

## **Chronic Hepatitis C Virus (HCV) Infection:**

***Interim* 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: December 22, 2014; last reviewed: December 22, 2014)

This interim revision (December 22, 2014) incorporates an update on the treatment of chronic HCV genotype 1, including the removal of peginterferon-based regimens, the recommendation for ledipasvir/sofosbuvir ± ribavirin or sofosbuvir plus simeprevir for 12-24 weeks, and regimens based on severity of cirrhosis (i.e., by Child-Turcotte-Pugh Score). Additional revisions include updates on the off-label use of ledipasvir/sofosbuvir for the treatment of chronic HCV genotypes 2, 3, 4, and in the pre- and post-liver transplant setting. The Panel recommends that HIV/HCV-coinfected patients receive the same HCV antiviral regimen as HCV-monoinfected patients. An Appendix was added, which includes new tables that summarize SVR rates for sofosbuvir-based regimens (Appendix, Tables 1 and 2) and drug interaction tables to provide clinicians with guidance on the concomitant use of HCV drugs and other drugs including HIV antiretroviral agents (Appendix, Tables 3 and 4).

## 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](http://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**

HCV Genotype	Treatment History	Cirrhosis Status	Preferred Regimen	Alternative Regimen
1	Naïve	Non-cirrhotic	Ledipasvir/Sofosbuvir x 12 weeks OR Ledipasvir/Sofosbuvir x 8 weeks if baseline HCV RNA <6million IU/mL	
			Sofosbuvir + Simeprevir x 12 weeks	
		Cirrhotic, CTP A	Ledipasvir/Sofosbuvir with or without Ribavirin x 12 weeks	
			Sofosbuvir + Simeprevir x 12 weeks (NOT FDA approved) or 24 weeks	
	Cirrhotic, CTP B and C	Ledipasvir/Sofosbuvir + Ribavirin x 12 weeks; NOT FDA approved		
	Experienced	Non-cirrhotic	Ledipasvir/Sofosbuvir x 12 weeks	
			Sofosbuvir + Simeprevir x 12 weeks <i>DO NOT USE if patient virologically failed boceprevir- or telaprevir-based therapy</i>	
	Experienced	Cirrhotic, CTP A	Ledipasvir/Sofosbuvir + Ribavirin x 12 weeks; NOT FDA approved	
			Ledipasvir/Sofosbuvir x 24 weeks	
			Sofosbuvir + Simeprevir x 12 weeks (NOT FDA approved) or 24 weeks <i>DO NOT USE if patient virologically failed boceprevir- or telaprevir-based therapy</i>	
	Cirrhotic, CTP B and C	Ledipasvir/Sofosbuvir + Ribavirin x 12 weeks; NOT FDA approved		
2	Naïve	Non-cirrhotic or Cirrhotic	Sofosbuvir + Ribavirin x 12 weeks	
	Experienced	Non-cirrhotic or Cirrhotic	Sofosbuvir + Ribavirin x 12-16 weeks	
			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 + Ribavirin x 24 weeks
	Experienced	Non-cirrhotic	Sofosbuvir + Ribavirin x 24 weeks	Sofosbuvir + PEG-IFN/Ribavirin x 12 weeks; NOT FDA approved
		Cirrhotic	Sofosbuvir + PEG-IFN/Ribavirin x 12 weeks; NOT FDA approved	Ledipasvir/Sofosbuvir + Ribavirin x 12-24 weeks; NOT FDA approved Sofosbuvir + Ribavirin x 24 weeks
4	Naïve or Experienced	Non-cirrhotic or Cirrhotic	Ledipasvir/Sofosbuvir ± Ribavirin x 12 weeks; NOT FDA approved	
			Sofosbuvir + PEG-IFN/Ribavirin x 12 weeks	

Abbreviations: CTP = Child-Turcotte-Pugh; PEG-IFN = peginterferon; RBV = ribavirin

Dosages: 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; simeprevir 150 mg orally daily with food; sofosbuvir 400 mg orally daily. Note: Ledipasvir/sofosbuvir, sofosbuvir or simeprevir should not be used in reduced dosages; neither drug should be restarted if discontinued. Sofosbuvir or simeprevir should not be used as monotherapy.

### 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.

The Veterans Health Administration (VHA) expects to treat all Veterans with chronic hepatitis C virus (HCV) infection who wish to be treated and are suitable for treatment. Furthermore, the 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 hepatitis C virus (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](http://www.hcvguidelines.org)), publicly available summaries from the 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 systematic 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).<sup>1</sup> 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](http://www.hepatitis.va.gov).

Table 1. Grading System

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	II: One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	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](http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf). Page A-3, Table 2. Accessed March 25, 2014.<sup>1</sup>

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<sub>12</sub> and SVR<sub>24</sub>, 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.<sup>2-4</sup> This document uses the term “SVR” without specification of SVR<sub>12</sub> or SVR<sub>24</sub> 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.<sup>5</sup> 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 the 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 the 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, co-morbidities, 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 in the electronic medical record system (i.e., computerized Patient Record System [CPRS]).

**Principles for patient selection for HCV 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. Urgent antiviral treatment should be considered in patients with advanced cirrhosis, selected patients with HCC awaiting liver transplant, post-transplant recipients, and patients with serious extra-hepatic manifestations of HCV. Patients with mild liver disease (METAVIR F0-2) have less urgency for treatment in the short-term, but should be informed of new treatments and their potential to cure HCV. Patients with mild liver disease can be offered antiviral treatment in a clinically appropriate time period.

