Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**	**Evidence grade**	**SVR% (N/N)**	**Comments**
Experienced GT1 ***(Other prior DAA-based therapy)***	Non-cirrhotic or Cirrhotic	**The optimal DAA-based therapy for this patient population should be determined in consultation with an expert (see Section XIV, Resources). Patients who previously failed treatment with an NS5A or NS5B inhibitor-containing regimen may have resistance-associated variants to currently available agents. Resistance testing is recommended to guide re-treatment options.**			

* 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 A4-A5.

** Ombitasvir/paritaprevir/ritonavir + dasabuvir should be avoided in patients who have the following: Presence of potentially serious drug interactions with ombitasvir/paritaprevir/ritonavir + dasabuvir for which there is no alternative; **OR** HIV/HCV co-infection in patients not receiving antiretroviral therapy **OR** where antiretroviral drug-interactions preclude the use of ombitasvir/paritaprevir/ritonavir + dasabuvir; **OR** decompensated liver disease; **OR** recipient of solid organ transplant; **OR** previous virologic failure to NS3/4A protease inhibitor- or NS5A-based regimen; **OR** patients who cannot receive ribavirin with ombitasvir/ paritaprevir/ritonavir + dasabuvir (if applicable) due to contraindications to ribavirin; **OR** genotype 1a patients with cirrhosis and history of prior null response to peginterferon/ribavirin or those who are known to have the IL-28B T/T polymorphism.

*** Contraindication and/or intolerance to ribavirin: 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 ribavirin-containing regimen.

Abbreviations: CTP = Child-Turcotte-Pugh; DAA = direct acting antiviral; PEG-IFN = peginterferon; RBV = ribavirin; [8]PEARL-III; [9]ION-3; [10]TURQUOISE-II; [11]TURQUOISE-III; [12]SOLAR-1; [13]SIRIUS; [14]ION-2.

Dosages: ledipasvir/sofosbuvir (90/400 mg): 1 tablet orally daily; ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg): 2 tablets once daily in the morning with food + dasabuvir 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; ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food; sofosbuvir 400 mg orally daily. Note: ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir + dasabuvir, or sofosbuvir should not be used in reduced dosages or restarted if discontinued. Dasabuvir or sofosbuvir should not be used as monotherapy.

Table 5. Genotype 1: Alternative Regimens and SVR Rates in HCV Monoinfection and HIV/HCV Coinfection*

SVR rates cannot be compared between trials.

Alternative Regimens					Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	**Comments**
Naïve GT1	Non-cirrhotic	ledipasvir/sofosbuvir	12 weeks if baseline HCV RNA ≥6 million IU/mL	A-I	96% (82/85, – RBV)[9] 99% (179/180, – RBV)[16] 97% (178/184, + RBV)[16]	
	Cirrhotic, CTP A	ledipasvir/sofosbuvir (may consider adding ribavirin)	12 weeks	A-I	94% (32/34, – RBV)[16] 100% (33/33, + RBV)[16]	
Experienced GT1 ***(prior PEG-IFN/RBV only)***	Non-cirrhotic	ledipasvir/sofosbuvir (may consider adding ribavirin)	12 weeks	A-I	95% (83/87, – RBV)[14] 100% (89/89, + RBV)[14]	Population includes 46-61% who failed boceprevir- or telaprevir-based therapy.[14]
	Cirrhotic, CTP A	If prior relapser or partial responder: ledipasvir/sofosbuvir + ribavirin	12 weeks	B-II	96% (74/77)[13]	SVR 97% (75/77) with ledipasvir/sofosbuvir x 24 weeks.[13]

* 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, Tables A4-A5.

** Ombitasvir/paritaprevir/ritonavir + dasabuvir should be avoided in patients who have the following: Presence of potentially serious drug interactions with ombitasvir/paritaprevir/ritonavir plus dasabuvir for which there is no alternative; **OR** HIV/HCV co-infection in patients not receiving antiretroviral therapy **OR** where antiretroviral drug-interactions preclude the use of ombitasvir/paritaprevir/ritonavir + dasabuvir; **OR** decompensated liver disease; **OR** recipient of solid organ transplant; **OR** previous virologic failure to NS3-4A protease inhibitor- or sofosbuvir-based regimen; **OR** patients who cannot receive ribavirin with ombitasvir/paritaprevir/ritonavir + dasabuvir (if applicable) due to contraindications to ribavirin; **OR** In genotype 1a patient with cirrhosis and history of prior null responder to peginterferon/ribavirin or who are known to have the IL-28B T/T polymorphism.

Abbreviations: CTP = Child-Turcotte-Pugh; DAA = direct acting antiviral; PEG-IFN = peginterferon; RBV = ribavirin; [9]ION-3; [16]ION-1; [14]ION-2; [13]SIRIUS.

Dosages: ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg): 2 tablets once daily in the morning with food + dasabuvir 250 mg orally twice daily (in the morning and in the evening with food); ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food; simeprevir 150 mg orally daily with food; sofosbuvir 400 mg orally daily. Note: ombitasvir/paritaprevir/ritonavir + dasabuvir or sofosbuvir should not be used in reduced dosages or restarted if discontinued. Sofosbuvir should not be used as monotherapy.

High SVR rates along with low adverse events and shortened treatment duration provide sufficient evidence to recommend ledipasvir/sofosbuvir (LDV/SOF, [HCV NS5A inhibitor/HCV nucleotide NS5B polymerase inhibitor])-based therapy and 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])-based therapy as the preferred treatment for HCV GT1 infection. **Refer to the Appendix A, Tables A1-A3 for a summary of clinical trials.**

Genotype 1-Infected Patients Who Failed Treatment with DAA-Based Therapy

Recommendations on re-treatment of patients who have failed a DAA-containing regimen are based on expert opinion, using basic principles of virological resistance/re-treatment as well as data from a small sample of patients who were re-treated after failing an initial DAA regimen. The recommendations are offered as guidance for patients who need re-treatment urgently. Consultation with an expert (see Section XIV, Resources) and, if possible, waiting until additional data or better drugs are available are recommended. The recommendations are likely to change as more data become available.

Patients who have failed treatment with a DAA-containing regimen may have HCV resistance-associated variants (RAVs) against the class of drugs that was used in the initial regimen. Patients who failed treatment with an NS3/4A protease inhibitor (e.g., simeprevir, boceprevir, telaprevir) are likely to be resistant to the current generation of NS3/4A protease inhibitors (e.g., paritaprevir); thus, re-treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir should be avoided, especially if HCV RAVs against the NS3/4A are identified. Re-treatment with LDV/SOF + RBV can be considered since this regimen does not include an NS3/4A protease inhibitor.

Patients who have failed treatment with an NS5A inhibitor-containing regimen (e.g., ombitasvir) are likely to have RAVs against the other available NS5A inhibitors (e.g., ledipasvir, daclatasvir). HCV RAV testing should be performed to guide re-treatment options. The presence of an RAV against an NS5A inhibitor reduces the effectiveness of other drugs in this class.

Sofosbuvir (SOF), an NS5B inhibitor, appears to have a high genetic barrier to resistance. Thus, RAVs to SOF are uncommon. Resistance to peginterferon (PEG-IFN) and ribavirin (RBV) also appear 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 is recommended; ribavirin should be included in the re-treatment regimen.

The VHA Public Health Reference Laboratory (PHRL) offers testing for HCV RAVs for Veterans who have failed regimens containing a DAA and who are being considered for re-treatment. For more information on testing for HCV RAVs in Veterans who have failed DAA treatment, contact the PHRL by email at V21PHRL@va.gov (see Section XV, Appendix B).

Patients who have failed treatment with peginterferon (PEG-IFN) + ribavirin (RBV) + an NS3/4A protease inhibitor (i.e., boceprevir, paritaprevir, simeprevir, telaprevir):
For those who failed PEG-IFN + RBV + an NS3/4A protease inhibitor, LDV/SOF is FDA approved for 12 weeks in patients without cirrhosis and 24 weeks in patients with cirrhosis, or LDV/SOF + RBV for 12 weeks with cirrhosis.[13,17] In a randomized, double-blind study 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. [13] Thus, LDV/SOF + RBV for 12 weeks can be considered for cirrhotic patients who failed PEG-IFN + RBV + an NS3/4A protease inhibitor.

Patients who have failed other NS3/4A protease inhibitor-containing regimens: Because of the likely presence of RAVs against NS3/4A protease inhibitors, patients who fail treatment with an NS3/4A-containing regimen should not be re-treated with an NS3/4A protease inhibitor. Thus, patients who fail SOF + simeprevir (SMV) or a paritaprevir-containing regimen should not be re-treated with an SMV- or paritaprevir-containing regimen. LDV/SOF + RBV for 12 weeks can be considered for patients who need re-treatment.

Patients who have failed an SOF-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%.[15,18] In a Phase II, open-label 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.[18] 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.[15] 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 (e.g., ledipasvir, ombitasvir, daclatasvir):
The optimal treatment for patients who 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 RAVs). SVR rates were reduced if baseline NS5A RAVs were present (SVR 60% [18/30]) compared with those without baseline NS5A RAVs (100% [11/11]).[19] It is unknown whether the addition of RBV would have improved the observed SVR rates in those with baseline NS5A RAVs. In another study, baseline NS5A RAVs 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.[20] Patients who failed an NS5A inhibitor-containing regimen should be tested for RAVs 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.

Ledipasvir/Sofosbuvir (LDV/SOF)

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.[16] 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 genotype 1a, 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 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 of cirrhosis. The most commonly reported adverse events were fatigue, headache, insomnia, nausea, weakness, and diarrhea, and they were more frequent in RBV-containing arms. Serious adverse events requiring treatment discontinuation were observed solely in the 24-week arms. 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-infected patients without cirrhosis.[9] In this unblinded study, 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; patients with METAVIR F4 were excluded. 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). Patients with characteristics historically associated with poor treatment outcomes had SVR rates (89-100%) that were similar to patients without these characteristics. In a post-hoc analysis, patients with a baseline HCV RNA <6 million IU/mL were found to have an SVR rate of 97% (119/123) in the 8-week arm and 96% (126/131) in the 12-week arm. Relapse occurred in 4% (23/647) of patients, most of which occurred in the 8-week treatment arms. In particular, 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. Fatigue, headache, and nausea were the most common side effects (67-69%) among patients receiving LDV/SOF, and the incidence of adverse events was higher among those receiving LDV/SOF + RBV, including hematologic adverse events. 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 3 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).[14] 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 the various 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 increased rate of response. Of the 62 patients who had an NS5A-resistant variant at baseline, 89% (55/62) achieved SVR; 6 of 11 patients who relapsed after treatment had NS5A-resistant variants at baseline. Adverse effects were less frequent in the 12-week LDV/SOF arm (67%) than in the other treatment arms (81-90%). All serious adverse events occurred in the 24-week treatment arms (6% in the LDV/SOF arm and 3% in the LDV/SOF + RBV arm).

