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

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I. What's New and Updates/Changes

(Last updated: July 28, 2015; last reviewed: July 28, 2015)

This revision (July 28, 2015) incorporates preferred regimens for chronic hepatitis C virus (HCV) genotypes 1 and 4, and extension to 16 weeks of treatment for HCV genotype 2 with cirrhosis. Additional revisions include updates on principles of patient identification, evaluation, and treatment; laboratory monitoring; drug use in renal insufficiency; and drug-drug interactions to provide clinicians with guidance on the concomitant use of HCV drugs and other drugs including HIV antiretroviral agents (Appendix, Tables 4 and 5). 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 is dynamic and 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. Based on patient characteristics, providers should consider the most clinically appropriate option when selecting a hepatitis C antiviral regimen.
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 sofosbuvir-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.
** Contraindication and/or intolerance to ribavirin: Contraindication is defined as history of significant or unstable cardiac disease, known pregnancy, positive pregnancy test, and men whose female partner is pregnant or plan to become pregnant, known hypersensitivity reaction, autoimmune hepatitis, hemoglobinopathies) and/or intolerance (i.e., baseline hemoglobin <12g/dL) and/or history of significant adverse events with previous ribavirin-containing regimen.

HCV Genotype (GT)	Treatment History	Cirrhosis Status	Preferred Regimen	Alternative Regimen
1	Naïve	Non-cirrhotic	* ombitasvir/paritaprevir/ritonavir + dasabuvir x 12 weeks; GT1a: add ribavirin, GT1b: ribavirin not required	ledipasvir/sofosbuvir x 12 weeks if baseline HCV RNA ≥6 million IU/mL
			ledipasvir/sofosbuvir x 8 weeks if baseline HCV RNA <6 million IU/mL	
		Cirrhotic, CTP A	* ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin x 12 weeks (GT1a: may consider 24 weeks; refer to Table 4a for details)	ledipasvir/sofosbuvir x 12 weeks (may consider adding ribavirin; refer to Table 4a 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 4a for details)
	Experienced **(Prior PEG-IFN/RBV only)**	Cirrhotic, CTP A	If prior relapser or partial responder: * ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin x 12 weeks; <u>GT1a</u>: may consider 24 weeks; refer to Table 4a for details	If prior relapser or partial responder: ledipasvir/sofosbuvir + ribavirin x 12 weeks; NOT FDA approved
			If GT1a null responder: ledipasvir/sofosbuvir + ribavirin x 12 weeks; NOT FDA approved	If GT1a null responder: * ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin x 24 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 DAA-based therapy)**	Non-cirrhotic or Cirrhotic	ledipasvir/sofosbuvir + ribavirin x 12 weeks; NOT FDA approved	

HCV Genotype (GT)	Treatment History	Cirrhosis Status	Preferred Regimen	Alternative Regimen
2	Naïve	Non-cirrhotic	sofosbuvir + ribavirin x 12 weeks	
		Cirrhotic	sofosbuvir + ribavirin x 16 weeks; FDA approved for 12 weeks	
	Experienced	Non-cirrhotic	sofosbuvir + ribavirin x 12 weeks (may consider 16 weeks for treatment-experienced null responders; NOT FDA approved)	
		Cirrhotic	sofosbuvir + ribavirin x 16 weeks; FDA approved for 12 weeks	
		Non-cirrhotic or Cirrhotic	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	
		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
	Experienced	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	
		Cirrhotic	sofosbuvir + PEG-IFN + ribavirin x 12 weeks; NOT FDA approved	ledipasvir/sofosbuvir + ribavirin x 12 weeks; NOT FDA approved
				sofosbuvir + ribavirin x 24 weeks
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 (may consider adding ribavirin); NOT FDA approved
				sofosbuvir + PEG-IFN + ribavirin x 12 weeks

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

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

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.

For definitions of treatment response, 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-definitions-of-response.asp).[1]

III. Introduction

The goal of hepatitis C antiviral treatment is to achieve a sustained virological response (SVR), defined as undetectable HCV RNA 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.

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

The following treatment considerations summarize the current best practices in the treatment of chronic HCV infection within VHA. These considerations are based on review of published data and abstracts, American Association for the Study of Liver Diseases (AASLD), 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 infection (HBV), 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).[2] 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 Public Health. 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/AdultandAdolescentGL.pdf. Page A-3, Table 2. Accessed March 25, 2014.[2]

Clinical benefit of achieving SVR (i.e., cure): SVR, defined as undetectable HCV RNA level in the blood 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 SVR at 12 weeks after completion of treatment as the primary endpoint for HCV clinical trials.[3-5] 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.[6] 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.

New HCV treatments allow a large 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, 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 drinking alcohol, using illicit drugs, including marijuana, or participating in opioid replacement programs should <u>not</u> be an exclusion for HCV treatment. There are no published data supporting a minimum length of abstinence or that these patients are less likely to achieve SVR with HCV treatment. 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 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 8, "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. 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 8, "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 8) • 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 in 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)[1]

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

Interferon-Free Regimens in Genotype 1 (GT1)

Preferred Regimens (see Table 4a for details)

Treatment-naïve patients without cirrhosis

- ** 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.*
- *Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily for 8 weeks if baseline HCV RNA <6 million IU/mL.*

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) + ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks; may consider 24 weeks for GT1a (refer to Table 4a for details).*

CTP B,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) + 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 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.* ***NOT FDA APPROVED.***

CTP B,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 DAA experienced)

- *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.***

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 sofosbuvir-based regimen; **OR p**atients 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.

****** There are minimal data on re-treatment of patients who failed a regimen containing an NS5A or NS5B inhibitor. The VA offers free testing of HCV resistance-associated variants for patients who have failed a DAA regimen. Consult an expert before re-treating.

Table 4a. 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 GT1a or 1b	Non-cirrhotic	** ombitasvir/ paritaprevir/ritonavir + dasabuvir **GT1a: add ribavirin** **GT1b: ribavirin not required**	12 weeks	A-I	GT1a: 91% (182/202, – RBV)[9] 96% (403/420, + RBV)[9] GT1b: 99% (207/209, – RBV)[10] >99% (209/210, + RBV)[10]	Pooled data for GT1a from SAPPHIRE-I and -II, PEARL IV, TURQUOISE-II[9]
		ledipasvir/sofosbuvir	8 weeks if baseline HCV RNA <6 million IU/mL	A-I	97% (119/123, – RBV)[7]	Relapse rates were higher with 8 weeks vs. 12 weeks of treatment if baseline HCV RNA ≥6 million IU/mL: 10% (9/92) vs. 1% (1/85), respectively.[7]
	Cirrhotic, CTP A	** ombitasvir/ paritaprevir/ritonavir + dasabuvir + ribavirin	12 weeks	A-I	GT1a: 12 weeks: 92% (59/64)[11] GT1b: 99% (67/68)[11]	GT1a: SVR 95% (53/56) with 24 weeks.[11] Consider extending to 24 weeks for slow on-treatment virologic response on a case-by-case basis. GT1b: 100% (51/51) with 24 weeks[11]