**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 for the patient.	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,”	A-1

	for guidance on diagnosis of cirrhosis.	
Decompensated cirrhosis, defined by one of the following: CTP score $\geq 7$ , 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, consult a specialist with 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 co-infection	Treatment is recommended for appropriate patients with HIV/HCV co-infection. Consult a specialist with experience in treating HIV prior to starting HCV treatment as some DAA agents interact with HIV antiviral regimens.	A-I

CTP = Child-Turcotte-Pugh

**Patient identification:** A population health-based approach for selection of patients for treatment should be considered. The HCV Clinical Case Registry (CCR) ([www.vistau.med.va.gov/VistaU/ccr/default.htm](http://www.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*
<ul style="list-style-type: none"> <li>• HCV genotype (including subtype, e.g., 1a or 1b)</li> <li>• HCV RNA (quantitative viral load) preferably within the past 6 months</li> <li>• Clinical assessment for cirrhosis (Refer to Table 8)</li> <li>• If cirrhotic, exclusion of hepatocellular carcinoma based on appropriate imaging study within the prior six months</li> </ul>

### Essential pre-treatment information\*

- Previous HCV treatment history and outcome
- HIV status and if HIV +, 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 pretreatment 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](http://www.hepatitis.va.gov/provider/guidelines/2012HCV-pretreatment-assessments.asp))<sup>6</sup>

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

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

**Table 4. Genotype 1: Preferred Regimens and SVR Rates from Supporting Data 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 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	Ledipasvir/ Sofosbuvir	8 weeks if baseline HCV RNA <6 million IU/mL	A-I	97% (119/123, -RBV) <sup>7</sup>	Relapse rates were higher with 8 weeks versus 12 weeks of treatment if baseline HCV RNA ≥6 million IU/mL: 10% (9/92) vs. 1% (1/85), respectively. <sup>7</sup>
			12 weeks if baseline HCV RNA ≥6 million IU/mL	A-I	95% (206/216, -RBV) <sup>7</sup> 99% (179/180, -RBV) <sup>8</sup> 97% (178/184, +RBV) <sup>8</sup>	
		Sofosbuvir + Simeprevir	12 weeks	A-II	Data not available	Based on data in METAVIR F3/F4 treatment-naïve patients, in which SVR 100% (19/19) was achieved. <sup>9</sup>
	Cirrhotic, CTP A	Ledipasvir/ Sofosbuvir with or without Ribavirin	12 weeks	A-I	94% (32/34, -RBV) <sup>8</sup> 100% (33/33, +RBV) <sup>8</sup>	

Preferred Regimens					Supporting Information	
Treatment history and HCV genotype (GT)	Cirrhosis status	Regimen and duration		Evidence grade	SVR% (N/N)	Comments
	Cirrhotic, CTP A	Sofosbuvir + Simeprevir	12 weeks <b>NOT FDA approved</b>	B-II	Without ribavirin: <sup>9</sup> F3: 100% (4/4) F4: 67% (2/3).  With ribavirin: <sup>9</sup> F3: 83% (5/6) F4: 100% (6/6)	With Q80K polymorphism: 91% (10/11) <sup>9</sup> (includes treatment-naïve and treatment-experienced patients).
			24 weeks	A-II	Without ribavirin: <sup>9</sup> F3: 100% (2/2) F4: 100% (6/6)  With ribavirin: <sup>9</sup> F3: 100% (10/10) F4: 100% (3/3)	With Q80K polymorphism: 100% (15/15) <sup>9</sup> (includes treatment-naïve and treatment-experienced patients)
	Cirrhotic, CTP B,C	Ledipasvir/ Sofosbuvir + Ribavirin	12 weeks <b>NOT FDA approved</b>	B-II	CTP B: 87% (26/30) <sup>10</sup> CTP C: 86% (19/22) <sup>10</sup>	24 weeks CTP B: 89% (24/27) <sup>10</sup> CTP C: 90% (18/20) <sup>10</sup>  Ribavirin initiated at 600 mg/day and increased as tolerated. <sup>10</sup>  SVR rates include treatment-naïve and treatment-experienced patients. <sup>10</sup>
Experienced GT1a or 1b	Non-cirrhotic	Ledipasvir/ Sofosbuvir	12 weeks	A-I	95% (83/87, -RBV) <sup>11</sup> 100% (89/89, +RBV) <sup>11</sup>	<b>In relapsers to sofosbuvir + ribavirin ± DAA:</b> SVR 100% (19/19) with ledipasvir/sofosbuvir + ribavirin x 12 weeks. <sup>12</sup>
		Sofosbuvir + Simeprevir	12 weeks	A-II	93% (13/14, -RBV) <sup>9</sup> 96% (26/27, +RBV) <sup>9</sup>	Null responders with Q80K polymorphism: 89% (24/27) <sup>9</sup>  <b>DO NOT USE</b> if patient virologically failed boceprevir- or telaprevir-based therapy.
	Cirrhotic, CTP A	Ledipasvir/ Sofosbuvir + Ribavirin	12 weeks <b>NOT FDA approved</b>	B-II	96% (74/77) <sup>13</sup>	SVR 97% (75/77) with ledipasvir/sofosbuvir x 24 weeks. <sup>13</sup>

Preferred Regimens				Supporting Information		
Treatment history and HCV genotype (GT)	Cirrhosis status	Regimen and duration		Evidence grade	SVR% (N/N)	Comments
Experienced GT1a or 1b	Cirrhotic, CTP A	Ledipasvir/ Sofosbuvir	24 weeks	A-I	100% (22/22, -RBV) <sup>11</sup> 100% (22/22, +RBV) <sup>11</sup>	SVR 82-86% with 12 weeks of treatment. <sup>11</sup>
		Sofosbuvir + Simeprevir	12 weeks  <b>NOT FDA approved</b>	B-II	Without ribavirin: <sup>9</sup> F3: 100% (3/3) F4: 100% (4/4)  With ribavirin: <sup>9</sup> F3: 100% (10/10) F4: 80% (4/5)	With Q80K polymorphism: 88% (23/26) <sup>9</sup> (includes treatment-naïve and treatment-experienced patients)  <b>DO NOT USE</b> if patient virologically failed boceprevir- or telaprevir-based therapy.
					24 weeks	A-II
	Cirrhotic, CTP B,C	Ledipasvir/ Sofosbuvir + Ribavirin	12 Weeks  <b>NOT FDA approved</b>	B-II	CTP B: 87% (26/30) <sup>10</sup> CTP C: 86% (19/22) <sup>10</sup>	24 weeks CTP B: 89% (24/27) <sup>10</sup> CTP C: 90% (18/20)  Ribavirin initiated at 600 mg/day and increased as tolerated. <sup>10</sup>  SVR rates include treatment-naïve and treatment-experienced patients. <sup>10</sup>

CTP = Child-Turcotte-Pugh, RBV = ribavirin; <sup>7</sup>ION-3, <sup>8</sup>ION-1, <sup>9</sup>COSMOS, <sup>10</sup>SOLAR, <sup>11</sup>ION-2, <sup>12</sup>ELECTRON-2, <sup>13</sup>SIRIUS; Ledipasvir/Sofosbuvir (90/400 mg) orally daily; Simeprevir 150 mg orally daily with food; Sofosbuvir 400 mg orally daily. Ledipasvir/Sofosbuvir, sofosbuvir or simeprevir should not be used as monotherapy or in reduced dosages; neither drug should be restarted if discontinued.