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. [13] 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).[18]

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.[12] 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 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 in 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) with or without ribavirin (RBV)

PEARL III and IV were Phase III placebo-controlled studies of HCV GT1 treatment-naïve non-cirrhotic patients receiving ombitasvir/paritaprevir/ritonavir + dasabuvir (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).[8] 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 stratified by age, baseline HCV RNA, body mass index (BMI), fibrosis stage (F0-F3), IL28B status, and race/ethnicity. 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%). Of the 16 patients receiving OBV/PTV/r + DSV without RBV who had virologic failure, 6 had virologic rebound while on treatment and 10 relapsed after treatment; adherence in these patients was greater than 95% except for 1 patient. Anemia and transient asymptomatic hyperbilirubinemia were more common in the OBV/PTV/r + DSV + RBV regimen (anemia: 4-9% vs. 0%, hyperbilirubinemia: 3-6% vs. <1%); 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 Phase III double-blind, placebo-controlled study of HCV GT1a and 1b treatment-naïve non-cirrhotic patients receiving OBV/PTV/r + DSV + RBV for 12 weeks.[21] 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 stratified by gender, race, BMI, fibrosis stage (METAVIR F0-F3), and baseline HCV RNA, 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.[22] 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; there were no patients with prior use of DAA therapy. No patients had cirrhosis; 13-15% had METAVIR F3, the remainder were METAVIR F0-F2. No patients had HIV/HCV coinfection. 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. Both regimens were superior to the historical SVR rate for telaprevir + PEG-IFN + RBV. Adverse effects of OBV/PTV/r + DSV without RBV were headache (23%), fatigue (16%), diarrhea (12%), pruritus (8%), nausea (6%), and insomnia (3%). Side effects were increased in the RBV-containing arm. Two patients discontinued due to adverse events; both were in the RBV-containing arm. 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, but did increase adverse events.

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 non-cirrhotic patients.[23] It is one of the only placebo-controlled trials of DAA agents overall and the first trial using all-oral therapy that was placebo controlled. Patients were randomly assigned in a 3:1 ratio to receive OBV/PTV/r + DSV + RBV or matching placebos, for a 12-week double-blind period. After the placebo group completed 12 weeks of placebo treatment, they were treated with OBV/PTV/r + DSV + RBV for 12 weeks during an open-label period. The patients were 58% GT1a and 41% GT1b. All patients were previously treated with PEG-IFN + RBV; none had previously received DAA therapy. The majority of patients had a prior null response (49%); the remainder were categorized as relapsers (29%) or partial responders (22%). No patient had cirrhosis; 14-15% had METAVIR F3; the remainder had METAVIR F0-F2. No patients had HIV/HCV coinfection. Results showed high SVR rates in treated patients, regardless of prior treatment history or subtype. In the active group (n = 297) there was an SVR rate of 96% (95% CI: 94-98). This rate was superior to the historical control rate. GT1a had an SVR rate of 96% and GT1b of 97%. Rates were 95% among patients with a prior relapse (n = 86), 100% among patients with a prior partial response (n = 65), and 95% among patients with a prior null response (n = 146). Three patients in the active-regimen group (1%) discontinued the study drugs owing to adverse events. This study demonstrated high SVR

rates with a 12-week regimen of OBV/PTV/r + DSV + RBV, in treatment-experienced patients with GT1a and 1b, 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.[10] Inclusion criteria included cirrhosis documented by liver biopsy or FibroScan® (≥14.6 kPa), platelet count ≥60,000/mm^3, serum albumin ≥2.8 g/dL, and bilirubin <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 = 0.089). 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, SVR rates were 93% (14/15) in those treated for 12 weeks and 100% (13/13) in those treated for 24 weeks. 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 (6.4%: 0.5% breakthrough and 5.9% relapse through post-treatment week 12) as compared with those receiving 24 weeks of treatment (3.2%: 1.7% breakthrough and 0.6% relapse through post-treatment week 12). Adverse events included fatigue (more common among patients receiving 24 weeks of treatment), headache, nausea, pruritus, and rash. 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 vs. 24 weeks in these subgroups.[10]

TURQUOISE III, a multicenter open-label Phase 3b study, evaluated the use of OBV/PTV/r + DSV without RBV in 60 GT1b-infected patients with compensated cirrhosis. Participants were mostly white (88%) and male (62%) with a median age of 59.5±9.5 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 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 for a recommendation to omit RBV from a regimen of OBV/PTV/r + DSV in GT1b patients with compensated cirrhosis.[11]

Sofosbuvir (SOF) + Simeprevir (SMV) ± Ribavirin (RBV)

In Phase III open-label 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).[24] In 103 treatment-naïve and -experienced patients with cirrhosis, SVR rates were 88% (44/50) and 79% (42/53), respectively. Lower SVR rates were attained in GT1a cirrhotic patients infected with HCV carrying a Q80K mutation as compared with those infected with HCV not carrying this mutation; SVR 74% (25/34) vs. 92% (n = 35/38). In GT1b patients, SVR was achieved in 84% (26/31).[25]

In an open-label, Phase IIa trial (COSMOS), the combination of SOF + SMV ± RBV was evaluated in 167 GT1-infected patients.[26] 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 genotype 2 infection depends on stage of liver disease, prior treatment history, and concomitant medications
- Treatment should be initiated with preferred regimens (see Table 6) unless patient-specific characteristics require an alternative regimen (see Table 7)
- The optimal treatment regimen has not been established for cirrhotic genotype 2 patients who cannot receive a preferred regimen 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 specimens sent to the VA Public Health Reference Laboratory for resistance testing (email V21PHRL@va.gov; see Section XV, Appendix B)

Preferred regimens (see Table 6 for details)

Treatment-naïve patients without cirrhosis

- *Sofosbuvir (400 mg/day) in combination with ribavirin (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

- *Sofosbuvir (400 mg/day) in combination with ribavirin (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

- *Sofosbuvir (400 mg/day) in combination with ribavirin (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.***
- *Sofosbuvir (400 mg/day) in combination with peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly plus ribavirin (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.***

Table 6. Genotype 2: Preferred 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.

Preferred Regimens					Supporting Information	Comments
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR (N/N)**	
Naïve GT2	Non-cirrhotic	sofosbuvir + ribavirin	12 weeks	A-I	97% (59/61)[27] 92% (85/92)[28] 97% (29/30)[28,29]	
	Cirrhotic	sofosbuvir + ribavirin	16 weeks	B-III	12 weeks 83% (10/12)[27] 94% (16/17)[28] 100% (2/2)[29]	**FDA approved for 12 weeks**
Experienced GT2 ***(Prior PEG-IFN/RBV only)***	Non-cirrhotic	sofosbuvir + ribavirin	16 weeks	A-II	Relapsers: 89% (24/27)[28] Nonresponders: 88% (7/8)[28]	**FDA approved for 12 weeks** 12 weeks 91% (30/33)[29] Relapsers: 86% (25/29)[28] Nonresponders: 70% (7/10)[28] 24 weeks SVR 100% (17/17 in cirrhotics)[30]
		sofosbuvir + peginterferon + ribavirin **NOT FDA approved**	12 weeks	B-II	100% (9/9)[31]	

Preferred Regimens					Supporting Information	Comments
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR (N/N)**	
Experienced GT2 ***(Prior PEG-IFN/RBV only)***	Cirrhotic	sofosbuvir + ribavirin	16 weeks	B-II	78% (7/9)[28] 87% (13/15)[30]	**FDA approved for 12 weeks** 12 weeks SVR 60% (6/10)[28] SVR 88% (7/8)[29] 24 weeks 100% (17/17)[30]
		sofosbuvir + peginterferon + ribavirin **NOT FDA approved**	12 weeks	B-II	93% (13/14)[31] 94% (15/16)[30]	
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.
Abbreviations: [27]FISSION, [28]POSITRON, [28]FUSION, [29]VALENCE, [30]BOSON, [31]LONESTAR-2.
Dosages: Peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly; ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food; sofosbuvir 400 mg orally daily. Sofosbuvir should not be used as monotherapy or in reduced dosages; it should not be restarted if discontinued.

Table 7. Genotype 2: Alternative Regimens and SVR Rates in HCV Monoinfection and HIV/HCV Coinfection with Ribavirin Intolerance or Contraindication*

Alternative Regimens					Supporting Information	Comments
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	
Naïve GT2	Non-cirrhotic	ledipasvir/sofosbuvir **NOT FDA approved**	12 weeks	B-II	96% (25/26)[32]	SVR rates include treatment-experienced and cirrhotic patients.
	Cirrhotic	**The optimal DAA-based therapy for this patient population is not known. Consult an expert to weigh the risks versus benefits of treatment (see Section XIV, Resources).**				
Experienced GT2 (Prior PEG-IFN/RBV only)	Non-cirrhotic	ledipasvir/sofosbuvir **NOT FDA approved**	12 weeks	B-II	96% (25/26)[32]	SVR rates include treatment-naïve and cirrhotic patients.
	Cirrhotic	**The optimal DAA-based therapy for this patient population is not known. Consult an expert to weigh the risks versus benefits of treatment (see Section XIV, Resources).**				

* Contraindication and/or intolerance to ribavirin: 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 previous ribavirin-containing regimen.
** For more information on testing for HCV RAVs in Veterans who have failed DAA treatment, contact the Public Health Reference Laboratory by email at V21PHRL@va.gov (see Section XV, Appendix B).

Sofosbuvir in Genotype 2 (GT2)

The preferred interferon-free treatment regimen for chronic HCV GT2 infection, sofosbuvir (SOF) plus ribavirin (RBV), is supported by the results of four Phase III studies.[27-29] SVR rates among these four studies were >90% in treatment-naïve and non-cirrhotic populations. Patients with cirrhosis and previous nonresponse to peginterferon-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.[29] 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).[28] 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.[30] Based on results from these studies, SOF + RBV for 16 weeks is preferred 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 peginterferon to SOF + RBV therapy for 12 weeks.[31] Among treatment-experienced cirrhotic patients from the Phase III BOSON study, SVR 94% (15/16) occurred with SOF + PEG-IFN + RBV for 12 weeks.[30] This regimen is not FDA approved.

In patients who have a contraindication or are intolerant to ribavirin, 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.[32]

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 genotype 3 infection depends on stage of liver disease, prior treatment history, and concomitant medications
- Patients with genotype 3 infection should have specimens sent to the VA Public Health Reference Laboratory for resistance testing prior to selection of a treatment regimen (email V21PHRL@va.gov; see Section XV, Appendix B), as should patients experiencing virologic failure
- Treatment should be initiated with preferred regimens (see Table 8) unless patient-specific characteristics require an alternative regimen (see Table 9)

Preferred regimens (see Table 8 for details)

Treatment-naïve patients without cirrhosis

- *Ledipasvir/sofosbuvir (90/400 mg/day) plus ribavirin (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

- *Daclatasvir (60 mg/day) plus sofosbuvir (400 mg/day) plus ribavirin (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 24 weeks in CTP B and C patients.*

Treatment-experienced patients without cirrhosis

- *Sofosbuvir (400 mg/day) in combination with peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly plus ribavirin (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.***
- *Ledipasvir/sofosbuvir (90/400 mg/day) plus ribavirin (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

- *Sofosbuvir (400 mg/day) in combination with peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly plus ribavirin (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.***
- *Daclatasvir (60 mg/day) plus sofosbuvir (400 mg/day) plus ribavirin (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 24 weeks in CTP B and C patients.*

Table 8. Genotype 3: Preferred 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.