Preferred Regimens					Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	**Comments**
	Cirrhotic, CTP B,C	ledipasvir/sofosbuvir + ribavirin	12 weeks **NOT FDA approved**	B-II	CTP B: 87% (26/30)[12] CTP C: 86% (19/22)[12]	24 weeks CTP B: 89% (24/27)[12] CTP C: 90% (18/20)[12] Ribavirin initiated at 600 mg/day and increase by 200 mg/day every 2 weeks only as tolerated.[12] Population includes treatment-naïve and treatment-experienced patients.[12]
Experienced ***(Prior PEG-IFN/RBV only)*** GT1a or 1b	Non-cirrhotic	** ombitasvir/ paritaprevir/ritonavir + dasabuvir **GT1a: add ribavirin** **GT1b: ribavirin not required**	12 weeks	A-I	GT1a: 94-100% (+ RBV)[9] GT1b: 100% (91/91, – RBV)[10] 97% (85/88, + RBV)[10]	Pooled data for GT1a from SAPPHIRE-I and -II, PEARL IV, TURQUOISE-II[9]
	Cirrhotic, CTP A	If prior relapser or partial responder: ** ombitasvir/ paritaprevir/ritonavir + dasabuvir + ribavirin	12 weeks	A-I	<u>GT1a</u> Relapser: 93% (14/15)[11] Partial Responder: 100% (11/11)[11] <u>GT1b</u> Relapser: 100% (14/14)[11] Partial Responder: 86% (6/7)[11] Null Responder: 100% (25/25)[11]	<u>GT1a with 24 weeks:</u> SVR 100% in relapsers (13/13) and partial responders (10/10)[11] Consider extending to 24 weeks for slow on-treatment virologic response. <u>GT1b with 24 weeks:</u> SVR 100% in relapsers (10/10), partial responders (3/3) and null responders (20/20)[11]

Preferred Regimens					Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	**Comments**
	Cirrhotic, CTP A	If GT1a, prior null responder: ledipasvir/sofosbuvir + ribavirin	12 weeks **NOT FDA approved**	B-II	96% (74/77)[14]	SVR 97% (75/77) with ledipasvir/sofosbuvir x 24 weeks.[14]
		*** If ribavirin-intolerant or contraindicated: ledipasvir/sofosbuvir	24 weeks	A-I	100% (22/22, – RBV)[13] 100% (22/22, + RBV)[13]	SVR 82-86% with 12 weeks[13] Population includes 46-61% who failed boceprevir- or telaprevir-based therapy.[13]
	Cirrhotic, CTP B,C	ledipasvir/sofosbuvir + ribavirin	12 weeks **NOT FDA approved**	B-II	CTP B: 87% (26/30)[12] CTP C: 86% (19/22)[12]	24 weeks CTP B: 89% (24/27)[12] CTP C: 90% (18/20) 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 ***(prior DAA-based therapy)*** GT1a or 1b	Non-cirrhotic	ledipasvir/sofosbuvir + ribavirin	12 weeks	B-II	97% (62/64)[13] 100% (19/19)[16] 100% (25/25) and 95% (20/21) in SOF + RBV with and without PEG-IFN failures, respectively[17]	The FDA label did not include recommendations for patients who failed an NS5A- or NS5B inhibitor-containing regimen. Consult an expert before re-treating. The VA offers free testing of HCV resistance-associated variants for patients who have failed a DAA regimen. Based on data in non-cirrhotics and cirrhotics (20%) who failed PI + PEG-IFN + RBV.[13] Based on data in relapsers to sofosbuvir + ribavirin ± NS5A or NS5B inhibitor.[16] Based on data in non-cirrhotics and cirrhotics (29%) who failed SOF + RBV ± PEG-IFN.[17]

Preferred Regimens					Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	**Comments**
	Cirrhotic	ledipasvir/sofosbuvir + ribavirin	12 weeks **NOT FDA approved**	B-II	97% (62/64)[13] 96% (74/77)[14] 100% (25/25) and 95% (20/21) in SOF + RBV with and without PEG-IFN failures, respectively[17]	The FDA label did not include recommendations for patients who failed an NS5A- or NS5B inhibitor-containing regimen. Consult an expert before re-treating. The VA offers free testing of HCV resistance-associated variants for patients who have failed a DAA regimen. Based on data in non-cirrhotics and cirrhotics (20%) who failed PI + PEG-IFN + RBV.[13] Based on data in cirrhotics who failed PI + PEG-IFN + RBV. SVR 97% (75/77) with ledipasvir/sofosbuvir x 24 weeks.[14] Based on data in non-cirrhotics and cirrhotics (29%) who failed SOF + RBV ± PEG-IFN.[17]

* 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, Tables 4-5.

** 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 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.

*** Contraindication and/or intolerance to ribavirin: Contraindication is defined as history of significant or unstable cardiac disease, known pregnancy, positive pregnancy test, and men whose female partner is pregnant or plan to become pregnant, known hypersensitivity reaction, autoimmune hepatitis, hemoglobinopathies) and/or intolerance (i.e., baseline hemoglobin <12g/dL) and/or history of significant adverse events with previous ribavirin-containing regimen.

Abbreviations: CTP = Child-Turcotte-Pugh; DAA = direct acting antiviral; PEG-IFN = peginterferon; RBV = ribavirin; [7]ION-3; [10]PEARL-III; [11]TURQUOISE-II; [12]SOLAR; [13]ION-2; [14]SIRIUS; [16]ELECTRON-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.

For definitions of treatment response, 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-definitions-of-response.asp).[1]

Table 4b. 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 GT1a or 1b	Non-cirrhotic	ledipasvir/sofosbuvir	12 weeks if baseline HCV RNA ≥6 million IU/mL	A-I	96% (82/85, – RBV)[7] 99% (179/180, – RBV)[8] 97% (178/184, + RBV)[8]	
	Cirrhotic, CTP A	ledipasvir/sofosbuvir (may consider adding ribavirin)	12 weeks	A-I	94% (32/34, – RBV)[8] 100% (33/33, + RBV)[8]	
Experienced ***(prior PEG-IFN/RBV only)*** GT1a or 1b	Non-cirrhotic	ledipasvir/sofosbuvir (may consider adding ribavirin)	12 weeks	A-I	95% (83/87, – RBV)[13] 100% (89/89, + RBV)[13]	Population includes 46-61% who failed boceprevir- or telaprevir-based therapy.[13]
	Cirrhotic, CTP A	If prior relapser or partial responder: ledipasvir/sofosbuvir + ribavirin	12 weeks **NOT FDA approved**	B-II	96% (74/77)[14]	SVR 97% (75/77) with ledipasvir/sofosbuvir x 24 weeks.[14]
		If GT1a, prior null responder: **ombitasvir/ paritaprevir/ritonavir + dasabuvir + ribavirin	24 weeks	A-I	93% (39/42)[11]	SVR 80% (40/50) with 12 weeks[11]

* 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, Tables 4-5.