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](http://www.hepatitis.va.gov/provider/guidelines/2012HCV-definitions-of-response.asp)).<sup>6</sup>

## Interferon-Free Regimens in Genotype 1 (GT1)

### ***Preferred Regimens (see Table 4 for details)***

#### ***Treatment-naïve patients without cirrhosis***

- *Ledipasvir/Sofosbuvir (90/400 mg/day) for 12 weeks. If baseline HCV RNA <6 million IU/mL, 8 weeks can be considered.*
- *Sofosbuvir 400 mg/day plus simeprevir 150 mg/day with food for 12 weeks.*

#### ***Treatment-naïve patients with cirrhosis***

##### *CTP A*

- *Ledipasvir/Sofosbuvir (90/400 mg/day) with or without ribavirin for 12 weeks.*
- *Sofosbuvir 400 mg/day plus simeprevir 150 mg/day with food for 12 weeks. **NOT FDA APPROVED***
- *Sofosbuvir 400 mg/day plus simeprevir 150 mg/day with food for 24 weeks.*

##### *CTP B,C*

- *Ledipasvir/Sofosbuvir (90/400 mg/day) plus ribavirin (600mg/day and increase as tolerated) for 12 weeks. **NOT FDA APPROVED***

#### ***Treatment-experienced patients without cirrhosis***

- *Ledipasvir/Sofosbuvir (90/400 mg/day) for 12 weeks.*
- *Sofosbuvir 400 mg/day plus simeprevir 150 mg/day with food for 12 weeks.*

#### ***Treatment-experienced patients with cirrhosis***

##### *CTP A*

- *Ledipasvir/Sofosbuvir (90/400 mg/day) plus ribavirin (1000mg/day if <75kg or 1,200 mg/day if ≥75 kg/day with food, in divided doses) for 12 weeks. **NOT FDA APPROVED***
- *Ledipasvir/Sofosbuvir (90/400 mg/day) for 24 weeks.*
- *Sofosbuvir 400 mg/day plus simeprevir 150 mg/day with food for 12 weeks. **NOT FDA APPROVED***
- *Sofosbuvir 400 mg/day plus simeprevir 150 mg/day with food for 24 weeks.*

##### *CTP B,C*

- *Ledipasvir/Sofosbuvir (90/400 mg/day) plus ribavirin (600mg/day and increase as tolerated) for 12 weeks. **NOT FDA APPROVED***

CTP = Child-Turcotte-Pugh

High SVR rates along with low adverse events and shortened treatment duration provide sufficient evidence to recommend ledipasvir/sofosbuvir (LDV/SOF)- and sofosbuvir/simeprevir (SOF/SMV)-based therapy as the preferred treatment for HCV GT1 infection. **Refer to the Appendix, Tables 1-2 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](http://www.hepatitis.va.gov/provider/guidelines/2012HCV-definitions-of-response.asp)).<sup>6</sup>

The following summarizes the pivotal trials supporting the FDA-approval of these regimens including data on specific subgroups of patients with cirrhosis or those with prior direct-acting antiviral treatment experience.

### **Ledipasvir/Sofosbuvir (LDV/SOF)**

ION-1 was a randomized, open label, phase 3 clinical trial examining the safety and efficacy of ledipasvir/sofosbuvir (LDV/SOF) in treatment-naïve patients with HCV genotype 1 infection.<sup>8</sup> Four treatment arms were compared: LDV/SOF for 12 and 24 weeks with and without ribavirin (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<sup>3</sup> 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 were more frequent in RBV-containing arms. Serious adverse events requiring treatment discontinuation were solely observed 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 genotype 1-infected patients without cirrhosis.<sup>7</sup> 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 genotype 1a (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 3.6% (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 9.8% (9/92) of patients with a baseline HCV RNA level ≥6 million IU/mL but in only 1.2% (1/85) of subjects 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 genotype 1a- 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 either patients with cirrhosis or in previously treated patients.

ION-2 was a phase 3 trial of 440 HCV genotype 1 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).<sup>11</sup> 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. A total of 20% of subjects in each treatment group 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 subjects 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). Although SVR rates were numerically higher with 24 weeks of LDV/SOF in patients with cirrhosis, confidence intervals were wide and overlapping, and this study was not powered to compare responses of 12 and 24 weeks of treatment or of regimens with and without ribavirin. In multivariate analysis, the absence of cirrhosis was the only baseline factor associated with increased rate of response. Of the 62 patients that had an NS5A-resistant variant at baseline, 89% (55/62) achieved SVR; 6 of 11 patients that 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 subjects 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) as 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.<sup>13</sup> Median age was 56 years, 94% of subjects had non-IL28B CC genotype, 17% had platelets less than 100,000/mm<sup>3</sup>, and 13% had albumin <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 less than 10 g/dL in one subject in each treatment arm. There were no deaths. This prospective study in a relatively large number of subjects 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).<sup>12</sup>

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 patients with CPT B (score 7-9) and 49 subjects with CPT C (score 10-13) with genotype 1 (n=56) or genotype 4 (n=3) infection.<sup>10</sup> Inclusion criteria included bilirubin  $\leq 10$  mg/dL, hemoglobin  $\geq 10$  g/dL, platelets  $>30,000/\text{mm}^3$  and eGFR  $\geq 40$  mL/min. In the initial report (AASLD 2014), 9 patients were excluded from SVR analysis (6 patients underwent transplant and 3 have not yet reached 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 subjects in each treatment arm (12 and 24 weeks). MELD score improved in most patients. There were four treatment-related serious adverse events (anemia [2], hepatic encephalopathy, peritoneal hemorrhage), two in CTP B and two in CTP C subjects. Three subjects discontinued treatment due to adverse events. Six subjects 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 SOF/LDV+RBV for 12 weeks can be considered in subjects with decompensated cirrhosis and eGFR  $>40$  mL/min. Patients need to be followed closely for adverse events.