Preferred Regimens					Supporting Information	Comments
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	
Naïve GT3	Non-cirrhotic	ledipasvir/sofosbuvir + ribavirin **NOT FDA approved**	12 weeks	A-II	100% (20/20)[33] <u>Preliminary VA data for SVR4:</u> 83% (52/63, ITT)[34] 90% (51/57, completed treatment)[34]	SVR rates include treatment-experienced patients.[34]
	Cirrhotic	daclatasvir + sofosbuvir + ribavirin **(NOT FDA approved with ribavirin)**	12 weeks if CTP A 24 weeks if CTP B or C	B-II	83% (15/18,+ RBV)[35] 100% (4/4, + RBV)[36] <u>CTP B or C</u> 70% (7/10, + RBV)[36] 71% (12/17, – RBV)[36] <u>CTP B</u> 86% (6/8, + RBV)[37] 80% (12/15, – RBV)[37] <u>CTP C</u> 100% (2/2, + RBV)[37] 75% (6/8, – RBV)[37]	SVR rates include treatment-experienced patients.[36,37] <u>CTP A</u> 12 weeks: 70% (23/33, – RBV)[36] 16 weeks: 89% (16/18, + RBV)[35] ** Test for NS5A RAVs prior to starting treatment. For patients with Y93H RAV, consider future treatment options unless urgent treatment is needed. Consult with an expert to weigh the risks versus benefits of treatment (see Section XIV, Resources).
Experienced GT3 **(Prior PEG-IFN/RBV only)**	Non-cirrhotic	sofosbuvir + peginterferon + ribavirin **NOT FDA approved**	12 weeks	A-II	94% (49/52)[30] 83% (10/12) [31]	

Preferred Regimens					Supporting Information	Comments
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	
Experienced GT3 **(Prior PEG-IFN/RBV only)**		ledipasvir/sofosbuvir + ribavirin **NOT FDA approved**	12 weeks	B-II	89% (25/28)[33] <u>Preliminary VA data for SVR4:</u> 83% (52/63, ITT)[34] 90% (51/57, completed treatment)[34]	SVR rates include includes treatment-naïve patients.[34] ** Test for NS5A RAVs prior to starting treatment. Consult with an expert to weigh the risks versus benefits of treatment (see Section XIV, Resources).
	Cirrhotic	sofosbuvir + peginterferon + ribavirin **NOT FDA approved**	12 weeks	A-II	86% (30/35)[30] 83% (10/12)[31]	
		daclatasvir + sofosbuvir + ribavirin **(NOT FDA approved with ribavirin)**	12 weeks if CTP A 24 weeks if CTP B or C	B-II	88% (14/16,+ RBV)[35] 100% (4/4, + RBV)[36] <u>CTP B or C</u> 70% (7/10, + RBV)[36] 71% (12/17, – RBV)[36] <u>CTP B</u> 86% (6/8, + RBV)[37] 80% (12/15, – RBV)[37] <u>CTP C</u> 100% (2/2, + RBV)[37] 75% (6/8, – RBV)[37]	SVR rates include treatment-naïve patients.[36,37] <u>CTP A</u> 12 weeks: 70% (23/33, – RBV)[36] 16 weeks: 86% (12/14, + RBV)[35] ** Test for NS5A RAVs prior to starting treatment. For patients with Y93H RAV, consider future treatment options unless urgent treatment is needed. Consult with an expert to weigh the risks versus benefits of treatment (see Section XIV, Resources).
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 variants 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.

** For more information on testing for HCV RAVs in Veterans who have failed DAA treatment, contact the Public Health Reference Laboratory by email at V21PHRL@va.gov (see Section XV, Appendix B).
Abbreviations: [33]ELECTRON-2, [35]ALLY-3+; [30]BOSON; [31]LONESTAR-2; CTP = Child-Turcotte-Pugh; ITT = intention to treat; RAVs = resistance-associated variants (RAVs).
Dosages: daclatasvir 60 mg orally daily (Note: 30 mg daily with strong CYP3A inhibitors or 90 mg daily with moderate CYP3A inducers); peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly; ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food; ledipasvir/sofosbuvir (90/400 mg) orally daily; sofosbuvir 400 mg orally daily. Note: Ledipasvir/sofosbuvir or sofosbuvir should not be used in reduced dosages or restarted if discontinued. Sofosbuvir should not be used as monotherapy.

Table 9. 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 preferred regimens.
SVR rates cannot be compared between trials.

Alternative Regimens					Supporting Information	Comments
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	
Naïve GT3	Non-cirrhotic	sofosbuvir + peginterferon + ribavirin **NOT FDA approved**	12 weeks	A-II	96% (68/71)[30]	If interferon eligible
		daclatasvir + sofosbuvir **(if ribavirin-intolerant or contraindicated)*** **	12 weeks	A/B-II	97% (73/75)[38] 96% (24/25)[36] (includes treatment experienced)	Consider future treatment options unless urgent treatment is needed. **Test for NS5A RAVs prior to starting treatment. For patients with Y93H RAV, consult with an expert to weigh the risks versus benefits of treatment (see Section XIV, Resources).
		sofosbuvir + ribavirin	24 weeks	A-I	94% (86/92) [29] 90% (65/72)[30] <u>Preliminary VA data for SVR4:</u> 81% (129/159, ITT)[34] 84% (110/131, completed treatment)[34] (includes treatment experienced)	
	Cirrhotic	sofosbuvir + peginterferon + ribavirin **NOT FDA approved**	12 weeks	A-III	91% (21/23)[30]	

Alternative Regimens					Supporting Information	Comments
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	
Experienced GT3 **(Prior PEG-IFN/RBV only)**	Non-cirrhotic	daclatasvir + sofosbuvir **(if ribavirin-intolerant or contraindicated)*****	12 weeks	A/B-II	94% (32/34)[38] 96% (24/25)[36] (includes treatment naïve)	Consider future treatment options unless urgent treatment is needed. **Test for NS5A RAVs prior to starting treatment. For patients with Y93H RAV, consult with an expert to weigh the risks versus benefits of treatment (see Section XIV, Resources).
		sofosbuvir + ribavirin	24 weeks	A-I	87% (87/100) [29] 82% (44/54)[30]	
	Cirrhotic	daclatasvir + sofosbuvir **(if ribavirin-intolerant or contraindicated)*****	24 weeks	B-II	CTP B or C 71% (12/17)[36] CTP B: 80% (12/15)[37] CTP C: 75% (6/8)[37]	SVR rates include treatment-naïve patients.[36,37]

* Refer to Section XII, Groups with Special Considerations for Therapy, on HCV treatment in patients with HIV/HCV coinfection.
** For more information on testing for HCV RAVs in Veterans who have failed DAA treatment, contact the Public Health Reference Laboratory by email at V21PHRL@va.gov (see Section XV, Appendix B).
*** Contraindication and/or intolerance to ribavirin: 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 previous ribavirin-containing regimen.
Abbreviations: [30]BOSON; [38]ALLY-3; [29]VALENCE; CTP = Child-Turcotte-Pugh; ITT = intention to treat; RAVs = resistance-associated variants.
Dosages: daclatasvir 60 mg orally daily (Note: 30 mg daily with strong CYP3A inhibitors or 90 mg daily with moderate CYP3A inducers); peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly; ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in 2 divided doses) with food; sofosbuvir 400 mg orally daily. Sofosbuvir should not be used as monotherapy or in reduced dosages; it should not be restarted if discontinued.

Treatment of Chronic HCV Genotype 3 (GT3)

The optimal treatment of HCV GT3, especially 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 RAVs 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 (daclatasvir [DCV] or ledipasvir [LDV]) with sofosbuvir and ribavirin (note: ribavirin 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 + sofosbuvir (SOF) + ribavirin (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-resistant associated variants (RAVs), particularly the Y93H RAV, are not fully understood. At baseline, approximately 10% of GT3-infected patients have the Y93H RAV. The presence of the Y93H RAV 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.[38] However, Y93H RAV 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 ribavirin was added to LDV/SOF.[33] Only 1 of 8 patients with baseline Y93H RAV 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 RAVS.[33] Nonetheless, RBV is recommended in all NS5A-containing DAA regimens used to treat GT3. Until more data are available, baseline testing for NS5A RAVs is essential, particularly for cirrhotic or treatment-experienced patients. If the Y93H RAV is present, the patient should be informed of the potential for a lower chance of SVR as well as the potential availability of more effective drugs in the future.

Another related concern is the potential development of NS5A RAVs among patients who do not achieve an SVR. The Y93H RAV 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 RAVs in those who fail therapy, the preferred regimen in this population is DCV + SOF + RBV for 24 weeks. 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.[30] Although this regimen requires the use of PEG-IFN, patients who fail to respond do not develop NS5A RAVs. 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 subjects because of the lower SVR (60-77%).[34]

In summary, an NS5A inhibitor (LDV or DCV) in combination with SOF and RBV is the preferred interferon-free regimen for GT3 treatment. Among cirrhotic patients, DCV + SOF + RBV is preferred for 12 weeks in CTP A patients and 24 weeks in CTP B or C patients. It is essential to test for Y93H RAV before starting treatment, particularly in any treatment-experienced or cirrhotic patient; if present, potential implications of this RAV 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 in the second half of 2016, is reasonable after discussion with the patients.

Summary of Pivotal Trials in Genotype 3-Infected Patients

Ledipasvir/sofosbuvir (LDV/SOF) + ribavirin (RBV)

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 real-world preliminary VA data (see Table 8). 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.[33] 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 ribavirin 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.[34]

Based on lower SVR rates, high virologic relapse rates in GT3 cirrhotic patients and the potential for increased risk of NS5A RAVs, LDV/SOF + RBV is not a preferred regimen for GT3 cirrhotic patients.[33] In GT3 patients without cirrhosis, the high SVR rates observed in a clinical trial (SVR 100% and 89% in treatment-naïve and -experienced non-cirrhotic patients, respectively)[33] along with the high SVR rates

from preliminary VA data support the recommendation of LDV/SOF + RBV for 12 weeks as a preferred regimen.

Daclatasvir (DCV) + Sofosbuvir (SOF) + Ribavirin (RBV)

Treatment of HCV GT3 infection with DCV + SOF is approved by the FDA; in patients with cirrhosis, this regimen is preferred *in combination with ribavirin for 12 weeks in CTP A, or 24 weeks in CTP B and C patients*. 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.[38] 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.[38]

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.[39]

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.[40]

The suboptimal SVR rates observed in cirrhotic patients receiving DCV + SOF for 12 weeks has prompted investigation of longer treatment duration and/or addition of ribavirin.

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.[35]

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 Child-Pugh 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.[36]

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.[37]

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 (SOF) + peginterferon (PEG-IFN) + ribavirin (RBV)

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 having the highest SVR rates in GT3 cirrhotics, patients who fail to respond to SOF + PEG-IFN + RBV do not develop RAVs and could potentially be treated 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. [31] 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).[30] In treatment-naïve patients, a 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, a 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 as the preferred treatment for those that are interferon eligible.