** 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; [7]ION-3; [8]ION-1; [11]TURQUOISE-II; [13]ION-2; [14]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, simeprevir or sofosbuvir should not be used in reduced dosages or restarted if discontinued. Simeprevir or sofosbuvir should not be used as monotherapy.

For definitions of treatment response, 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-definitions-of-response.asp).[1]

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 (3D, [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, Tables 1-3 for a summary of clinical trials.** For definitions of treatment response, 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-definitions-of-response.asp).[1]

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 the few 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 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 failed treatment with a DAA-containing regimen are likely to have hepatitis C 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 have HCV viruses that are resistant to the current generation of NS3/4A protease inhibitors (e.g., paritaprevir); thus, re-treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir should be avoided. Re-treatment with LDV/SOF + RBV should be considered since this regimen does not include an NS3/4A protease inhibitor.

Patients who failed treatment with an NS5A inhibitor (e.g., ombitasvir) are likely to have RAVs against NS5A-acting drugs (e.g., ledipasvir, daclatasvir); thus, resistance testing should be performed before re-treatment. The presence of an RAV against an NS3/4A or an NS5A inhibitor reduces the effectiveness of other drugs in this class. However, the presence of RAVs to one HCV target in a multi-DAA regimen does not preclude achievement of an SVR, particularly if the re-treatment regimen contains sofosbuvir + ribavirin + another DAA (or peginterferon).

RAVs do not appear to develop or, if they develop, they do not persist, against sofosbuvir (SOF) or peginterferon (PEG-IFN) or ribavirin (RBV). Nevertheless, it is recommended that patients who failed a SOF- or PEG-IFN-based regimen be re-treated with SOF + a DAA that targets an HCV protein that was not included in the prior regimen (e.g., include a drug that targets NS5A if the initial treatment did not include an NS5A inhibitor).

The VHA Office of Public Health Reference Laboratory (PHRL) offers free testing for hepatitis C 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 Public Health Reference Laboratory by email at V21PHRL@va.gov.

Patients who failed treatment with peginterferon (PEG-IFN) + ribavirin (RBV) + a protease inhibitor: LDV/SOF is FDA approved for 12 weeks in patients without cirrhosis and 24 weeks in patients with cirrhosis for those who failed PEG-IFN + RBV + a protease inhibitor. However, recent data support use of LDV/SOF + RBV for 12 weeks in this population.[14] 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-based 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.[14] Thus, LDV/SOF + RBV for 12 weeks can be considered for non-cirrhotic or cirrhotic patients who failed PEG-IFN + RBV + a protease inhibitor.

Patients who failed NS3/4A-based treatments (i.e., boceprevir, paritaprevir, simeprevir, telaprevir): Because of the likely presence of RAVs against NS3/4A, patients who fail treatment with a regimen that contains a protease inhibitor should not be re-treated with a protease inhibitor. Thus, patients who fail SOF + SMV or a paritaprevir-containing regimen should not be re-treated with a regimen that contains either SMV or paritaprevir. LDV/SOF + RBV for 12 weeks can be considered for patients who need re-treatment urgently, although there are no data available regarding the effectiveness of this regimen.

Patients who failed a regimen that contained sofosbuvir: Among patients who have failed SOF-based therapy, re-treatment with LDV/SOF ± RBV for 12 weeks achieved SVR rates 98-100%.[16,17,19] In a Phase II, open-label study of patients without cirrhosis who virologically relapsed following a 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.[16] 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.[17] In another trial, re-treatment with LDV/SOF for 12 weeks achieved SVR in 100% (14/14) of patients who initially failed SOF + RBV.[19] 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 failed a regimen containing an NS5A inhibitor (e.g., daclatasvir, ledipasvir, ombitasvir): The optimal treatment for patients who failed a treatment that contained an NS5A inhibitor is not known. However, one patient who failed treatment with LDF/SOF for 12 weeks (in a clinical trial) and who had RAVs to SOF and to LDV achieved an SVR when treated for 24 weeks with LDV/SOF + RBV. RAVs to NS5A are present in approximately 15% of patients prior to starting treatment, and the presence of NS5A RAVs minimally decreases the effectiveness of LDV/SOF in achieving an SVR. It is recommended that patients who failed treatment with an NS5A inhibitor be tested for presence of RAVs to NS5A (see above for information on how to test for RAVs) prior to considering re-treatment. For patients who must be re-treated urgently, LDV/SOF + RBV for 12-24 weeks can be considered.

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.[8] Four treatment arms were compared: LDV/SOF for 12 and 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, subgenotype (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.[7] In this non-blinded 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 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).[13] Across the four groups, 41-46% of patients were non-responders and 54-59% were either 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 was 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, IL28B status, 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 in those receiving 12 weeks of treatment was 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 was 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.

Other studies suggest that LDV/SOF + RBV for 12 weeks can achieve a high SVR rate in treatment-experienced patients with cirrhosis. The SIRIUS study 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.[14] Median age was 56 years, 94% of patients had non-IL28B 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 minimal. Hemoglobin decreased to <10 g/dL in 1 patient in each treatment arm. There were no deaths. This prospective study in a relatively large cohort with

compensated cirrhosis suggests that 12 weeks of LDV/SOF + RBV is safe and effective in the treatment of compensated cirrhosis.

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 appears 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).[16]

LDV/SOF + RBV (starting at 600mg/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 was 87% (26/30) and 89% (24/27) with LDV/SOF + RBV for 12 weeks and 24 weeks, respectively. In patients with CTP C, SVR was 86% (19/22) and 90% (18/20) 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 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 (3D) 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 (3D) ± RBV for 12 weeks. In patients with GT1b, SVR was achieved in ≥99% of those receiving 3D with RBV (209/210) or without RBV (207/209).[10] The addition of RBV provided no additional benefit in GT1b patients. In GT1a patients who received 3D + 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 3D 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 3D 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 3D + 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 3D + RBV for 12 weeks.[20] 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 3D ± RBV in HCV GT1b treatment-experienced non-cirrhotic patients.[18] The trial was open-label and had two arms that were treated for 12 weeks: 3D + RBV (n = 91) and 3D without RBV (n = 95). All patients were previously treated with PEG-IFN + RBV; there were no patients with prior use of DAA therapy. All patients were without 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 3D + RBV and without RBV, respectively. Patients with prior relapse, partial response, and null response achieved SVR 100% in the 3D without RBV and 93-100% in the 3D + RBV arms. Both regimens were noninferior and superior to the historical SVR rate for telaprevir + PEG-IFN + RBV. Adverse effects of 3D 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 3D ± 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 3D + RBV for 12 weeks in treatment-experienced non-cirrhotic patients.[21] 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 3D + 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 3D + 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; there were no patients with prior use of DAA therapy. The majority of patients had a prior null response (49%) and the remainder were 29% relapse and 22% partial response. All patients were without cirrhosis; 14-15% had METAVIR F3; the remainder were 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 noninferior and 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 from this

12-week regimen of 3D + RBV, in treatment-experienced patients with GT1a and 1b, including prior null responders.