### **Sofosbuvir + Simeprevir $\pm$ Ribavirin**

In an open-label, Phase IIa trial (COSMOS), the combination of SOF + simeprevir (SMV)  $\pm$  RBV was evaluated in 167 GT1-infected patients.<sup>9</sup> In treatment-naïve patients with cirrhosis, SVR rates were 100% (6/6) and 67% (2/3) with 12 weeks of SOF + SMV with or without RBV, respectively; with 24 weeks of treatment, SVR was achieved in 100% (9/9) with SOF + SMV  $\pm$  ribavirin. In 41 null responders with METAVIR F0-F2, SVR rates were 96% and 93% with 12 weeks of SOF + SMV with and without ribavirin, respectively. In null responders with METAVIR F3, SVR was achieved in 100% (13/13) with 12 weeks of SOF + SMV  $\pm$  ribavirin; SVR was achieved in 86% (6/7) and 100% (4/4) with 24 weeks of SOF + SMV with and without ribavirin, respectively. In null responders with METAVIR F4, SVR was achieved in 80% (4/5) and 100% (4/4) with 12 weeks of SOF + SMV with and without ribavirin, respectively; SVR was achieved in 90% (9/10) and 100% (4/4) with 24 weeks of SOF + SMV with and without ribavirin, 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 ribavirin, respectively, and 4% and 7% in the 12-week regimens with and without ribavirin, respectively. Serious adverse events

occurred in 6% and 3% of patients receiving 24-week regimens with and without ribavirin, respectively, compared with 0% in patients receiving 12-week regimens.

**Genotype 1-Infected Patients Who Previously Failed Treatment with a DAA agent**

LDV/SOF for 12 weeks is FDA-approved for the treatment of non-cirrhotics who have failed prior HCV treatment while 24 weeks of LDV/SOF is the approved regimen for cirrhotic patients who have failed prior treatment. In a Phase II, open label study of patients without cirrhosis who virologically relapsed on a prior 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.<sup>12</sup> As described above, a randomized, double-blind study of LDV/SOF + RBV for 12 weeks achieved high SVR rates in patients with cirrhosis who failed boceprevir- or telaprevir-based therapy (SVR 96%, 74/77).<sup>13</sup>

Based on concerns of potential cross-resistance, a SOF + SMV regimen should be avoided in patients who had a previous virologic failure to a boceprevir- or telaprevir-based regimen.

## V. Chronic HCV Genotype 2 Infection (including HIV co-infection\*)

\*Refer to Section X. Groups with Special Considerations for Therapy on HCV treatment in patients with HIV/HCV coinfection;

**Table 5. Genotype 2: Preferred Regimens and SVR Rates from Supporting Data in HCV Mono-infection 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) <sup>14</sup> 92% (85/92) <sup>15</sup> 97% (29/30) <sup>15, 16</sup>	
	Cirrhotic	Sofosbuvir + Ribavirin 12 weeks	A-II	83% (10/12) <sup>14</sup> 94% (16/17) <sup>15</sup> 100% (2/2) <sup>16</sup>	
Experienced GT2	Non-cirrhotic	Sofosbuvir + Ribavirin 12 weeks	A-II	91% (30/33) <sup>16</sup> Relapsers: 86% (25/29) <sup>15</sup> Nonresponders: 70% (7/10) <sup>15</sup>	
			16 weeks	B-II	Relapsers: 89% (24/27) <sup>15</sup> Nonresponders: 88% (7/8) <sup>15</sup>
		Sofosbuvir + Peginterferon+ Ribavirin 12 weeks	B-II	100% (9/9) <sup>17</sup>	If interferon eligible
		<b>NOT FDA approved</b>			
	Cirrhotic	Sofosbuvir + Ribavirin 12 weeks	A-II	88% (7/8) <sup>16</sup> 60% (6/10) <sup>15</sup>	
			16 weeks	B-II	78% (7/9) <sup>15</sup>
Sofosbuvir + Peginterferon + Ribavirin 12 weeks		B-II	93% (13/14) <sup>17</sup>	If interferon eligible	
	<b>NOT FDA approved</b>				

\*Refer to Section X. Groups with Special Considerations for Therapy on HCV treatment in patients with HIV/HCV coinfection;  
<sup>14</sup>FISSION, <sup>15</sup>POSITRON, <sup>15</sup>FUSION, <sup>16</sup>VALENCE, <sup>17</sup>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 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.

## Sofosbuvir in Genotype 2 (GT2)

### Preferred regimens (see Table 5 for details)

#### **Treatment-naïve 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/day with food, in divided doses) 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/day with food, in divided doses) for 12 weeks or 16 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/day with food, in divided doses) for 12 weeks. **NOT FDA APPROVED**

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.<sup>14-16</sup> 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.<sup>16</sup> 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).<sup>15</sup> 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, sofosbuvir 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.<sup>17</sup> This regimen is not FDA approved.

## VI. Chronic HCV Genotype 3 Infection (including HIV co-infection\*)

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

**Table 6. Genotype 3: Preferred Regimens and SVR Rates from Supporting Data 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 <b>NOT FDA approved</b>	12 weeks	A-II	100% (26/26) <sup>12</sup>	Includes 16% of patients with cirrhosis.  SVR rate lower without ribavirin: 64% (16/25) <sup>12</sup>
		Sofosbuvir + Ribavirin	24 weeks	A-I	94% (86/92) <sup>16</sup>	
	Cirrhotic	Ledipasvir/Sofosbuvir + Ribavirin <b>NOT FDA approved</b>	12 weeks	A-II	100% (26/26) <sup>12</sup>	Includes non-cirrhotics; cirrhosis present in 16%.  SVR was lower without ribavirin: 64% (16/25) <sup>12</sup>
Experienced GT3	Non-cirrhotic	Ledipasvir/Sofosbuvir + Ribavirin <b>NOT FDA approved</b>	12 weeks	A-II	89% (25/28) <sup>12</sup>	
		Sofosbuvir + Ribavirin	24 weeks	A-I	87% (87/100) <sup>16</sup>	
	Cirrhotic	Sofosbuvir + Peginterferon + Ribavirin <b>NOT FDA approved</b>	12 weeks	A-II	83% (10/12) <sup>17</sup>	If interferon eligible

\* Refer to Section X. Groups with Special Considerations for Therapy on HCV treatment in patients with HIV/HCV coinfection;  
<sup>12</sup>ELECTRON-2, <sup>16</sup>VALENCE, <sup>17</sup>LONESTAR-2; 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 7. Genotype 3: Alternative Regimens and SVR Rates from Supporting Data 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.*