Sofosbuvir (SOF) + Ribavirin (RBV)

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.[24] 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 SOF + RBV in the 24-week 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 SOF + RBV in the 24-week 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%).[22, 23, 28, 30] 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, SVR4 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 genotype 4 infection depend on concomitant medications
- The preferred regimen for genotype 4 patients is ombitasvir/paritaprevir/ritonavir (without dasabuvir) with ribavirin for 12 weeks. Ledipasvir/sofosbuvir or sofosbuvir/ribavirin for 12 weeks are alternative regimens
- Patients experiencing virologic failure with a DAA-based regimen should have specimens sent to the VA Public Health Reference Laboratory for resistance testing prior to re-treatment (email V21PHRL@va.gov; see Section XV, Appendix B)

Sofosbuvir for Genotype 4 (GT4)

Preferred regimens

Treatment-naïve and treatment-experienced patients with or without cirrhosis:

- *** Ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg): 2 tablets once daily in the morning with food + ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks;* ***dasabuvir not needed. Note: DO NOT USE if patient virologically failed DAA-based therapy.***

Alternative regimens

Treatment-naïve and treatment-experienced patients with or without cirrhosis:

- *Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily for 12 weeks.*
- *Sofosbuvir (400 mg/day): 1 tablet daily in combination with ribavirin (1,000 mg/day if <75 kg and 1,200 mg/day if ≥75 kg with food, in divided doses) and peginterferon for 12 weeks.*

** Ombitasvir/paritaprevir/ritonavir + dasabuvir should be avoided in patients who have the following: Presence of potentially serious drug interactions with ombitasvir/paritaprevir/ritonavir + dasabuvir for which there is no alternative; **OR** HIV/HCV co-infection in patients not receiving antiretroviral therapy **OR** where antiretroviral drug-interactions preclude the use of ombitasvir/paritaprevir/ritonavir + dasabuvir; **OR** decompensated liver disease; **OR** recipient of solid-organ transplant; **OR** previous virologic failure to NS3/4A protease inhibitor- or NS5A-based regimen; **OR** patients who cannot receive ribavirin with ombitasvir/ paritaprevir/ritonavir + dasabuvir (if applicable) due to contraindications to ribavirin; **OR** genotype 1a patients with cirrhosis and a history of prior null response to peginterferon/ribavirin or those who are known to have the IL-28B T/T polymorphism.

In a Phase III, open-label, single-arm clinical trial of treatment-naïve HCV GT4-monoinfected patients, SVR was achieved in 96% (27/28) with SOF in combination with PEG-IFN and RBV for 12 weeks.[27]

LDV/SOF for 12 weeks was evaluated in 21 patients with GT4 infection in the NIAID SYNERGY study.[41] The cohort included treatment-naïve and treatment-experienced patients who failed PEG-IFN + RBV; 43% were Black, 33% had F3 disease, and 10% had F4 disease. SVR was achieved in 95% (19/20).

In an open-label Phase IIb study of 86 treatment-naive GT4-infected patients who received ombitasvir/paritaprevir/ritonavir (without dasabuvir) ± 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. In the

same study, 49 treatment-experienced GT4-infected patients who previously failed PEG-IFN + RBV were re-treated with ombitasvir/paritaprevir/ritonavir + RBV for 12 weeks; 10% had METAVIR ≥F3 fibrosis and 47% were prior null responders. SVR was achieved in 100% (49/49).[42]

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 10. 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 imaging (ARFI)	• 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 are not recommended for routine use 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 10): 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 one 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 (www.haltctrial.org/cirrhosis.html) uses standard clinical data to predict the likelihood of a patient having cirrhosis. A score of >0.6 (i.e., >60%) is generally considered as an indication of cirrhosis. A Lok HALT-C HCC score greater than 3.25 (www.haltctrial.org/hccform.html) is associated with increased risk of developing HCC in the subsequent 3-5 years.

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 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 11. Discontinuing HCV Treatment Based on Lack of Virologic Response

Treatment Monitoring Considerations
• Patients should have an HCV RNA level assessed at week 4 of treatment. (A-lll) • If the HCV RNA is quantifiable* at week 4 or at any time point thereafter, reassess HCV RNA in 2 weeks. If the repeated HCV RNA increases (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all treatment should be strongly considered. (A-lll) • HCV RNA levels should be assessed at **12 weeks after completion of treatment** to determine whether SVR was achieved. (A-l)

*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.

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.[43] 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 ribavirin-containing regimens should be managed by ribavirin dose 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 facility to report such events to the VA Adverse Drug Event Reporting System (VA ADERS; http://www.pbm.va.gov/PBM/vacenterformedicationsafety/tools/VHA_Adverse_Drug_Event_Reporting_System.pdf) as well as the U.S. Food and Drug Administration's MedWatch program (http://www.fda.gov/Safety/MedWatch/).

Daclatasvir + sofosbuvir (DCV + SOF)[44]

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 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 drug-drug interactions table for additional information (Appendix A, Table A4).

Ledipasvir/sofosbuvir (LDV/SOF)[15, 2015 #42]

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 upper limit of normal (<1-3%) and transient, asymptomatic lipase elevations of >3 times the upper limit of normal (<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 drug-drug interactions table for additional information (Appendix A, Table A4).

Ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin (OBV/PTV/r + DSV ± RBV)[45]

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 upper limit of normal (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. 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.

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. If ALT levels are elevated above baseline, they should be repeated and monitored closely. Treatment 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 or international normalized ratio (INR), or in patients who develop hepatic decompensation (e.g., ascites, jaundice, hepatic encephalopathy, variceal hemorrhage).

Sofosbuvir + simeprevir ± ribavirin (SOF + SMV ± RBV)[26,46]

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 drug-drug interactions table for additional information (Appendix A, Table A4).

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 a 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 (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 patients treated with placebo. 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 (SOF + RBV)[47]

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 level 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 (SOF + PEG-IFN + RBV)[47]

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 ribavirin 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 ribavirin 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 ribavirin-containing regimens should be managed by ribavirin dosage reduction. ESA use should comply with PBM Criteria for Use of these agents (available at http://www.pbm.va.gov/PBM/clinicalguidance/criteriaforuse/Erythropoiesis_Stimulating_Agent_CFU_for_Hepatitis_C_treatment_related_anemia.doc)

XI. Proper Use

Key Points

- Drug-drug interactions (DDI) must be considered when selecting a treatment regimen
- Providers should consult a knowledgeable clinical pharmacist for specific questions regarding drug-drug interactions
- The VA Computerized Patient Record System has been updated to alert providers about potential drug-drug interactions with all approved HCV anti-viral treatment regimens

Drug-Drug Interactions[15, 2015 #14,17,44-46]

Refer to the Appendix A, Tables A4-A5 for summary of drug-drug interactions.

All current HCV DAA-based treatment regimens have potentially significant interactions with commonly used drugs. A list of drug-drug interactions (DDI), summarized from the product inserts, is found in Appendix A, Tables A4-A5. 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 (http://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.

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.

Paritaprevir and ritonavir are primarily metabolized by CYP3A enzymes; coadministration with strong inhibitors of CYP3A may increase paritaprevir and ritonavir concentrations. Dasabuvir is primarily metabolized by CYP2C8 enzymes; coadministration with drugs that inhibit CYP2C8 may increase dasabuvir plasma concentrations.

Ombitasvir, paritaprevir, and dasabuvir are inhibitors of UGT1A1, and ritonavir is an inhibitor of CYP3A4. Paritaprevir is an inhibitor of OATP1B1 and OATP1B3 and paritaprevir, ritonavir, and dasabuvir 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.

Ombitasvir, paritaprevir, dasabuvir, and ritonavir are substrates of P-gp. Ombitasvir, paritaprevir, and dasabuvir are substrates of BCRP. Paritaprevir is a substrate of OATP1B1 and OATP1B3; inhibition of P-gp, BCRP, OATP1B1, or OATP1B3 may increase the plasma concentrations of HCV drugs.

Daclatasvir 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 daclatasvir. Conversely, strong inhibitors of CYP3A may increase the plasma levels of daclatasvir. In general, when administered with a strong CYP3A inhibitor, the daclatasvir dosage should be reduced to 30 mg once daily. Daclatasvir is contraindicated with strong CYP3A inducers as this may lead to lower exposure and loss of efficacy of daclatasvir; when administered with a moderate CYP3A inducer, the daclatasvir dosage should be increased to 90 mg once daily.

Because daclatasvir is also an inhibitor of P-gp, OATP 1B1 and 1B3, and BCRP, administration of daclatasvir 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.

Storage and Stability[17,44-47]

LDV, SOF, and SMV can be stored at room temperature (<86°F), but exposure of the medication to direct sunlight should be avoided. Ombitasvir/paritaprevir/ritonavir plus dasabuvir can be stored at room temperature (<86°F). DCV should be stored at room temperature between 68°F and 77°F.

Humidity can alter SOF stability. However, SOF and LDV/SOF was stable for 45 days in an open petri dish at 77°F with 60-75% relative humidity.

Missed Doses[17,44-47]

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 ombitasvir/paritaprevir/ritonavir within 12 hours of the scheduled dose and to take the missed dose of dasabuvir within 6 hours of the scheduled dose. If more than 12 hours has passed since ombitasvir/paritaprevir/ritonavir is usually taken or more than 6 hours has passed since dasabuvir 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 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 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
- Drug-drug interactions 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
- Ombitasvir/paritaprevir/ritonavir + dasabuvir should not be used in patients with moderate to severe hepatic impairment (CTP B and C)

HIV/HCV Coinfection

For preferred HCV antiviral treatments in HIV/HCV coinfection, refer to Tables 4-7.

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 drug-drug interactions 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 is preferred in HIV/HCV-coinfected patients who are not receiving HIV antiretroviral therapy **OR** who have drug-drug interactions that would preclude use of other HCV DAA agents. If an ombitasvir/paritaprevir/ritonavir + dasabuvir (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 ritonavir in the OBV/PTV/r + DSV regimen. HIV antiretroviral regimens that have been evaluated in OBV/PTV/r + DSV studies and may be acceptable include tenofovir/emtricitabine in combination with either atazanavir 300 mg (without ritonavir) once daily or raltegravir 400 mg twice daily. HIV antiretroviral regimens containing efavirenz, darunavir/ritonavir,

lopinavir/ritonavir, or rilpivirine are not recommended for use with the OBV/PTV/r + DSV regimen. Refer to the Appendix A, Tables A4-A5, and the product prescribing insert 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. 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 only with the consultation of an HIV and hepatitis C treatment specialist. In patients with a CD4 count of <200 cells/mm^3, HIV treatment should be initiated first; initiation of HCV treatment should be delayed until the HIV patient is on a stable HIV antiretroviral regimen. Optimal candidates for HCV treatment are patients who are on a stable regimen for HIV (i.e., suppressed HIV RNA for at least 8 weeks).

In selecting an antiretroviral regimen selection, potential drug-drug interactions with HCV antiviral medications (see Appendix A, Table A5) should be taken into account. Changes in HIV therapy may be warranted prior to initiating HCV treatment to avoid known or potential drug-drug interactions. In HIV/HCV-coinfected patients who are HIV virally suppressed, HIV RNA level should be checked 4-8 weeks after modification of HIV therapy to ensure HIV viral suppression is maintained before initiating HCV therapy. If a prior HIV regimen is to be reinitiated after HCV treatment is completed, the modified ART regimen 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 drug-drug interactions 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 are as follows:

ERADICATE is an open-label, uncontrolled study examining LDV/SOF for 12 weeks in 50 genotype 1 treatment-naïve, HIV/HCV-coinfected patients without cirrhosis.[48] The majority (74%) of patients was receiving HIV antiretroviral therapy (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.