Genotype 1-Infected Patients with Cirrhosis, Compensated

The combination of 3D + RBV for 12 or 24 weeks was evaluated in a prospective, randomized study of 380 patients with compensated (CTP A) cirrhosis.[11] 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 rate was 92% (191/208) with 12 weeks of 3D + RBV and 96% (165/172) with 24 weeks (p = 0.089). Among GT1a, SVR with 12 and 24 weeks of treatment was 89% (124/140) and 94% (114/121), respectively. Among GT1b, SVR was 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 3D + 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 rate was 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 3D + 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 3D + RBV. However, these data suggest that 12 weeks of 3D + 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.[11]

<u>Sofosbuvir (SOF) + Simeprevir (SMV) ± Ribavirin (RBV)</u>

In an open-label, Phase IIa trial (COSMOS), the combination of SOF + SMV ± RBV was evaluated in 167 GT1-infected patients.[15] In treatment-naïve patients with cirrhosis, SVR rates were 100% (6/6) and 67% (2/3) with 12 weeks of SOF + SMV ± RBV, respectively; with 24 weeks of treatment, SVR was achieved in 100% (9/9) with SOF + SMV ± RBV. In 41 null responders with METAVIR F0-F2, SVR rates were 96% and 93% with 12 weeks of SOF + SMV ± RBV, respectively. In null responders with METAVIR F3, SVR was achieved in 100% (13/13) with 12 weeks of SOF + SMV ± RBV; SVR was achieved in 86% (6/7) and 100% (4/4) with 24 weeks of SOF + SMV ± RBV, respectively. In null responders with METAVIR F4, SVR was achieved in 80% (4/5) and 100% (4/4) with 12 weeks of SOF + SMV ± RBV, respectively; SVR was achieved

in 90% (9/10) and 100% (4/4) with 24 weeks of SOF + SMV ± RBV, respectively. In patients with a baseline Q80K mutation, SVR was 88% (51/58) regardless of treatment duration. All relapses occurred in patients with GT1a infection; relapse occurred in 3 null responders with METAVIR F0-F2 and the Q80K polymorphism, and in 3 patients with METAVIR F3-F4. The incidence of Grade 3 or 4 adverse events in the 24-week regimens were 17% and 13% with and without RBV, respectively, and 4% and 7% in the 12-week regimens with and without RBV, respectively. Serious adverse events occurred in 6% and 3% of patients receiving 24-week regimens with and without RBV, respectively, compared with 0% in patients receiving 12-week regimens.

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.

Preferred regimens (see Table 5 for details)

Treatment-naïve patients without cirrhosis

- *Sofosbuvir (400 mg/day) in combination with ribavirin (1,000 mg/day if <75kg 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 <75kg 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 <75kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks or 16 weeks if non-cirrhotic, and 16 weeks if cirrhotic.* ***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 <75kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks.* ***NOT FDA APPROVED.***

Table 5. 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)[22] 92% (85/92)[23] 97% (29/30)[23, 24]	
	Cirrhotic	sofosbuvir + ribavirin	16 weeks	B-III	12 weeks: 83% (10/12)[22] 94% (16/17)[23] 100% (2/2)[24]	**FDA approved for 12 weeks**

Preferred Regimens					Supporting Information	Comments
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR (N/N)**	
Experienced GT2	Non-cirrhotic	sofosbuvir + ribavirin	12 weeks	A-II	91% (30/33)[24] Relapsers: 86% (25/29)[23] Nonresponders: 70% (7/10)[23]	
			16 weeks	B-II	Relapsers: 89% (24/27)[23] Nonresponders: 88% (7/8)[23]	**FDA approved for 12 weeks**
		sofosbuvir + peginterferon + ribavirin **NOT FDA approved**	12 weeks	B-II	100% (9/9)[25]	If interferon eligible
	Cirrhotic	sofosbuvir + ribavirin	16 weeks	B-II	78% (7/9)[23]	**FDA approved for 12 weeks** 12 weeks: SVR 60% (6/10)[23] SVR 88% (7/8)[24]
		sofosbuvir + peginterferon + ribavirin **NOT FDA approved**	12 weeks	B-II	93% (13/14)[25]	If interferon eligible

* Refer to Section XII "Groups with Special Considerations for Therapy" on HCV treatment in patients with HIV/HCV coinfection; [22]FISSION, [23]POSITRON, [23]FUSION, [24]VALENCE, [25]LONESTAR-2; 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.

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.[22-24] 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.[24] In the FUSION study, a statistically insignificant increase in SVR rates was seen 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).[23] Based on results from this small study, SOF + RBV for 16 weeks may be considered as an option in treatment-experienced patients; however, this 16-week regimen is not FDA approved.

In interferon eligible, treatment-experienced patients, SOF plus peginterferon/ribavirin 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.[25] This regimen is not FDA approved.

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.

Preferred regimens (see Table 6 for details)

Treatment-naïve patients without cirrhosis

- *Ledipasvir/sofosbuvir (90/400 mg/day) plus ribavirin (1,000 mg/day if <75kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks.* ***NOT FDA APPROVED.***
- *Sofosbuvir (400 mg/day) plus ribavirin (1,000 mg/day if <75 kg or 1,200 mg if ≥75 kg with food, in divided doses) for 24 weeks.*

Treatment-naïve patients with cirrhosis

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

Treatment-experienced patient without cirrhosis

- *Ledipasvir/sofosbuvir (90/400 mg/day) plus ribavirin (1,000 mg/day if <75kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks.* ***NOT FDA APPROVED.***
- *Sofosbuvir (400 mg/day) plus ribavirin (1,000 mg/day if <75 kg or 1,200 mg if ≥75 kg with food, in divided doses) for 24 weeks.*

Treatment-experienced patient 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 <75kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks.* ***NOT FDA APPROVED.***

Table 6. 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% (26/26)[16] (includes cirrhotics)	Cirrhosis present in 16% SVR rate lower without ribavirin: 64% (16/25)[16]
		sofosbuvir + ribavirin	24 weeks	A-I	94% (86/92)[24]	
	Cirrhotic	ledipasvir/sofosbuvir + ribavirin **NOT FDA approved**	12 weeks	A-II	100% (26/26)[26] (includes non-cirrhotics)	Cirrhosis present in 16% SVR was lower without ribavirin: 64% (16/25)[16]
Experienced GT3	Non-cirrhotic	ledipasvir/sofosbuvir + ribavirin **NOT FDA approved**	12 weeks	A-II	89% (25/28)[26]	
		sofosbuvir + ribavirin	24 weeks	A-I	87% (87/100)[24]	
	Cirrhotic	sofosbuvir + peginterferon + ribavirin **NOT FDA approved**	12 weeks	A-II	83% (10/12)[25]	If interferon eligible