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	Sofosbuvir + Peginterferon + Ribavirin <b>NOT FDA approved</b>	12 weeks	A-II	92% (23/25) <sup>18</sup> ; represents combined GT2 and GT3 data	If interferon eligible
	Cirrhotic	Sofosbuvir + Peginterferon + Ribavirin <b>NOT FDA approved</b>	12 weeks	A-III	Data not available	If interferon eligible
		Sofosbuvir + Ribavirin	24 weeks	A-I	92% (12/13) <sup>18</sup>	
Experienced GT3	Non-cirrhotic	Sofosbuvir + Peginterferon + Ribavirin <b>NOT FDA approved</b>	12 weeks	A-II	83% (10/12) <sup>17</sup>	If interferon eligible
	Cirrhotic	Ledipasvir/Sofosbuvir + Ribavirin <b>NOT FDA approved</b>	12-24 weeks	B-II/III	73% (16/22) with 12 weeks <sup>19</sup>	No data available for 24 weeks
		Sofosbuvir + Ribavirin	24 weeks	A-I	60% (27/45) <sup>16</sup>	

<sup>18</sup>PROTON, <sup>17</sup>LONESTAR-2, <sup>19</sup>Gane: LB-11; <sup>16</sup>VALENCE 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 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.

## Sofosbuvir for Genotype 3 (GT3)

### **Preferred regimens (see Table 6 for details)**

#### **Treatment-naïve patients without cirrhosis**

- *Ledipasvir/Sofosbuvir (90/400 mg/day) plus ribavirin (1000mg/day if <75kg or 1,200 mg/day if ≥75 kg/day 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 (1000mg/day if <75kg or 1,200 mg/day if ≥75 kg/day with food, in divided doses) for 12 weeks. **NOT FDA APPROVED***

#### **Treatment-experienced patient without cirrhosis**

- *Ledipasvir/Sofosbuvir (90/400 mg/day) plus ribavirin (1000mg/day if <75kg or 1,200 mg/day if ≥75 kg/day 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/day with food, in divided doses) for 12 weeks. **NOT FDA APPROVED***

The preferred regimen for chronic HCV GT3 is supported by the results of a Phase III, randomized study (VALENCE) that evaluated treatment with sofosbuvir and ribavirin for 24 weeks in GT3 patients (n=250).<sup>16</sup> 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.<sup>16</sup> In other studies, shorter treatment duration (12-16 weeks) with sofosbuvir and ribavirin resulted in lower SVR rates (21-68%).<sup>14, 15, 20</sup>

In a Phase II, open-label study (PROTON) with sofosbuvir, peginterferon, and ribavirin for 12 weeks in treatment-naïve patients without cirrhosis, SVR was achieved in 92%; however, these results represent combined GT2 and GT3 data.<sup>18</sup> In GT3 treatment-experienced patients (n=24), a Phase II, open-label study (LONESTAR-2) evaluated treatment with sofosbuvir, peginterferon, and ribavirin for 12 weeks; 50% of patients were cirrhotic. SVR occurred in 83% (10/12) of patients without cirrhosis and 83% (10/12) of those with cirrhosis.<sup>17</sup> This regimen is not FDA approved.

LDV/SOF with or without ribavirin for 12 weeks was evaluated in an open-label study (ELECTRON-2) of 51 treatment naïve GT3 patients, of whom 88% were white and 16% had cirrhosis.<sup>12</sup> SVR rates were 100% (26/26) in patients who received LDV/SOF with ribavirin whereas SVR rates were 64% (16/25) in the group that did not receive ribavirin. Grade 3/4 or serious adverse effects occurred in 3 and 4 patients,

receiving LDV/SOF and in no patients receiving LDV/SOF with ribavirin, respectively. This regimen is not FDA approved.

## VII. Chronic HCV Genotype 4 Infection (including HIV co-infection\*)

\*Refer to Section X. 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:**

- Sofosbuvir (400 mg/day) 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.
- Ledipasvir/Sofosbuvir (90/400 mg/day) ± ribavirin for 12 weeks. **NOT FDA APPROVED**

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 sofosbuvir in combination with peginterferon and ribavirin for 12 weeks.<sup>14</sup>

LDV/SOF was evaluated in 21 patients with GT4 infection in the NAIAD SYNERGY study.<sup>21</sup> 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).<sup>10, 22</sup> This regimen is not FDA approved for the treatment of GT4 infection.

## VIII. Identifying Treatment Candidates Based on Liver Disease Stage and Presence of Hepatocellular Carcinoma

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 (Child-Turcotte-Pugh Class B or C; CTP score ≥7) have a poor prognosis, with a median survival of 24 months or less. However, antiviral treatment options are limited for patients with decompensated cirrhosis. At the present time, 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
<b>Clinical Findings</b>	<ul style="list-style-type: none"> <li>Physical exam findings (splenomegaly, palmar erythema or spider angioma)</li> <li>Low platelet count (&lt;140,000-150,000/mm<sup>3</sup>)* or other serum markers of fibrosis/cirrhosis (see below)</li> <li>Abdominal imaging findings (see below)</li> </ul>
<b>Abdominal Imaging</b> <ul style="list-style-type: none"> <li>Ultrasound</li> <li>Computed tomography (CT)</li> <li>Magnetic resonance imaging (MRI)</li> </ul>	<ul style="list-style-type: none"> <li>Surface abnormalities (e.g., nodularity, and left lobe/caudate lobe hypertrophy) are suggestive of cirrhosis.</li> <li>Features of portal hypertension (e.g., splenomegaly, recanalization of umbilical vein, collaterals) and ascites are strongly suggestive of cirrhosis.</li> </ul>
<b>Liver Fibrosis Imaging</b> <ul style="list-style-type: none"> <li>Vibration-controlled transient elastography (FibroScan®)</li> <li>Acoustic radiation force impulse imaging (ARFI)</li> </ul>	<ul style="list-style-type: none"> <li>Both elastography and ARFI are FDA-approved, ultrasound-based techniques for estimating the extent of liver fibrosis.</li> <li>Fibroscan® value of &gt;12.5 kilopascals has been associated with histologic cirrhosis.</li> <li>ARFI value of &gt;1.75 meters/second has been associated with histologic cirrhosis.</li> </ul>
<b>Serum Markers of Fibrosis/Cirrhosis</b> <ul style="list-style-type: none"> <li>Platelet count</li> <li>APRI</li> <li>FIB-4</li> <li>HALT-C cirrhosis score</li> <li>FibroSure®, FibroTest®, FIBROSpect®</li> </ul>	<ul style="list-style-type: none"> <li>Platelet count less than 140,000 - 150,000/mm<sup>3</sup> 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.</li> <li>APRI and FIB-4 scores are easily calculated using standard clinical labs (<a href="http://www.hepatitisc.uw.edu/page/clinical-calculators/apri">http://www.hepatitisc.uw.edu/page/clinical-calculators/apri</a>, <a href="http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4">http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4</a>).</li> <li>APRI &gt;1.5 has been associated with advanced fibrosis (METAVIR F3); APRI &gt;2.0 has been associated with cirrhosis (METAVIR F4) in the setting of chronic HCV infection.</li> <li>FIB-4 &gt;3.25 has been associated with advanced fibrosis (METAVIR F3-F4) in the setting of chronic HCV infection.</li> <li>HALT-C cirrhosis score (<a href="http://www.haltctrial.org/cirrhosis.html">www.haltctrial.org/cirrhosis.html</a>) predicts likelihood of having cirrhosis based on standard clinical data.</li> <li>FibroSure®, FibroTest®, and FIBROSpect® are proprietary, costly serum fibrosis assays that are not recommended for routine use in the diagnosis of cirrhosis.</li> </ul>
<b>Liver Biopsy</b>	<ul style="list-style-type: none"> <li>Liver biopsy may be considered, but it is invasive and limited by potential sampling error.</li> <li>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.</li> </ul>