The multicenter, open-label Phase II/III clinical trial TURQUOISE-1 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).[49] 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.[49]

The use of SOF + RBV (1,000 mg or 1,200 mg daily) in HIV/HCV-coinfected patients with a mean CD4 count of >500 cells/mm^3 was examined in PHOTON-1 and PHOTON-2.[50,51] 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 GT 1, 2, 3, or 4 infection from Europe and Australia. Pooled analysis of PHOTON-1 and PHOTON-2 data by genotype and treatment history showed an SVR rate of 81% for treatment-naïve GT1 patients treated for 24 weeks; similar SVR for treatment-naïve GT2 patients treated for 12 weeks (89%) and treatment-experienced GT2 patients treated for 24 weeks; differences in SVR for GT3 patients treated for 12 weeks (treatment naïve: 67%) and 24 weeks (treatment-naïve: 91%; treatment-experienced: 88%); and SVR 84% for treatment-naïve GT4 patients. Pooled analysis of PHOTON-1 and PHOTON-2 data by genotype and liver disease stage showed, for GT1a, an SVR of 65% and 85% in patients with cirrhosis and without cirrhosis, respectively; for GT1b, 60% and 67% (but the sample size was small); for GT2, 100% and 88%; for GT3 treatment-naïve 100% and 91% and GT3 treatment-experienced 79% and 95%; and GT4 88% and 83%. 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 from these studies suggest that 12 weeks of SOF + RBV therapy for GT2 patients regardless of treatment history can achieve an 89-90% response rate and that 24 weeks of therapy for GT3 patients can achieve an 88-91% response rate. However, SOF + RBV should be used with caution in treatment-experienced GT3 monoinfected-patients with cirrhosis as SVR rates of 60% (27/45).

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%).[47] 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; 5 patients were switched from atazanavir to darunavir. Approximately 20% of HIV/HCV-coinfected patients developed Grade 2 anemia (hemoglobin level of <10 g/dL) but 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.[52]

Although there are few data on the use of simeprevir (SMV) in HIV/HCV-coinfected patients, the use of SOF + SMV (±RBV) for 12 weeks can be considered in GT1-infected patients, particularly those who are HCV treatment experienced. SMV use in HIV/HCV-coinfected patients is not addressed in the FDA labeling.

HIV/HCV Drug-Drug Interactions[1,17,44-47,53-57]

Refer to Appendix A, Table A5 for drug-drug interactions. 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.

Laboratory Monitoring[1,6,17,44-47,54-57]

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]

Renal Insufficiency or Hepatic Impairment[17,44-47,52,54-57]

Table 12. Modification of Drug Use in Patients with Renal Insufficiency or Hepatic Impairment

Condition	Treatment	Comment	Grade
Renal Insufficiency	daclatasvir	No dosage adjustment needed.	A-I
	ledipasvir	No dosage adjustment needed.	A-I
	ombitasvir/paritaprevir/ ritonavir + dasabuvir	No dosage adjustment needed.	A-II
	peginterferon alfa-2a	Dosage reduce to 135 mcg/week subcutaneously once weekly for CrCl <30 mL/min, including hemodialysis.	A-I
	peginterferon alfa-2b	Dosage reduce by 25% for CrCl 30-50 mL/min and by 50% for CrCl <30 mL/min, including hemodialysis.	A-I
	ribavirin	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
	simeprevir	Has not been studied in HCV-infected patients with CrCl <30 mL/min.	A-I
	sofosbuvir	Should not be used if CrCl <30 mL/min or end-stage renal disease.	A-I
Hepatic Impairment	daclatasvir	No dosage adjustment needed.	A-I
	ledipasvir	No dosage adjustment needed.	A-I
	ombitasvir/paritaprevir/ ritonavir + dasabuvir	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
	peginterferon	Should not be used in patients with moderate or severe hepatic impairment (CTP B or C; CTP score ≥7).	A-I
	simeprevir	No dosage recommendation can be given for moderate or severe hepatic impairment (CTP B or C; CTP score ≥7) due to higher simeprevir exposures, which have been associated with increased frequency of adverse reactions including rash and photosensitivity.	A-I
	sofosbuvir	No dosage adjustment is required for patients with mild, moderate, or severe hepatic impairment (CTP A, B, or C).	A-I

Abbreviations: CrCL = creatinine clearance; CTP = Child-Turcotte-Pugh.

Daclatasvir (DCV)[44]
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. Using observed data, 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 Child-Pugh A, B, or C compared with a corresponding matched control group.

Ledipasvir (LDV)[17]
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[45,58]
Pharmacokinetic data suggest that the elimination of the ombitasvir/paritaprevir/ritonavir + dasabuvir are 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 ombitasvir/paritaprevir/ritonavir + dasabuvir appear similar compared with historical Phase 3 clinical trials. All 13 GT1a patients received ribavirin 200 mg daily; 8 patients required RBV dose interruption because of anemia.[59] SVR was achieved in 90% (18/20).[60]

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 (SMV)[46]
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 (SOF)[47]

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.

Because PEG-IFN is not recommended and no dosage recommendation can be given for simeprevir 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 (HCC)

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 drug-drug interactions should be thoroughly evaluated in post-transplant patients (See Appendix A, Table A4).

Table 13. Treatment Considerations for Patients Who Will or Have Received a Solid Organ Transplant, AFTER DISCUSSION WITH THE TRANSPLANT CENTER

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

Treatment Considerations					Supporting Information	
Transplant status	**HCV genotype (GT)**	**Regimen and duration**		**Evidence grade**	**SVR % (N/N)**	**Comments**
Pre-Liver Transplant (including CTP A, B, and C, as well as HCC)	GT1	ledipasvir/ sofosbuvir + ribavirin **NOT FDA APPROVED**	12 weeks	B-II	CTP B: 87% (26/30)[12] CTP C: 86% (19/22)[12]	<u>24 weeks</u> CTP B: 89% (24/27)[12] CTP C: 87% (20/23)[12]
Pre-Liver Transplant (including HCC)	GT2	sofosbuvir + ribavirin (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.[61] Patients had HCC with compensated liver disease (CTP score <7).[61]
Post-Liver Transplant	GT1	ledipasvir/ sofosbuvir + ribavirin **NOT FDA APPROVED**	12 weeks	B-II	F0-F3: 96% (53/55)[12] CTP A: 96% (25/26)[12] CTP B: 85% (22/26)[12] CTP C: 60% (3/5)[12]	<u>24 weeks</u> F0-F3: 98% (55/56)[12] CTP A: 96% (24/25)[12] CTP B: 88% (23/26)[12] CTP C: 75% (3/4)[12] Ribavirin dosage was weight-based for patients without cirrhosis and CPT A; in CPT B and C patients, ribavirin was initiated at 600 mg/day and increased as tolerated.[62] Refer to Appendix A, Table A4, for drug-drug interactions.
Post-Liver Transplant	GT1	*In patients who cannot tolerate ribavirin*: ledipasvir/ sofosbuvir **NOT FDA APPROVED**	24 weeks	B-III	Data not available	Effectiveness is presumed, based on use in non-transplant, treatment-experienced patients with cirrhosis.

Treatment Considerations					Supporting Information	
Transplant status	**HCV genotype (GT)**	**Regimen and duration**		**Evidence grade**	**SVR % (N/N)**	**Comments**
Post-Liver Transplant	GT2	sofosbuvir + ribavirin (PEG-IFN may be considered) **NOT FDA APPROVED**	24 weeks	B-III	77% (31/40)[63] 60% (19/32)[64] 50% (6/12)[64] with PEG-IFN	SVR rates included GT1, 3 and 4 patients. Refer to Appendix A, Table A4, for drug-drug interactions.
Pre- or Post-Liver Transplant	GT3, GT4	Consult with a transplant center prior to starting treatment. In general, the preferred treatment is the same treatment as is recommended for treatment-naïve or treatment-experienced (as appropriate) patients. **Ledipasvir/sofosbuvir + ribavirin and sofosbuvir + ribavirin + 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 (peg)interferon-containing regimens in these populations. Sofosbuvir has not been studied in non-liver transplant recipients.**				

Abbreviations: CTP = Child-Turcotte-Pugh; HCC = hepatocellular carcinoma; PEG-IFN = peginterferon.
Dosages: PEG-IFN alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly; ribavirin 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food; sofosbuvir 400 mg orally daily. Note: Sofosbuvir should not be used as monotherapy or in reduced dosages; it should not be restarted if discontinued.

Table 14. Alternative Treatments for Patients Who Have Received a Solid Organ Transplant, AFTER DISCUSSION WITH THE TRANSPLANT CENTER

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

Treatment Considerations					Supporting Information	
Transplant status	**HCV genotype (GT)**	**Regimen and duration**		**Evidence grade**	**SVR % (N/N)**	**Comments**
Post-Liver Transplant	GT1	sofosbuvir + simeprevir **NOT FDA APPROVED**	12-24 weeks	B-II	12 weeks: 91% (-RBV)[58] 89% (+RBV)[58] F0-2: 97%[58] F3-4: 64%[58]	**AVOID USE in patients receiving cyclosporine**; refer to Appendix A, Table A4, for drug-drug interactions. Can be considered for patients who cannot tolerate ribavirin.

Treatment Considerations					Supporting Information	
Transplant status	HCV genotype (GT)	Regimen and duration		Evidence grade	SVR % (N/N)	Comments
Post-Liver Transplant	GT1	ombitasvir/ paritaprevir/ ritonavir + dasabuvir + ribavirin	12 weeks	B-II	F0-2: 97% (33/34) [65]	Dosage of tacrolimus or cyclosporine needs to be reduced because of drug-drug interactions. Refer to Appendix A, Table A4, for drug-drug interactions.

Treatment in Pre-Liver Transplant Patients

Preferred regimens (See Table 13)
The decision to treat, regimen selection, and management of treatment should be coordinated with the transplant center and/or specialists.

Genotype 1, including patients with CTP A, B, or C and suitable patients with HCC

- *Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily + ribavirin 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 ribavirin 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.***

Genotype 2, including patients including suitable patients with HCC

- *Sofosbuvir (400 mg/day): 1 tablet daily + ribavirin (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.*

Genotype 3 or 4

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

CTP = Child-Turcotte-Pugh

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 4-9).

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.[64] 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.[64]

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

Preferred regimens (See Table 13)

Genotype 1

- *Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily + ribavirin (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.***
- *If ribavirin intolerant: Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily for 24 weeks.* ***NOT FDA APPROVED.***

Genotype 2

- *Sofosbuvir (400 mg/day): 1 tablet daily + ribavirin (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.***

Genotype 3

- *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.*

Genotype 4

- *Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily + ribavirin (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.***
- *If ribavirin intolerant: Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily for 24 weeks.* ***NOT FDA APPROVED.***

The decision to treat patients with recurrent HCV after a liver transplant should be discussed with the transplant center prior to starting treatment. Drug-drug interactions with HCV DAA agents and post-transplant immunosuppressive agents should be thoroughly evaluated and are listed in Appendix A, Table A4.