* Refer to Section XII "Groups with Special Considerations for Therapy" on HCV treatment in patients with HIV/HCV coinfection; [16]ELECTRON-2, [24]VALENCE, [25]LONESTAR-2; PEG-IFN = 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 7. 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	92% (23/25)[27]; represents combined GT2 and GT3 data	If interferon eligible
	Cirrhotic	sofosbuvir + peginterferon + ribavirin **NOT FDA approved**	12 weeks	A-III	Data not available	If interferon eligible
		sofosbuvir + ribavirin	24 weeks	A-I	92% (12/13)[27]	
Experienced GT3	Non-cirrhotic	sofosbuvir + peginterferon + ribavirin **NOT FDA approved**	12 weeks	A-II	83% (10/12)[25]	If interferon eligible
	*Cirrhotic	ledipasvir/sofosbuvir + ribavirin **NOT FDA approved**	12 weeks	B-II	73% (16/22) with 12 weeks[26]	Given concerns about development of RAVs, consult a practitioner with expertise to weigh the risks versus benefits of treatment. May consider extending treatment to 24 weeks; no data available.
		sofosbuvir + ribavirin	24 weeks	A-I	60% (27/45)[24]	

* Refer to text below regarding treatment issues.
[24]VALENCE, [25]LONESTAR-2, [26]Gane et al., [27]PROTON; 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.

Sofosbuvir for Genotype 3 (GT3)

The FDA-approved regimen for chronic HCV GT3 is supported by the results of a Phase III randomized study (VALENCE) that evaluated treatment with SOF and RBV for 24 weeks in GT3 patients (n = 250).[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] In other studies, shorter treatment duration (12-16 weeks) with SOF and RBV resulted in lower SVR rates (21-68%).[22, 23, 28]

In vitro (i.e., HCV replicon studies) ledipasvir has minimal efficacy against HCV GT3. Despite the minimal efficacy *in vitro*, LDV/SOF with or without RBV for 12 weeks has been evaluated as a treatment for GT3. In an open-label study (ELECTRON-2) of 51 treatment-naïve GT3 patients, of whom 88% were White and 16% had cirrhosis, SVR rates were 100% (26/26) in patients who received LDV/SOF + RBV and 64% (16/25) in the group that did not receive RBV.[16] Grade 3/4 or serious adverse effects occurred in 3 and 4 patients receiving LDV/SOF and in no patients receiving LDV/SOF + RBV, respectively. LDV/SOF + RBV is not FDA approved for treatment of GT3.

The recommended treatment for patients who have failed prior PEG-IFN + RBV treatment is complicated, particularly in those with cirrhosis. LDV/SOF + RBV for 12 weeks was evaluated in an open-label study of 50 treatment-experienced GT3 patients, of whom 80% were White and 44% had cirrhosis.[26] SVR rates were 89% (25/28) and 73% (16/22) among patients without and with cirrhosis, respectively. An SVR rate of 89% (25/28) is sufficiently high to recommend LDV/SOF + RBV for 12 weeks in treatment-experienced GT3 patients without cirrhosis, although this regimen is not approved by the FDA for this indication. However, virologic failure following LDV/SOF + RBV in treatment-experienced patients with cirrhosis (of approximately 27%) may increase the risk of NS5A RAVs, which might preclude the use of anticipated future treatments with an NS5A inhibitor. Given concerns about development of RAVs in GT3 treatment-experienced cirrhotics, consult a practitioner with expertise to weigh the risks vs. benefits of LDV/SOF + RBV treatment for 12 weeks.

The most effective treatment for interferon-tolerant, GT3-infected cirrhotics appears to be SOF + PEG-IFN + RBV. In GT3 treatment-experienced patients (n = 24), a Phase II, open-label study (LONESTAR-2) evaluated treatment with SOF + PEG-IFN + RBV for 12 weeks; 50% of patients were cirrhotic. SVR was achieved in 83% (10/12) of patients without cirrhosis and 83% (10/12) of those with cirrhosis.[25] SOF + PEG-IFN + RBV is not FDA approved for this indication.

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.

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 <75kg 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 ± ribavirin for 12 weeks.* ***NOT FDA APPROVED.***
- *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 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 plus 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 plus 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.

In a Phase III, open-label, single-arm clinical trial of monoinfected, treatment-naïve GT4-infected patients, SVR was achieved in 96% (27/28) with SOF in combination with PEG-IFN and RBV for 12 weeks.[22]

LDV/SOF was evaluated in 21 patients with GT4 infection in the NIAID SYNERGY study.[29] 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). Other open-label studies of LDV/SOF + RBV treatment for 12-24 weeks have included small numbers of GT4-infected patients (n = 5).[12,30] This regimen is not FDA approved for the treatment of GT4 infection.

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).[31]

VIII. Identifying Treatment Candidates Based on Liver Disease Stage

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 Class 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.

Table 8. 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);

Method	Comment
	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 (www.haltctrial.org/cirrhosis.html) 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 8): 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, prone to sampling error and variability in histopathologic interpretation; and it carries a small risk of complications to the patient.

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 8). 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 facilities offer these studies.

IX. Laboratory Monitoring

Table 9. 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 needs to be obtained to determine whether SVR was achieved. HCV RNA levels at 24 weeks after the completion of treatment is optional. For further guidance on 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-supplement.asp, Supplemental Table 1).[1]

Use and Interpretation of HCV RNA Results

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. Several 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.[32] 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 Effects

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/).

Ledipasvir/sofosbuvir (LDV/SOF)[33]

The most common adverse events associated with 8, 12, or 24 weeks of LDV/SOF 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 limits of normal (<1-3%) and transient, asymptomatic lipase elevations of >3 times the upper limits of normal (<1-3%) have been observed with LDV/SOF treatment.

Ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin (3D ± RBV)[34]

The most common reported adverse events (>10%) with 3D + RBV were fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. Without RBV, the most commonly reported adverse events (≥5% of patients) with 3D were nausea, pruritus, and insomnia.

During clinical trials with 3D ± 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 3D ± 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 3D ± RBV treatment.

Hepatic laboratory testing should be performed during the first 4 weeks of starting treatment and as clinically indicated thereafter. If ALT is elevated above baseline levels, it should be repeated and monitored closely. Treatment discontinuation should be considered 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).

Sofosbuvir + simeprevir ± ribavirin (SOF + SMV ± RBV)[15]

The most common adverse events associated with SOF + SMV ± RBV for 12 weeks 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.

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 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 x ULN) to moderate (Grade 2; >1.5 to ≤2.5 x 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)[35]

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)[35]

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.

XI. Proper Use

Drug-Drug Interactions[33-36]

Refer to the Appendix, Tables 4-5 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, Tables 4-5. Practitioners are encouraged 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 with potential DDI with all VA-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 OATP1B1/3. 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.

Storage and Stability[33-36]

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).