Abbreviations: APRI = [(AST/upper limit of normal AST) x 100]/platelet count (10<sup>9</sup>/L); FIB-4 = [Age (years) x AST]/platelet count (10<sup>9</sup>/L) x ALT<sup>1/2</sup>; HALT-C cirrhosis score (see [www.haltctrial.org/cirrhosis.html](http://www.haltctrial.org/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](http://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](http://www.haltctrial.org/hccform.html)) is associated with increased risk of developing hepatocellular carcinoma 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 less than 140,000 – 150,000/mm<sup>3</sup> 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<sup>3</sup> have increased risk of developing HCC, whereas patients with platelet counts of <100,000/mm<sup>3</sup> 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.

## Hepatocellular carcinoma

The following is based on expert opinion, given that minimal data are available. Achieving an SVR has the potential to improve outcome among patients in whom curative treatment of HCC is planned (e.g., transplant, surgical resection, and, potentially, radiofrequency ablation or TACE of small HCC). Thus, HCV antiviral treatment in these patients is reasonable, particularly for those awaiting liver transplantation

and for those with a CTP score <7. 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.

## IX. Laboratory Monitoring

**Table 9. Discontinuing HCV Treatment Based on Lack of Virologic Response**

Treatment Monitoring Considerations
<ul style="list-style-type: none"> <li>• Patients should have an HCV RNA level assessed at week 4 of treatment. (A-III)</li> <li>• If the HCV RNA is detectable* at week 4 or at any time point thereafter, reassess HCV RNA in 2 weeks. If the repeated HCV RNA increases (i.e., &gt;1 log<sub>10</sub> IU/mL from nadir), discontinuation of all treatment should be strongly considered. (A-III)</li> <li>• HCV RNA levels should be assessed at <b>12 weeks after completion of treatment</b> to determine if SVR was achieved. (A-I)</li> </ul>

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

Periodic laboratory monitoring of liver enzymes, bilirubin, and hemoglobin (particularly if receiving ribavirin) 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 if SVR was achieved. HCV RNA levels at 24 weeks after the end-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](http://www.hepatitis.va.gov/provider/guidelines/2012HCV-supplement.asp), Supplemental Table 1).<sup>6</sup>

### 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 is strongly recommended.<sup>GhanyAASLD2009</sup> 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 detectable after 4 or more weeks of sofosbuvir-based therapy, HCV RNA should be reassessed in 2 weeks. If the repeated HCV RNA level has increased (i.e., >1 log<sub>10</sub> IU/mL from nadir), discontinuation of all therapy should be strongly considered.

## X. Adverse Effects

### **Ledipasvir/Sofosbuvir (LDV/SOF)**<sup>23</sup>

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%) have also been reported with ledipasvir/sofosbuvir treatment. Rarely, elevated bilirubin levels of greater than 1.5 times the upper limits of normal (<1-3%) and transient, asymptomatic lipase elevations of greater than 3 times the upper limits of normal (<1-3%) have been observed with ledipasvir/sofosbuvir treatment.

### **Sofosbuvir + Simeprevir ± Ribavirin (SOF + SMV ± RBV)**<sup>9</sup>

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 ribavirin-containing arm (11% versus 7%). Grade 3 or 4 adverse events were higher in the 24-week regimens (17% and 13% with and without ribavirin, respectively) compared to the 12-week regimens (4% and 7% with and without ribavirin, respectively). In the 24 week arms, dizziness (16%) and diarrhea (16%) were also reported.

### **Sofosbuvir + Ribavirin (SOF + RBV)**<sup>24</sup>

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<sup>3</sup>) and thrombocytopenia (platelet counts of <50,000/mm<sup>3</sup>) were not observed. Rarely, total bilirubin elevation of more than 2.5 times the upper limits of normal 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)**<sup>24</sup>

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 ribavirin dosage reduction in all studies, and <1% of patients received a blood transfusion.

### **Simeprevir + Peginterferon + Ribavirin (SMV + PEG-IFN + RBV)**<sup>25</sup>

The most common adverse effects of SMV + PEG-IFN + RBV regimens were rash including photosensitivity (28%), pruritus (22%), nausea (22%), dyspnea (12%), and hyperbilirubinemia (49%).

#### **Rash and Photosensitivity**

Rash including photosensitivity occurred most frequently in the first 4 weeks of treatment with a SMV + PEG-IFN + RBV regimen, 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 simeprevir-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 simeprevir-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 simeprevir-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 simeprevir 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.