Ledipasvir/Sofosbuvir (LDV/SOF) 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.[62] RBV dosing was weight-based for patients without cirrhosis and with CTP A; in CTP B and C patients, ribavirin 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 and INR remained at baseline levels. Hemoglobin 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 ribavirin. 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.[63] 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) peginterferon for 24 weeks. The decision to use peginterferon 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.[63] 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 (OBV/PTV/r + DSV + RBV) 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.[65] 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 drug-drug interactions 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. SVR_{12} and SVR_{24} 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 ombitasvir, paritaprevir, dasabuvir, or ribavirin. Although OBV/PTV/r + DSV is FDA approved for use in post-transplant patients, because of the greater likelihood of drug-drug interactions 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 (SOF) and Simeprevir (SMV) 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 genotype 1 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% were treatment-experienced.[58] 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 ribavirin. 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 drug-drug interaction between SMV and cyclosporine (see Appendix A, Table A4), 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 drug-drug interaction 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 15. 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)

Mental Health Disorders

HCV-infected patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, posttraumatic 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.

East Asian Ancestry[46]

Higher simeprevir exposure occurred among individuals of East Asian ancestry (e.g., Vietnamese) and has been associated with increased adverse reactions, including rash and photosensitivity.

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 daclatasvir. In general during pregnancy, these drugs should be used only if the benefits outweigh the risks to the fetus.

Ribavirin-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 ribavirin should be consulted. Two forms of effective contraception is required during ribavirin therapy and for 6 months after the last dose.[54,55]

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

VA HCV Treatment Considerations: Helen.Yee@va.gov

National Viral Hepatitis Program: VHAHIVhphpp@va.gov

HCV Resistance Testing: V21PHRL@va.gov

Current VA policies and information: www.hepatitis.va.gov

VA-specific data: vaww.hepatitis.va.gov

PBM Criteria for Use: http://www.pbm.va.gov/PBM/clinicalguidance/criteriaforuse.asp

HCV Drug-Drug Interactions: http://www.hep-druginteractions.org/

XV. Appendix A

Table A1. Summary of SVR Results from Phase II/III Studies of Sofosbuvir-Based Therapy in Genotype 1-Infected, Treatment-Naïve Patients

Trial	Treatment Category	Non-Cirrhotic (SVR, %)	Cirrhotic (SVR, %)
ION-1[16]			
LDV/SOF ± RBV x 12 weeks	Naïve	179/180 (99, – RBV) 178/184 (97, + RBV)	32/34 (94, – RBV) 33/33 (100, + RBV)
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[9]			
LDV/SOF ± RBV x 8 weeks	Naïve	202/215 (94, – RBV) 201/216 (93, + RBV)	Not studied
LDV/SOF x 12 weeks	Naïve	206/216 (95)	Not studied
ELECTRON-2[18]			
LDV/SOF x 12 weeks	Naïve	Not studied	13/20 (65) (all were CTP B)
ERADICATE[48]			
LDV/SOF x 12 weeks	Naïve, HCV/HIV coinfected	10/10 (100, ARV untreated) SVR_4: 22/22 (100, ARV treated)	Not studied
COSMOS[26]			
SOF + SMV ± RBV x 12 weeks	Naïve	Not studied	2/3 (67, – RBV) 6/6 (100, + RBV)
SOF + SMV ± RBV x 24 weeks	Naïve	Not studied	5/5 (100, – RBV) 3/3 (100, + RBV)

Table A2. Summary of SVR Results from Phase II/III Studies of Sofosbuvir-based Therapy in Genotype 1-infected, Treatment-experienced Patients

Trial	Treatment Category	Non-Cirrhotic (SVR, %)	Cirrhotic (SVR, %)
ION-2[14]			
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)
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[41]			
LDV/SOF x 12 weeks	Experienced (SOF + RBV relapsers)	7/7 (100)	7/7 (100)
ELECTRON-2[18]			
LDV/SOF + RBV x 12 weeks	Experienced (SOF + RBV ± DAA)	19/19 (100)	Not studied
COSMOS[26]			
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)
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 A3. 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	Treatment Category	Cirrhotic	SVR, %
SAPPHIRE-I,[21] n = 631			
OBV/PTV/r + DSV + RBV x 12 weeks	GT1, Naïve	No	96% (455/473)
SAPPHIRE-II,[23] n = 394			
OBV/PTV/r + DSV + RBV x 12 weeks	GT1, Experienced	No	96% (285/297) (95% in prior null responders)
PEARL-II,[22] n = 186			
OBV/PTV/r + DSV ± RBV x 12 weeks	GT1b, Experienced	No	100% (91/91, – RBV) 97% (85/88, + RBV)
PEARL-III,[8] n = 419			
OBV/PTV/r + DSV ± RBV x 12 weeks	GT1b, Naïve	No	99% (207/209, – RBV) >99% (209/210, + RBV)
PEARL-IV,[8] n = 305			
OBV/PTV/r + DSV ± RBV x 12 weeks	GT1a, Naïve	No	90% (185/205, – RBV) 97% (97/100, + RBV)
TURQUOISE-II,[10] 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)
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,[11] 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 A4. Drug-Drug Interactions with HCV Antiviral Agents[17,44-47,66]

	HCV Direct-Acting Antiviral Agents				
Selected Drugs	**NS5A/ Protease Inhibitor/ NS5B Inhibitor**	**NS5A/NS5B Inhibitor**	**NS5A Inhibitor**	**NS5B Inhibitor**	**Protease Inhibitor**
	Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)	**Ledipasvir (LDV)/ sofosbuvir (SOF)**	**Daclatasvir (DCV)**	**Sofosbuvir (SOF)**	**Simeprevir (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 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.	?	use caution and monitor (may ↑ digoxin concentration)
amiodarone	use caution and monitor (may ↑ amiodarone concentration)	✘ (↑ amiodarone concentration;	✘(if given with SOF) (↑ amiodarone concentration;	✘(if given with SMV or DCV) (↑ amiodarone	use caution and monitor (may ↑ amiodarone concentration)

	HCV Direct-Acting Antiviral Agents				
Selected Drugs	**NS5A/ Protease Inhibitor/ NS5B Inhibitor**	**NS5A/NS5B Inhibitor**	**NS5A Inhibitor**	**NS5B Inhibitor**	**Protease Inhibitor**
	Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)	**Ledipasvir (LDV)/ sofosbuvir (SOF)**	**Daclatasvir (DCV)**	**Sofosbuvir (SOF)**	**Simeprevir (SMV)**
		may increase risk of bradycardia and cardiac arrest; if amiodarone required, monitor inpatient for first 48 hrs, then daily outpatient for 2 wks)	may increase risk of bradycardia and cardiac arrest; if amiodarone required, monitor inpatient for first 48 hrs, then daily outpatient for 2 wks)	concentration--may increase risk bradycardia and cardiac arrest; if amiodarone required, monitor inpatient for first 48 hrs, then daily outpatient for 2 wks)	✘(if given with SOF)
bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	use caution and monitor (may ↑ antiarrhythmic concentration)	?	?	?	use caution and monitor (may ↑ antiarrhythmic concentration)
Anticoagulant					
dabigatran	?	?	✘ (↑ dabigatran concentration in specific renal impairment groups)	?	?
Anticonvulsants					
carbamazepine, phenytoin, phenobarbital, oxcarbazepine	✘ (may ↓ OBV/PTV/r + DSV concentrations)	✘ (may ↓ LDV/SOF concentration)	✘ (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)

	HCV Direct-Acting Antiviral Agents				
Selected Drugs	**NS5A/ Protease Inhibitor/ NS5B Inhibitor**	**NS5A/NS5B Inhibitor**	**NS5A Inhibitor**	**NS5B Inhibitor**	**Protease Inhibitor**
	Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)	**Ledipasvir (LDV)/ sofosbuvir (SOF)**	**Daclatasvir (DCV)**	**Sofosbuvir (SOF)**	**Simeprevir (SMV)**
ketoconazole	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)
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	?	?	✓ (↑ DCV dose to 90 mg/day)	?	?
Antimycobacterials					
rifampin, rifabutin	✘ (rifampin may ↓ OBV/PTV/r + DSV concentrations)	✘ (may ↓ LDV/SOF concentration)	✘ (may ↓ DCV concentration)	✘ (may ↓ SOF concentration)	✘ (may ↓ SMV concentration)

	HCV Direct-Acting Antiviral Agents				
Selected Drugs	**NS5A/ Protease Inhibitor/ NS5B Inhibitor**	**NS5A/NS5B Inhibitor**	**NS5A Inhibitor**	**NS5B Inhibitor**	**Protease Inhibitor**
	Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)	**Ledipasvir (LDV)/ sofosbuvir (SOF)**	**Daclatasvir (DCV)**	**Sofosbuvir (SOF)**	**Simeprevir (SMV)**
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 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,	?	?	?	?	✓

	HCV Direct-Acting Antiviral Agents				
Selected Drugs	**NS5A/ Protease Inhibitor/ NS5B Inhibitor**	**NS5A/NS5B Inhibitor**	**NS5A Inhibitor**	**NS5B Inhibitor**	**Protease Inhibitor**
	Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)	**Ledipasvir (LDV)/ sofosbuvir (SOF)**	**Daclatasvir (DCV)**	**Sofosbuvir (SOF)**	**Simeprevir (SMV)**
methylprednisone, prednisone					
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	?	?	✓ (↑ DCV dose to 90 mg/day)	?	?
Ergot derivatives					
ergotamine, dihydroergotamine, ergonovine, methylergonovine	✘ (acute ergot toxicity)	?	?	?	?
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					
simeprevir	?	✘ (↑ LDV/SOF concentration)	?	✓	

	HCV Direct-Acting Antiviral Agents				
Selected Drugs	**NS5A/ Protease Inhibitor/ NS5B Inhibitor**	**NS5A/NS5B Inhibitor**	**NS5A Inhibitor**	**NS5B Inhibitor**	**Protease Inhibitor**
	Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)	**Ledipasvir (LDV)/ sofosbuvir (SOF)**	**Daclatasvir (DCV)**	**Sofosbuvir (SOF)**	**Simeprevir (SMV)**
Herbal supplements					
St. John's wort (Hypericum perforatum)	✘ (may ↓ OBV/PTV/r +DSV concentrations)	✘ (may ↓ LDV/SOF concentration)	✘ (may ↓ DCV concentration)	✘	✘ (may ↓ SMV concentration)
milk thistle	?	?	?	?	✘ (may ↑ SMV concentration)
HIV ARVs	For a complete listing of drug-interactions associated with HIV antiretrovirals, refer to **Appendix Table A5: Drug-Drug Interactions with HIV Antiretrovirals**				
HMG Co-A Reductase Inhibitors					
rosuvastatin	✓ dose ≤10 mg daily (↑ statin concentration)	✘ (may ↑ statin concentration; potential for myopathy and rhabdomyolysis)	? (may ↑ statin concentration; potential for myopathy)	?	✓ initiate at 5 mg once daily; dose ≤10 mg daily
atorvastatin	?	?	? (may ↑ statin concentration; potential for myopathy)	?	✓ dose ≤40 mg once daily
simvastatin, lovastatin	✘ (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