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

Missed Doses[33-36]

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 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

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 coinfected patients 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 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 (3D) regimen is being considered, the patient also 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 3D regimen. HIV antiretroviral regimens that have been evaluated in 3D 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 3D regimen. Refer to the Appendix, Tables 4-5, 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/µL. Studies involving HIV/HCV-coinfected patients have excluded patients with a CD4 count of <200 cells/µL; HCV antiviral treatment of a Veteran with a CD4 cell count of <200 cells/µL should be initiated only with the consultation of an HIV and hepatitis C treatment specialist. In patients with a CD4 count of <200 cells/µL, HIV treatment should be initiated first; potential 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, Table 5) 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.[2]

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.[37] 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 2/3 clinical trial TURQUOISE-1 examined the safety and efficacy of 12 and 24 weeks of the fixed-drug combination of 3D + weight-based RBV (1,000 or 1,200 mg daily according to body weight <75kg and ≥75kg, respectively) in HIV/HCV-coinfected patients with HCV GT1 infection (treatment naïve and experienced including those with cirrhosis).[38] The mean CD4 count of study participants was >500 cells/µL; 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.[38]

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/µL was examined in PHOTON-1 and PHOTON-2.[28, 39] 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%).[35] 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.[40]

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[33-36]

Refer to Appendix, Table 5 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[33-36]

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*.[2]

Renal Insufficiency or Hepatic Impairment[33-36]

Table 10. Modification of Drug Use in Patients with Renal Insufficiency or Hepatic Impairment

Condition	Treatment	Comment	Grade
Renal Insufficiency	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	ledipasvir	No dosage adjustment needed.	A-I
	ombitasvir/paritaprevir/ ritonavir + dasabuvir	No dosage adjustment needed with mild hepatic impairment (CTP Class A). Should not be used in patients with moderate or severe hepatic impairment (CTP Class B or C; CTP score ≥7).	A-I
	peginterferon	Should not be used in patients with moderate or severe hepatic impairment (CTP Class B or C; CTP score ≥7).	A-I
	simeprevir	No dosage recommendation can be given for patients with moderate or severe hepatic impairment (CTP Class 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 Class A, B, or C).	A-I

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

Ledipasvir (LDV)[33]
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 Class 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.

Sofosbuvir (SOF)[35]

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 are not 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 Class 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.

Simeprevir (SMV)[36]
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 (biliary excretion). However, SMV does not require dosage adjustment in patients with mild hepatic impairment (CTP Class A). In HCV-negative patients, the mean steady-state AUC of SMV was 2.4-fold higher with moderate hepatic impairment (CTP Class B) and 5.2-fold higher with severe hepatic impairment (CTP Class C). The safety and efficacy of SMV have not been established in HCV-infected patients with CTP Class 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 Class B or C).

Ombitasvir/paritaprevir/ritonavir + dasabuvir[34]
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. (RUBY-1, EASL 2015)

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

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

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, Table 4).

Table 11a. 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) including HCC	GT1	ledipasvir/ sofosbuvir + ribavirin **NOT FDA APPROVED**	12 weeks	B-II	CTP B: 87% (26/30)[12] CTP C: 86% (19/22)[12]	24 weeks CTP B: 89% (24/27)[12] CTP C: 90% (18/20)[12]

Treatment Considerations					Supporting Information	
Transplant status	**HCV genotype (GT)**	**Regimen and duration**		**Evidence grade**	**SVR % (N/N)**	**Comments**
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)[41] for GT1, 2, 3, and 4. Patients had HCC with compensated liver disease (CTP score <7).[41]
Post-Liver Transplant	GT1	ledipasvir/ sofosbuvir + ribavirin **NOT FDA APPROVED**	12 weeks	B-II	F0-F3: 96% (53/55)[30] CTP A: 96% (25/26)[30] CTP B: 85% (22/26)[30] CTP C: 60% (3/5)[30]	24 weeks F0-F3: 98% (55/56)[30] CTP A: 96% (24/25)[30] CTP B: 83% (15/18)[30] CTP C: 67% (2/3)[30] 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.[30] Refer to Appendix, Table 4, 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.
Post-Liver Transplant	GT2	sofosbuvir + ribavirin (PEG-IFN may be considered) **NOT FDA APPROVED**	24 weeks	B-III	77% (31/40)[42] 60% (19/32)[43] 50% (6/12)[43] with PEG-IFN	SVR rates included GT1, 3 and 4 patients. Refer to Appendix, Table 4, 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**				

Treatment Considerations				Supporting Information	
Transplant status	**HCV genotype (GT)**	**Regimen and duration**	**Evidence grade**	**SVR % (N/N)**	**Comments**
		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
PEG-IFN = Peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly; RBV = 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. Sofosbuvir should not be used as monotherapy or in reduced dosages; it should not be restarted if discontinued.

Table 11b. 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)[45] 89% (+RBV)[45] F0-2: 97%[45] F3-4: 64%[45]	**AVOID USE in patients receiving cyclosporine**; refer to Appendix, Table 4, for drug-drug interactions. Can be considered for patients who cannot tolerate ribavirin.
		ombitasvir/ paritaprevir/ ritonavir + dasabuvir + ribavirin	12 weeks	B-II	F0-2: 97% (33/34) [44]	Dosage of tacrolimus or cyclosporine needs to be reduced because of drug-drug interactions. Refer to Appendix, Table 4, for drug-drug interactions.

Treatment in Pre-Liver Transplant

Preferred regimens (See Table 11a)
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 including patients with CTP A; in CPT B and C patients, ribavirin 600 mg/day 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***

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 4-7).

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.

The longer the duration of pre-transplant viral negativity (i.e., >30 days), the less likely virologic recurrence will occur 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. 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.

Treatment in Post-Liver or -Other Solid Organ Transplant

Preferred regimens (See Table 11)

Post-Liver Transplant

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, Table 4.

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.[30] 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 class 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 sofosbuvir and ribavirin 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.[42] 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 rate was 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.[42] 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 (3D + RBV) in the Post-Liver Transplant Setting

CORAL-1 was a Phase II, open-label study of 3D + RBV for 12 weeks in 34 patients with recurrent HCV GT1 after liver transplantation.[44] 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 3D 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, 3D 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.[45] 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, Table 4), SMV use is contraindicated for use in patients receiving cyclosporine.