## **XI. Proper Use**

### **Drug-Drug Interactions**<sup>23-25</sup>

Both ledipasvir and sofosbuvir are substrates for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and as such, P-gp inducers may decrease ledipasvir and/or sofosbuvir plasma concentrations. Ledipasvir is also an inhibitor of intestinal P-gp and BCRP. Ledipasvir is subject to slow oxidative metabolism but there is no metabolism by cytochrome P450 (CYP) isoenzymes; sofosbuvir 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.

Simeprevir 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 simeprevir concentrations, respectively. Simeprevir is an inhibitor of P-gp and the drug transporter OATP1B1/3. Simeprevir mildly inhibits CYP1A2 activity and intestinal CYP3A4 activity, but does not affect hepatic CYP3A4 activity. Co-

administration of simeprevir with drugs that are primarily metabolized by CYP3A4 may result in increased plasma concentrations of those drugs.

**Refer to the Appendix, Tables 3-4 for summary of drug-drug interactions.**

### **Storage and Stability**<sup>23-25</sup>

Ledipasvir, sofosbuvir and simeprevir can be stored at room temperature (<86°F), but exposure of the medication to direct sunlight should be avoided.

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

### **Missed Doses**<sup>23-25</sup>

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

Patients should be instructed to take a missed simeprevir dose if it is less than 12 hours from the next scheduled simeprevir dose and to take the next simeprevir 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, treatment for HCV in all HIV-infected patients is encouraged.

### **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 cell count  $\geq 500$  cells/ $\mu$ L. Studies involving HIV/HCV co-infected patients have excluded patients with a CD4 cell count of  $<200$  cell/ $\mu$ L; HCV antiviral treatment of a Veteran with a CD4 cell count of  $<200$  cell/ $\mu$ L should only be initiated with the consultation of an HIV and hepatitis C treatment specialist. In patients with a CD4 cell count of  $<200$  cells/ $\mu$ L, 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).

Antiretroviral regimen selection should take into account potential drug-drug interactions with HCV antiviral medications (see Appendix, Table 4). 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 potential risk of drug-drug interactions if a prior HIV regimen is resumed soon after HCV treatment is completed.<sup>1</sup>

### **HIV/HCV Coinfection Clinical Trials**

A summary of results from HCV clinical trials 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.<sup>26</sup> 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 one 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. No clinically significant changes in absolute CD4 cell count, HIV viral load or renal function occurred. No serious adverse events were reported, but Grade 3/4 changes in serum amylase, lipase, CPK, and neutrophil count were reported.

The use of SOF + RBV (1000mg or 1200 mg daily) in HIV/HCV-coinfected patients with a mean CD4 count >500 cells/ $\mu$ L was examined in PHOTON-1 and PHOTON-2.<sup>20,27</sup> PHOTON-1 included 223 treatment-naïve genotype 1 patients and both treatment-naïve and-experienced genotype-2 and 3 patients from the US and Puerto Rico. PHOTON-2 included 274 HIV/HCV-coinfected patients with genotype 1, 2, 3, or 4 infection from Europe and Australia. Pooled analysis of PHOTON-1 and -2 data by genotype and treatment history showed an SVR 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 SVR12 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 -2 data by genotype and liver disease stage showed for GT1a, an SVR of 65% and 85% in those 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 -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 which 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 regardless of treatment history can achieve an 88-91% response rate. In treatment-naïve GT1 and GT4 patients, 24 weeks of SOF + RBV therapy should be administered. However, in those with GT1 infection and cirrhosis, SOF + RBV should be used with caution as SVR rates were between 60 and 65%.

While 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.

A Phase II, single-center, open-label, single-arm trial evaluated 23 HCV treatment-naïve, non-cirrhotic, GT1-4 HIV/HCV-coinfected patients who received SOF + PEG-IFN + RBV (1,000 or 1,200 mg/day) for 12 weeks.<sup>28</sup> Patients were required to be on a stable HIV antiretroviral regimen with suppressed HIV RNA. Overall SVR was achieved in 91% (21/23). SVR occurred in 89% (17/19) of GT1-, 100% (1/1) of GT2-, 100% (2/2) of GT3-, and 100% (1/1) of GT4-infected patients.

#### **HIV/HCV Drug-Drug Interactions<sup>23-25</sup>**

Refer to Appendix, Table 4 for drug-drug interactions.

#### **Adverse Effects in HIV/HCV Coinfection<sup>24</sup>**

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%). 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 ribavirin dosage-reduction for management of anemia. For additional information, refer to Sofosbuvir (NDA 204671). Presentation to: FDA Antiviral Drugs Advisory Committee; October 25, 2013.

#### **Laboratory Monitoring<sup>23-25</sup>**

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*.<sup>1</sup>

## Renal Insufficiency or Hepatic Impairment<sup>23-25</sup>

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

Treatment Considerations			
Condition	Treatment	Comment	Grade
Renal Insufficiency	Ledipasvir	No dosage adjustment needed.	A-I
	Simeprevir	Has not been studied in HCV-infected patients with CrCl <30 mL/min. However, no dosage adjustment is needed.	A-I
	Sofosbuvir	Should not be used if CrCl <30 mL/min or end-stage renal disease.	A-I
	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
Hepatic Impairment	Ledipasvir	No dosage adjustment needed.	A-I
	Simeprevir	No dosage recommendation can be given for patients with moderate or severe hepatic impairment (Child-Turcotte-Pugh 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 (Child-Turcotte-Pugh Class A, B, or C). Safety and efficacy of sofosbuvir have not been established in patients with decompensated cirrhosis.	A-I
	Peginterferon	Should not be used in patients with moderate or severe hepatic impairment (Child-Turcotte-Pugh Class B or C; CTP score ≥7).	A-I

CTP = Child-Turcotte-Pugh

### Ledipasvir (LDV)<sup>23</sup>

Following administration of a single dose of 90 mg LDV in HCV negative subjects, 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 subjects with severe hepatic impairment (Child-Pugh 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)<sup>24</sup>**

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  $\geq$ 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-hr 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 (Child-Turcotte-Pugh Class B or C; CTP score  $\geq$ 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)<sup>25</sup>**

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 (Child-Turcotte-Pugh Class A). In HCV negative patients, the mean steady-state AUC of SMV was 2.4-fold higher with moderate hepatic impairment (Child-Turcotte-Pugh Class B) and 5.2-fold higher with severe hepatic impairment (Child-Turcotte-Pugh Class C). The safety and efficacy of SMV have not been established in HCV-infected patients with Child-Turcotte-Pugh 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 (Child-Turcotte-Pugh Class B or C).