	HCV Direct-Acting Antiviral Agents				
Selected Drugs	**NS5A/ Protease Inhibitor/ NS5B Inhibitor** **Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)**	**NS5A/NS5B Inhibitor** **Ledipasvir (LDV)/ sofosbuvir (SOF)**	**NS5A Inhibitor** **Daclatasvir (DCV)**	**NS5B Inhibitor** **Sofosbuvir (SOF)**	**Protease Inhibitor** **Simeprevir (SMV)**
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	?	?	? (may ↑ statin concentration; potential for myopathy)	?	✓
Immunosuppressants					
cyclosporine (CSA)	✓ (↑ 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	✓ (↑ 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 concentrations)

	HCV Direct-Acting Antiviral Agents				
Selected Drugs	**NS5A/ Protease Inhibitor/ NS5B Inhibitor**	**NS5A/NS5B Inhibitor**	**NS5A Inhibitor**	**NS5B Inhibitor**	**Protease Inhibitor**
	Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)	**Ledipasvir (LDV)/ sofosbuvir (SOF)**	**Daclatasvir (DCV)**	**Sofosbuvir (SOF)**	**Simeprevir (SMV)**
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 monitor (may ↑ concentration of PDE-5 inhibitor)
sildenafil	✘ (potential for sildenafil-associated AEs in doses taken	?	?	?	use caution and monitor (may ↑ concentration of PDE-5 inhibitor)

	HCV Direct-Acting Antiviral Agents				
Selected Drugs	**NS5A/ Protease Inhibitor/ NS5B Inhibitor**	**NS5A/NS5B Inhibitor**	**NS5A Inhibitor**	**NS5B Inhibitor**	**Protease Inhibitor**
	Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)	**Ledipasvir (LDV)/ sofosbuvir (SOF)**	**Daclatasvir (DCV)**	**Sofosbuvir (SOF)**	**Simeprevir (SMV)**
	for pulmonary artery hypertension)				
Proton Pump Inhibitors (PPI)					
omeprazole	✓ ↓ omeprazole concentrations, monitor for decreased omeprazole efficacy; avoid dose >40 mg per day	✓ dose ≤20 mg/day; administer simultaneously under fasting conditions	✓	?	✓
Other PPI	?	✓ PPI doses comparable to omeprazole ≤20 mg/day can be administered simultaneously, fasting	✓	?	✓
Propulsive					
cisapride	?	?	?	?	✘
Quinolone					
ciprofloxacin	?	?	✓ (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	✓	?	?	?	?

	HCV Direct-Acting Antiviral Agents				
Selected Drugs	**NS5A/ Protease Inhibitor/ NS5B Inhibitor**	**NS5A/NS5B Inhibitor**	**NS5A Inhibitor**	**NS5B Inhibitor**	**Protease Inhibitor**
	Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)	**Ledipasvir (LDV)/ sofosbuvir (SOF)**	**Daclatasvir (DCV)**	**Sofosbuvir (SOF)**	**Simeprevir (SMV)**
Stimulant					
methylphenidate	?	?	?	?	✓
modafinil			✓ (↑ DCV dose to 90mg/day)		
SSRI/SNRI					
escitalopram	✓	?	✓	?	✓
duloxetine	✓	?	?	?	?
nefazodone	?	?	✓ (↓ DCV dose to 30 mg/day)	?	?

✓ = drug that can be used concomitantly

✘ = drug not recommended

? = data limited or not available on pharmacokinetic interactions

Table A5. Drug-Drug Interactions with HIV Antiretrovirals[17,44-47,53,66]

(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*)* **http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/26/hiv-hcv**)[1]

	HCV Direct-Acting Antiviral Agents				
	Co-Formulated NS5A/Protease Inhibitor + NS5B Inhibitor	**Co-Formulated NS5A/NS5B Inhibitors**	**NS5A Inhibitor**	**NS5B Inhibitor**	**Protease Inhibitor**
Selected HIV drugs	**Ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) + dasabuvir (DSV)**	**Ledipasvir (LDV)/SOF**	**Daclatasvir (DCV)**	**Sofosbuvir (SOF)**	**Simeprevir (SMV)**
Nucleoside Reverse Transcriptase Inhibitors					
FTC	✓	✓	✓	✓	✓
3TC	✓	✓	✓	✓	✓
ABC	✓	✓	✓	✓	✓
TDF	✓	✓ Monitor for TDF toxicity	✓	✓	✓
ZDV [a]	✓	✓	✓	✓	✓
HIV Protease Inhibitors					
ATV (unboosted)	✓ reduce ATV dose to 300 mg in the morning at the same time as OBV/PTV/r + DSV; if RTV cannot be used, choose an alternative HCV regimen	✓ 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])	✓ (monitor for DCV adverse events)	✓	✘
ATV/r or ATV/c	✓ 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	✘ (↓ DRV trough concentrations)		✓ (monitor for DCV adverse events)	✓	✘
FPV or FPV/r	✘		✓ (monitor for DCV adverse events)	✓	✘
IDV/r	?		?		

Selected HIV drugs	HCV Direct-Acting Antiviral Agents				
	Co-Formulated NS5A/Protease Inhibitor + NS5B Inhibitor	Co-Formulated NS5A/NS5B Inhibitors	NS5A Inhibitor	NS5B Inhibitor	Protease Inhibitor
	Ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) + dasabuvir (DSV)	Ledipasvir (LDV)/SOF	Daclatasvir (DCV)	Sofosbuvir (SOF)	Simeprevir (SMV)
LPV/r	✘ (may ↑ PTV concentrations)		✓ (monitor for DCV adverse events)	✓	✘
SQV/r	✘		?	✓	✘
TPV/r	✘	✘	?	✘	✘
Nonnucleoside Reverse Transcriptase Inhibitors					
EFV	✘ (poorly tolerated and liver enzyme elevations)	✓ If EFV used with TDF/FTC, monitor for TDF toxicity due to ↑TDF concentrations	✓ (↑ DCV dose to 90 mg/day)	✓	✘
RPV	✘ (may ↑ RPV concentrations; potential QT prolongation)	✓	✓	✓	✓
ETR	✘	✓	✓ (↑ DCV dose to 90 mg/day)	✓	✘
NVP	✘	✓		✓	✘
Integrase Strand Transfer Inhibitors					
DTG	?	✓	✓	✓	✓
EVG/c/TDF/FTC	✘	✘	✓ (↓ DCV dose to 30 mg/day)	✓	✘
EVG + (PI/r without COBI)	Refer to recommendations for individual ritonavir-boosted PI				✘
RAL	✓	✓	✓	✓	✓
CCR5 Antagonist					
MVC	✘	✓	✓	✓	✓

Abbreviations: 3TC = lamivudine; ABC = abacavir; ATV/r = atazanavir/ritonavir; ATV/c = atazanavir/cobicistat; COBI = cobicistat; DAA = direct-acting antiviral agents; DCV = daclatasvir; 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; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine.

✓ = agents that can be used concomitantly
✖ = agents not recommended
? = data limited or not available on pharmacokinetic interactions with antiretroviral drug

[a] Concomitant use of ZDV with ribavirin is not recommended due to potential for worsening anemia; concomitant use with peginterferon is not recommended due to potential for worsening neutropenia.

[b] Regimens containing TDF and an HIV protease inhibitor/ritonavir 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 drug-drug interactions and dosage adjustments of concomitantly prescribed medications.[17,44-47]

Daclatasvir product prescribing information: packageinserts.bms.com/pi/pi_daklinza.pdf
Ledipasvir/sofosbuvir product prescribing information: www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf
Ombitasvir/paritaprevir/ritonavir+ dasabuvir product prescribing information: www.accessdata.fda.gov/drugsatfda_docs/label/2014/206619lbl.pdf
Sofosbuvir product prescribing information: www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf
Simeprevir product prescribing information: www.olysio.com/shared/product/olysio/prescribing-information.pdf

XV. Appendix B

HCV Resistance Genotyping

The Public Health Reference Laboratory (PHRL) at the VA Palo Alto provides 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 occuring) 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 genotype 3, thus, NS3/4A Resistance Genotyping for genotype 3 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 genotype 3 patients for daclatasvir [FDA-approved indication], however, a resistance interpretation for ledipasvir [non FDA-approved indication for genotype 3] 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 Test

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.

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.
5. Currently, there is no cost to the requesting VHA facility for HCV resistance testing.

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 to PHRL on dry ice or frozen ice packs.

U.S. Department of Veterans Affairs

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

XVI. References

1. *Panel on Antiretroviral Guidelines for Adults and Adolescents.* Department of Health and Human Services.
2. Martinot-Peignoux M, Stern C, Maylin S, et al. Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. *Hepatology.* 2010;51(4):1122-1126.
3. Medrano J, Barreiro P, Resino S, et al. Rate and timing of hepatitis C virus relapse after a successful course of pegylated interferon plus ribavirin in HIV-infected and HIV-uninfected patients. *Clin Infect Dis.* 2009;49(9):1397-1401.
4. Chen J, Florian J, Carter W, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. *Gastroenterology.* 2013;144(7):1450-1455 e1452.
5. Morgan TR, Ghany MG, Kim HY, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology.* 2010;52(3):833-844.
6. Yee HS, Chang MF, Pocha C, et al. 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. *Am J Gastroenterol.* 2012;107(5):669-689.
7. Everson GT, Dusheiko G, Coakley E, et al. Integrated Efficacy Analysis of Four Phase 3 Studies in HCV Genotype 1a-Infected Patients Treated with ABT-450/r/Ombitasvir and Dasabuvir With or Without Ribavirin. Paper presented at: Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver Diseases; November 7-12, 2014, November 7-12, 2014; Boston, MA.
8. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med.* 2014;370(21):1983-1992.
9. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med.* 2014;370(20):1879-1888.
10. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med.* 2014;370(21):1973-1982.
11. Feld JJ, Moreno C, Trinh R, et al. TURQUOISE-III: Safety and Efficacy of 12-week Ribavirin-Free Treatment for Patients with HCV Genotype 1b and Cirrhosis. Paper presented at: 15th Annual International Symposium on Viral Hepatitis and Liver Disease; June 26-28, 2015. Abstract P226; Berlin, Germany.
12. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. *Gastroenterology.* 2015;149(3):649-659.
13. Bourliere M, Bronowicki JP, de Ledinghen V, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). *Lancet Infect Dis.* 2015;15(4):397-404.
14. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med.* 2014;370(16):1483-1493.
15. Wyles D, Pockros P, Morelli G, et al. Ledipasvir-sofosbuvir plus ribavirin for patients with genotype 1 hepatitis C virus previously treated in clinical trials of sofosbuvir regimens. *Hepatology.* 2015;61(6):1793-1797.
16. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med.* 2014;370(20):1889-1898.