Treatment of Solid Organ Transplants Other Than Liver

SOF has not been studied in the setting of solid organ transplant 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 12. 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[36]

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

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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XV. Appendix

Table 1. 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[8]			
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[7]			
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[16]			
LDV/SOF x 12 weeks	Naïve	Not studied	13/20 (65) (all were CTP Class B)
ERADICATE[46]			
LDV/SOF x 12 weeks	Naïve, HCV/HIV coinfected	10/10 (100, ARV untreated) SVR_4: 22/22 (100, ARV treated)	Not studied
COSMOS[15]			
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 2. 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[13]			
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[47]			
LDV/SOF x 12 weeks	Experienced (SOF + RBV relapsers)	7/7 (100)	7/7 (100)
ELECTRON-2[16]			
LDV/SOF + RBV x 12 weeks	Experienced (SOF + RBV ± DAA)	19/19 (100)	Not studied
COSMOS[15]			
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 3. Summary of SVR Results from Phase III Studies of Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir (3D)-Based Therapy in Genotype 1-Infected Patients

Trial	Treatment Category	Cirrhotic	SVR, %
SAPPHIRE-I,[20] n = 631			
3D + RBV x 12 weeks	GT1, Naïve	No	96% (455/473)
SAPPHIRE-II,[21] n = 394			
3D + RBV x 12 weeks	GT1, Experienced	No	96% (285/297) (95% in prior null responders)
PEARL-II,[18] n = 186			
3D ± RBV x 12 weeks	GT1b, Experienced	No	100% (91/91, –RBV) 97% (85/88, +RBV)
PEARL-III,[10] n = 419			
3D ± RBV x 12 weeks	GT1b, Naïve	No	99% (207/209, –RBV) >99% (209/210, +RBV)
PEARL-IV,[10] n = 305			
3D ± RBV x 12 weeks	GT1a, Naïve	No	90% (185/205, –RBV) 97% (97/100, +RBV)
TURQUOISE-II,[11] n = 380			
3D + 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)
3D + 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)

Table 4. Drug-Drug Interactions with HCV Antiviral Agents[32-36,48,49]

	HCV Direct-Acting Antiviral Agents			
	NS5A/NS5B Inhibitor	**NS5B Inhibitor**	**NS5A/ Protease Inhibitor/NS5B Inhibitor**	**Protease Inhibitor**
Selected Drugs	**Ledipasvir (LDV)/ sofosbuvir (SOF)**	**Sofosbuvir (SOF)**	**Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)**	**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 closely (may ↑ digoxin concentration)	?	✓	use caution and monitor closely (may ↑ concentration of antiarrhythmic)
amiodarone	✘ (↑ amiodarone concentration--may increase risk bradycardia and cardiac arrest)	✘ (if given with another HCV direct acting antiviral agent; ↑ amiodarone concentration--may increase risk bradycardia and cardiac arrest)	use caution and monitor closely (may ↑ amiodarone concentration)	use caution and monitor closely (may ↑ amiodarone concentration) ✘ (if given with SOF)
bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	?	?	use caution and monitor closely (may ↑ antiarrhythmic concentration)	use caution and monitor closely (may ↑ antiarrhythmic concentration)
Anticonvulsants				

Selected Drugs	HCV Direct-Acting Antiviral Agents			
	NS5A/NS5B Inhibitor	**NS5B Inhibitor**	**NS5A/ Protease Inhibitor/NS5B Inhibitor**	**Protease Inhibitor**
	Ledipasvir (LDV)/ sofosbuvir (SOF)	**Sofosbuvir (SOF)**	**Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)**	**Simeprevir (SMV)**
carbamazepine, phenytoin, phenobarbital, oxcarbazepine	✘ (may ↓ LDV/SOF concentration)	✘ (may ↓ SOF concentration)	✘ (may ↓ OBV/PTV/r + DSV concentrations)	✘ (may ↓ SMV concentration)
Antifungals				
fluconazole, itraconazole, posaconazole	?	?	?	✘ (may ↑ SMV concentration)
ketoconazole	?	?	use caution and monitor closely (↑ ketoconazole concentration, dose ≤200 mg per day)	✘ (may ↑ SMV concentration)
voriconazole	?	?	✘ (↓voriconazole concentration)	✘ (may ↑ SMV concentration)
Antihyperlipidemic				
gemfibrozil	?	?	✘ (↑ DSV concentration--may increase risk of QT prolongation)	?
Antiinfectives				
clarithromycin, erythromycin, telithromycin	?	?	?	✘ (may ↑ SMV concentration)
Antimycobacterials				
rifabutin, rifampin, rifapentine	✘ (may ↓ LDV/SOF concentration)	✘ (may ↓ SOF concentration)	✘ (rifampin may ↓ OBV/PTV/r +DSV concentrations)	✘ (may ↓ SMV concentration)
Calcium Channel Blockers (CCB)				
amlodipine	?	?	monitor blood pressure closely (may ↑ amlodipine concentration, consider amlodipine dose reduction)	use caution and monitor closely (may ↑ CCB concentration)
diltiazem, felodipine, nicardipine, nifedipine	?	?	?	use caution and monitor closely (may ↑ CCB

	HCV Direct-Acting Antiviral Agents			
Selected Drugs	**NS5A/NS5B Inhibitor**	**NS5B Inhibitor**	**NS5A/ Protease Inhibitor/NS5B Inhibitor**	**Protease Inhibitor**
	Ledipasvir (LDV)/ sofosbuvir (SOF)	**Sofosbuvir (SOF)**	**Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)**	**Simeprevir (SMV)**
				concentration)
verapamil	✓	?	?	use caution and monitor closely (may ↑ CCB concentration)
Corticosteroids				
dexamethasone *(systemic)*	?	?	?	✘ (may ↓ SMV concentration)
budesonide, methylprednisone, prednisone	?	?	?	✓
fluticasone	?	?	monitor closely (may ↑ fluticasone concentration; may ↓ serum cortisol concentrations. Alternative corticosteroids should be considered, particularly for long term use	✓
Diuretics				
furosemide	?	?	use caution and monitor closely – adjust dose based on response (may ↑ furosemide concentration)	?
Ergot derivatives				
ergotamine, dihydroergotamine, ergonovine, methylergonovine	?	?	✘ (acute ergot toxicity)	?
H_2-Receptor Antagonists	do not exceed equivalent of famotidine 40 mg twice daily; administer simultaneously or 12 hours apart	do not exceed equivalent of famotidine 40 mg twice daily	?	✓
HCV drug				

	HCV Direct-Acting Antiviral Agents			
Selected Drugs	**NS5A/NS5B Inhibitor**	**NS5B Inhibitor**	**NS5A/ Protease Inhibitor/NS5B Inhibitor**	**Protease Inhibitor**
	Ledipasvir (LDV)/ sofosbuvir (SOF)	**Sofosbuvir (SOF)**	**Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)**	**Simeprevir (SMV)**
simeprevir	✗ (↑ LDV/SOF concentration)	✓	?	
Herbal supplements				
St. John's wort (Hypericum perforatum)	✗ (may ↓ LDV/SOF concentration)	✗	✗ (may ↓ OBV/PTV/r +DSV concentrations)	✗ (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 5: Drug-Drug Interactions with HIV Antiretrovirals**			
HMG CO-A Reductase Inhibitors				
rosuvastatin	✗ (may ↑ rosuvastatin concentration; potential for myopathy and rhabdomyolysis)	?	✓ dose ≤10 mg daily (↑ rosuvastatin concentration)	✓ initiate at 5 mg once daily; dose ≤10 mg daily
atorvastatin	?	?	?	✓ dose ≤40 mg once daily
simvastatin, lovastatin	?	?	✗ (potential for myopathy and rhabdomyolysis)	✓ use lowest necessary dosage, titrate carefully; monitor closely for potential ↑ statin concentration
pitavastatin	?	?	?	✓ use lowest necessary dosage, titrate carefully; monitor closely for potential ↑ statin