17. *Ledipasvir/sofosbuvir (HARVONI®) prescribing information.* Foster City, California: Gilead Sciences;2015.
18. Gane EJ, Hyland RH, An D, et al. Sofosbuvir/ledipasvir fixed dose combination is safe and effective in difficult-to-treat populations including genotype-3 patients, decompensated genotype-1 patients, and genotype-1 patients with prior sofosbuvir treatment experience. Paper presented at: Program and abstracts of the 49th European Association for the Study of the Liver International Liver CongressApril 9-13, 2014; London, England.
19. Lawitz E, Flamm S, J.C. Y, et al. Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks. Paper presented at: The International Liver Congress 2015, 50th Annual Meeting of the European Association for the Study of the Liver; April 22-26, 2015; Vienna, Austria.
20. Zeuzem S, Mizokami M, Pianko S, et al. Prevalence of pre-treatment NS5A resistance associated variants in gentoype 1 patients across different regions using deep sequencing and effect on treatment outcome on LDV/SOF. Paper presented at: Program and abstracts of the 66th Annual Meeting of the American Association for the Study of Liver Diseases; November 13-17, 2015, 2015; San Francisco, CA. Abstract 91.
21. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med.* 2014;370(17):1594-1603.
22. Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. *Gastroenterology.* 2014;147(2):359-365 e351.
23. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med.* 2014;370(17):1604-1614.
24. Kwo P GN, Nahass R, et al. A phase 3, randomised, open-label study to evaluate the efficacy and safety of 12 and 8 weeks of simeprevir (SMV) plus sofosbuvir (SOF) in treatment-naive and -experienced patients with chronic HCV genotype 1 infection without cirrhosis: OPTIMIST-1. Paper presented at: Program and abstracts of the 50th Annual Meeting of the European Association for the Study of the Liver; April 22-26, 2015; Abstract LB14 Vienna, Austria.
25. Lawitz E MG, DeJesus E, et al. A phase 3, open-label, single-arm study to evaluate the efficacy and safety of 12 weeks of simeprevir (SMV) plus sofosbuvir (SOF) in treatment-naive or –experienced patients with chronic HCV genotype 1 infection and cirrhosis: OPTIMIST-2. Paper presented at: Program and abstracts of the 50th Annual Meeting of the European Association for the Study of the Liver; April 22-26, 2015; Abstract LP04; Vienna, Austria.
26. Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. *Lancet.* 2014.
27. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med.* 2013;368(20):1878-1887.
28. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med.* 2013;368(20):1867-1877.
29. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med.* 2014;370(21):1993-2001.
30. Foster GR, Pianko S, Brown A, et al. Sofosbuvir plus Peg-IFN/RBV for 12 weeks vs sofosbuvir/RBV for 16 or 24 weeks in genotype 3 HCV-infected patients and treatment-experienced cirrhotic patients with genotype 2 HCV: The BOSON Study. Paper presented at: The International Liver

Congress™ 2015, 50th Annual Meeting of the European Association for the Study of the Liver (EASL); April 22-26, 2015; Vienna, Austria.
31. Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. *Lancet.* 2014;383(9916):515-523.
32. Gane EJ, Hyland RH, Yang Y, et al. Ledipasvir/sofosbuvir single tablet regimen is effective in patients with HCV genotype 2 infection. Paper presented at: ISVHLD 2015; Berlin, Germany.
33. Gane EJ, Hyland RH, An D, et al. Efficacy of Ledipasvir and Sofosbuvir, With or Without Ribavirin, for 12 Weeks in Patients With HCV Genotype 3 or 6 Infection. *Gastroenterology.* 2015.
34. *Veterans Affairs internal data, HCV Clinical Case Registry.* Population Health Services.
35. Leroy V, Angus W, Bronowicki J, et al. All-oral treatment with daclatasvir (DCV) plus sofosbuvir (SOF) plus ribavirin (RBV) for 12 or 16 weeks in HCV genotype (GT) 3-infected patients with advanced fibrosis or cirrhosis: The ALL Y-3+ Phase 3 Study. Paper presented at: Program and abstracts of the 66th Annual Meeting of the American Association for the Study of Liver Diseases; November 13-17, 2015; San Francisco, CA.
36. Hézode C, DeLedinghen V, Fontaine H, et al. Daclatasvir plus sofosbuvir with or without ribavirin in patients with HCV genotype 3 infection: interim analysis of a French multicenter compassionate use program. Paper presented at: Program and abstracts of the 66th Annual Meeting of the American Association for the Study of Liver Diseases; November 13-17, 2015; San Francisco, CA. Abstract 206.
37. Welzel TM, Petersen J, Ferenci P, et al. Safety and efficacy of daclatasvir plus sofosbuvir with or without ribavirin for the treatment of chronic HCV genotype 3 infection: interim results of a multicenter European Compassionate Use Program. Paper presented at: Program and abstracts of the 66th Annual Meeting of the American Association for the Study of Liver Diseases; November 13-17, 2015; San Francisco, CA. Abstract 36.
38. Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology.* 2015;61(4):1127-1135.
39. Foster GR MJ, Irving W, et al. Treatment of decompensated HCV cirrhosis in patients with diverse genotypes: 12 weeks sofosbuvir and NS5A inhibitors with/without ribavirin is effective in HCV genotypes 1 and 3. Paper presented at: The International Liver Congress™ 2015, 50th annual meeting of the European Association for the Study of the Liver (EASL); April 22-26, 2015; Vienna, Austria. Oral O002.
40. Poordad F, Schiff E, Vierling J, et al. Daclatasvir, sofosbuvir, and ribavirin combination for HCV patients with advanced cirrhosis or post-transplant recurrence: ALLY-1 Phase 3 Study. Paper presented at: The International Liver Congress™ 2015, 50th annual meeting of the European Association for the Study of the Liver (EASL); April 22-26, 2015. ; Vienna, Austria. Abstract L08.
41. Kohli A, Kapoor R, Sims Z, et al. Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study. *Lancet Infect Dis.* 2015;15(9):1049-1054.
42. Pol S, Reddy KR, Hezode C, et al. Interferon-Free Regimens of Ombitasvir and ABT-450/r with or without Ribavirin in Patients with HCV Genotype 4 Infection: PEARL-I Study Results. Paper presented at: Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver DiseasesNovember 7-12, 2014; Boston, Massachusetts.
43. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology.* 2009;49(4):1335-1374.

44. *Daclatasvir (DAKLINZA™) prescribing information.* Princeton, NJ: Bristol-Myers Squibb Company;2015.
45. *Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir (VIEKIRA PAK™) prescribing information.* North Chicago, IL: AbbVie Inc.;2015.
46. *Simeprevir (OLYSIO®) prescribing information.* Titusville, NJ: Janssen Therapeutics;2015.
47. *Sofosbuvir (SOVALDI®) prescribing information.* Foster City, California: Gilead Sciences;2015.
48. Osinusi A, Townsend K, Kohli A, et al. Virologic response following combined ledipasvir and sofosbuvir administration in patients with HCV genotype 1 and HIV co-infection. *JAMA.* 2015;313(12):1232-1239.
49. Wyles DL, Sulkowski MS, Eron J, et al. TURQUOISE-I: 94% SVR12 in HCV/HIV-1 Coinfected Patients Treated with ABT-450/r/Ombitasvir, Dasabuvir and Ribavirin. Paper presented at: Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver DiseasesNovember 7-11, 2014; Boston, Massachusetts.
50. Sulkowski MS, Naggie S, Lalezari J, et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. *JAMA.* 2014;312(4):353-361.
51. Molina M, Orkin C, Iser DM, et al. All-oral therapy with sofosbuvir plus ribavirin for the treatment of HCV genotypes 1, 2, 3 and 4 infection in patients co-infected with HIV (PHOTON-2). Paper presented at: Program and abstracts of the 20th International AIDS ConferenceJuly 20-25, 2014; Melbourne, Australia.
52. *Sofosbuvir (NDA 204671) Presentation to FDA Antiretroviral Drugs Advisory Committee.* October 25, 2013.
53. German P, Pang P, West S, Han L, Saiwani K, Mathias A. Drug interactions between direct acting anti-HCV antivirals sofosbuvir and ledipasvir and HIV antiretrovirals. Paper presented at: Program and abstracts of the 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis TherapyMay 19-21, 2014; Washington, DC.
54. *Ribavirin (REBETOL®) prescribing information* Whitehouse Station, NJ: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc;2013.
55. *Ribavirin (COPEGUS®) prescribing information.* South San Francisco, CA: Hoffmann-La Roche, Inc. c/o Genentech, Inc.;2015.
56. *Peginterferon alfa-2a (PEGASYS®) prescribing information.* South San Francisco, CA: Hoffmann-La Roche, Inc. c/o Genentech, Inc.;2015.
57. *Peginterferon alfa-2b (PEGINTRON®) prescribing information.* Whitehouse Station, NJ: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc;2013.
58. Pungpapong S, Werner KT, Aqel B, et al. Multicenter Experience using Sofosbuvir and Simeprevir with/without Ribavirin to Treat HCV Genotype 1 after Liver Transplantation. Paper presented at: Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver DiseasesNovember 7-11, 2014; Boston, Massachusetts.
59. Pockros P, Reddy KR, Mantry PS, et al. Safety of Ombitasvir/Paritaprevir/Ritonavir Plus Dasabuvir for Treating HCV GT1 Infection in Patients With Severe Renal Impairment or End-Stage Renal Disease: The RUBY-1 Study Paper presented at: The International Liver Congress 2015, 50th Annual Meeting of the European Association for the Study of the Liver; April 22-26, 2015; Vienna, Austria.
60. Pockros P, Reddy KR, Mantry PS, et al. RUBY-1: Ombitasvir/paritaprevir/ritonavir + dasabuvir +/- ribavirin in non-cirrhotic HCV genotype 1-infected patients with severe renal impairment or end-stage renal disease. Paper presented at: Program and abstracts of the 66th Annual Meeting of the American Association for the Study of Liver Diseases; November 13-17, 2015; San Francisco, CA. Abstract 1039.

61. Curry MP, Forns X, Chung RT, et al. Sofosbuvir and Ribavirin Prevent Recurrence of HCV Infection After Liver Transplantation: An Open-Label Study. *Gastroenterology.* 2015 Jan;148(1):100-107. e101.
62. Reddy KR, Everson GT, Flamm SL, et al. Ledipasvir/sofosbuvir with ribavirin for the treatment of HCV in patients with post-transplant recurrence: preliminary results of a prospective, multicenter study. Paper presented at: Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver DiseasesNovember 7-11, 2014; Boston, Massachusetts.
63. Charlton MR, Gane EJ, Manns MP, et al. Sofosbuvir and ribavirin for the treatment of established recurrent hepatitis C infection after liver transplantation: preliminary results of a prospective multicenter study. *Hepatology: Special Issue: The 64th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2013;.*58(6):1378A.
64. Forns X, Fontana RJ, Moonka D, McHutchison JG, Symonds WT, Charlton MR. Initial evaluation of the sofosbuvir compassionate use program for patients with severe recurrent HCV following liver transplantation. *Hepatology: Special Issue: The 64th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2013.*58(4):732A-733A.
65. Kwo PY, Mantry PS, Coakley E, et al. An interferon-free antiviral regimen for HCV after liver transplantation. *N Engl J Med.* 2014;371(25):2375-2382.
66. Kiser JJ, Burton JR, Jr., Everson GT. Drug-drug interactions during antiviral therapy for chronic hepatitis C. *Nat Rev Gastroenterol Hepatol.* 2013;10(10):596-606.