	HCV Direct-Acting Antiviral Agents			
Selected Drugs	**NS5A/NS5B Inhibitor**	**NS5B Inhibitor**	**NS5A/ Protease Inhibitor/NS5B Inhibitor**	**Protease Inhibitor**
	Ledipasvir (LDV)/ sofosbuvir (SOF)	**Sofosbuvir (SOF)**	**Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)**	**Simeprevir (SMV)**
				concentration
pravastatin	✓	?	✓ dose ≤40 mg once daily (↑ pravastatin concentration)	✓ use lowest necessary dosage, titrate carefully; monitor closely for potential ↑ statin concentration
fluvastatin	?	?	?	✓
Immunosuppressants				
cyclosporine (CSA)	✓	✓	✓ (↑ CSA concentrations, reduce CSA dosage to 1/5th current dosage; measure CSA levels to determine dosage modifications; frequent assessment of renal function and CSA-related side effects is recommended)	✗ (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 closely (potential ↑ SMV and/or ↓ tacrolimus concentrations)
sirolimus	?	?	?	use caution and monitor closely (potential ↑ SMV and/or ↓/↑ sirolimus concentrations)
Narcotic analgesic				
buprenorphine, naloxone	?	?	✓ (↑ buprenorphine or naloxone concentrations, monitor for sedation and cognitive effects)	?
methadone	✓	✓	✓	✓
Neuroleptic				

	HCV Direct-Acting Antiviral Agents			
	NS5A/NS5B Inhibitor	**NS5B Inhibitor**	**NS5A/ Protease Inhibitor/NS5B Inhibitor**	**Protease Inhibitor**
Selected Drugs	**Ledipasvir (LDV)/ sofosbuvir (SOF)**	**Sofosbuvir (SOF)**	**Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)**	**Simeprevir (SMV)**
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 closely (may ↑ concentration of PDE-5 inhibitor)
sildenafil	?	?	✘ (potential for sildenafil-associated AEs in doses taken for pulmonary artery hypertension)	use caution and monitor closely (may ↑ concentration of PDE-5 inhibitor)
Proton Pump Inhibitors (PPI)				
omeprazole	✓ dose ≤20 mg once daily; administer simultaneously under fasted conditions	?	✓ ↓ omeprazole concentrations, monitor for decreased omeprazole efficacy; avoid dose >40 mg per day	✓
Other PPI	✓ PPI doses comparable to omeprazole ≤20 mg once daily can be	?	?	✓

	HCV Direct-Acting Antiviral Agents			
Selected Drugs	**NS5A/NS5B Inhibitor**	**NS5B Inhibitor**	**NS5A/ Protease Inhibitor/NS5B Inhibitor**	**Protease Inhibitor**
	Ledipasvir (LDV)/ sofosbuvir (SOF)	**Sofosbuvir (SOF)**	**Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/r) + dasabuvir (DSV)**	**Simeprevir (SMV)**
	administered simultaneously, fasting			
Propulsive				
cisapride	?	?	?	✘
Sedatives/Anxiolytics				
oral midazolam, triazolam	?	?	✘ (may ↑ concentration of sedative)	use caution and monitor closely (may ↑ concentration of sedative)
alprazolam	?	?	✓ monitor closely (↑ alprazolam concentration)	
zolpidem	?	?	✓	?
Stimulant				
methylphenidate	?	?	?	✓
SSRI/SNRI				
escitalopram	?	?	✓	✓
duloxetine	?	?	✓	?

✓ = drug that can be used concomitantly

✘ = drug not recommended

? = data limited or not available on pharmacokinetic interactions

Table 5. Drug-Drug Interactions with HIV Antiretrovirals[32-36,48,49]
(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)[2]

	HCV Direct-Acting Antiviral Agents			
	Co-Formulated NS5A/NS5B Inhibitors	**NS5B Inhibitor**	**Co-Formulated NS5A/Protease Inhibitor + NS5B Inhibitor**	**Protease Inhibitor**
Selected HIV drugs	**Ledipasvir (LDV)/SOF**	**Sofosbuvir (SOF)**	**Ombitasvir/paritaprevir/ritonavir + dasabuvir**	**Simeprevir (SMV)**
Nucleoside Reverse Transcriptase Inhibitors				
FTC	✓	✓	✓	✓
3TC	✓	✓	✓	✓
ABC	✓	✓	✓	✓
TDF	✓ Monitor for TDF toxicity	✓	✓	✓
ZDV [a]	✓	✓	✓	✓
HIV Protease Inhibitors				
ATV (unboosted)	✓ 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])	✓	✓ reduce ATV dose to 300 mg in the morning at the same time as ombitasvir/paritaprevir/r + dasabuvir; if RTV cannot be used, choose an alternative HCV regimen	✗
ATV/r or ATV/c		✓	✓ take ATV 300 mg in the morning at same time as ombitasvir/paritaprevir/r + dasabuvir; discontinue RTV or COBI in HIV regimen until HCV therapy completed	✗
DRV/r or DRV/c		✓	✗ (↓ DRV trough concentrations)	✗
FPV or FPV/r		✓	✗	✗
LPV/r		✓	✗ (may ↑ paritaprevir concentrations)	✗
SQV/r		✓	✗	✗
TPV/r	✗	✗	✗	✗

	HCV Direct-Acting Antiviral Agents			
	Co-Formulated NS5A/NS5B Inhibitors	**NS5B Inhibitor**	**Co-Formulated NS5A/Protease Inhibitor + NS5B Inhibitor**	**Protease Inhibitor**
Nonnucleoside Reverse Transcriptase Inhibitors				
EFV	✓ If EFV used with TDF/FTC, monitor for TDF toxicity due to ↑TDF concentrations	✓	✗ (poorly tolerated and liver enzyme elevations)	✗
RPV	✓	✓	✗ (may ↑ RPV concentrations; potential QT prolongation)	✓
ETR	✓	✓	✗	✗
NVP	✓	✓	✗	✗
Integrase Strand Transfer Inhibitors				
DTG	✓	✓	?	✓
EVG/c/ TDF/ FTC	✗	✓	✗	✗
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; 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.[32-36]

Ledipasvir/Sofosbuvir product prescribing information: [33] http://hcp.harvoni.com/interactive-pi#top
Ombitasvir/paritaprevir/ritonavir+ dasabuvir product prescribing information:[34]
www.abbvie.com/content/dam/abbviecorp/us/desktop/contentrooms/downloads/ProductFactsheet_ViekiraPak_US.pdf
Sofosbuvir product prescribing information:[35] www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf
Simeprevir product prescribing information:[36] www.olysio.com/shared/product/olysio/prescribing-information.pdf