## Treatment in Pre-Liver Transplant and Post-Liver or -Other Solid Organ Transplant

**Table 11. Treatment Considerations for Patients Who Will or Have Received a Solid Organ Transplant, AFTER DISCUSSION WITH THE TRANSPLANT CENTER –**

Treatment Considerations				Supporting Information	
Transplant status	HCV genotype (GT)	Regimen and duration	Evidence grade	SVR % (N/N)	Comments
Pre-liver transplant (CTP B and C)	GT1	Ledipasvir/ Sofosbuvir + Ribavirin  <b>NOT FDA APPROVED</b>	12 weeks	B-II  CTP B: 87% (26/30) <sup>10</sup> CTP C: 86% (19/22) <sup>10</sup>	24 weeks CTP B: 89% (24/27) <sup>10</sup> CTP C: 90% (18/20) <sup>10</sup>
Pre-Liver Transplant for Patients with HCC	GT2	Sofosbuvir + Ribavirin  (combination with PEG-IFN may be considered but is not FDA approved)	24-48 weeks	B-II  64% (25/39) <sup>29</sup>	SVR rates included GT1, 3 and 4 patients.  Patients had HCC with compensated liver disease (CTP score <7). <sup>29</sup>  <b>The decision to treat, regimen selection and management of treatment should be coordinated with the transplant center and/or specialists.</b>
Post-Liver Transplant	GT1	Ledipasvir/ Sofosbuvir + Ribavirin  <b>NOT FDA APPROVED</b>	12 weeks	B-II  F0-F3: 96% (53/55) <sup>22</sup> CTP A: 96% (25/26) <sup>22</sup> CTP B: 85% (22/26) <sup>22</sup> CTP C: 60% (3/5) <sup>22</sup>	24 weeks F0-F3: 98% (55/56) <sup>22</sup> CTP A: 96% (24/25) <sup>22</sup> CTP B: 83% (15/18) <sup>22</sup> CTP C: 67% (2/3) <sup>22</sup>  Ribavirin dose was weight-based for patients without cirrhosis and CPT A; in CPT B and C patients, ribavirin was initiated at 600mg/day and increased as tolerated. <sup>22</sup>  Refer to Appendix, Table 3 for drug-drug interactions.

Treatment Considerations				Supporting Information		
Transplant status	HCV genotype (GT)	Regimen and duration		Evidence grade	SVR % (N/N)	Comments
Post-Liver Transplant	GT1	<i>In patients who cannot tolerate Ribavirin:</i> Ledipasvir/ Sofosbuvir  <b>NOT FDA APPROVED</b>	24 weeks	B-III	Data not available	Effectiveness is presumed, based on use in non-transplant, treatment-experienced patients with cirrhosis.
Post-liver transplant	GT1	Sofosbuvir + Simeprevir  <b>NOT FDA APPROVED</b>	12-24 weeks	B-II	12 weeks: 91% (-RBV) 89% (+RBV)  F0-2: 97% F3-4: 64%	<b>AVOID USE in patients receiving cyclosporine;</b> refer to Appendix, Table 3 for drug-drug interactions.  Can be considered for patients who cannot tolerate ribavirin.
Post-Liver Transplant	GT2	Sofosbuvir + Ribavirin  (PEG-IFN may be considered)  <b>NOT FDA APPROVED</b>	24 weeks	B-III	77% (31/40) <sup>30</sup>  60% (19/32) <sup>31</sup>  50% (6/12) <sup>31</sup> with PEG-IFN	SVR rates included GT1, 3 and 4 patients  <b>The decision to treat, regimen selection and management of treatment should be coordinated with the transplant center and/or specialists.</b>  Refer to Appendix, Table 3 for drug-drug interactions.
Pre- or Post-Liver Transplant	GT3, GT4	Discuss with transplant center. 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.  <b>Ledipasvir/Sofosbuvir + Ribavirin and Sofosbuvir + Ribavirin + Peginterferon have not been well studied in GT3 or GT4 pre- or post-liver transplant patients.</b>				
Post-Other Solid Organ Transplant (Kidney, Heart, or Lung)	GT1, 2, 3, or 4	Discuss with transplant center.  <b>DO NOT USE (peg)interferon-containing regimens in these populations. Sofosbuvir has not been studied in non-liver transplant recipients.</b>				

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.

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 3).

### Treatment in Pre-Liver Transplant

#### ***Preferred regimens (See Table 11)***

##### **Genotype 1**

- *Ledipasvir/Sofosbuvir (90/400 mg/day) plus ribavirin (1000mg/day if <75kg or 1,200 mg/day if ≥75 kg/day with food, in divided doses) for 12 weeks. **NOT FDA APPROVED***

##### **Genotype 2**

- *With HCC: 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 to 48 weeks or until the time of transplantation, whichever occurs first.*
- *Without HCC: 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 3 or 4**

- *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.*

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).

Among 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 on "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 on "Genotype 1-Infected Patients with Cirrhosis, Decompensated", LDV/SOF + RBV for 12 weeks achieve a SVR of 87-89% among GT1-infected patients with decompensated cirrhosis. Studies of the treatment efficacy in decompensated cirrhosis among non-genotype 1 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 of 8, CTP score <7) treated with sofosbuvir plus ribavirin 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 carefully considered 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) plus ribavirin (1000mg/day if <75kg or 1,200 mg/day if ≥75 kg/day with food, in divided doses) for 12 weeks. **NOT FDA APPROVED***
- *If ribavirin intolerant: Ledipasvir/Sofosbuvir (90/400 mg/day) for 24 weeks. **NOT FDA APPROVED***
- *Sofosbuvir 400 mg/day plus simeprevir 150 mg/day with food for 12 to 24 weeks. **NOT FDA APPROVED***

##### **Genotype 2**

- *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. **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) plus ribavirin (1000mg/day if <75kg or 1,200 mg/day if ≥75 kg/day with food, in divided doses) for 12 weeks. **NOT FDA APPROVED***
- *If ribavirin intolerant: Ledipasvir/Sofosbuvir (90/400 mg/day) 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, particularly given lack of FDA approval. Drug-drug interactions with HCV DAA agents and post-transplant immunosuppressive agents should be thoroughly evaluated and are listed in **Appendix, Table 3**.

### **Ledipasvir/Sofosbuvir in the Post-transplant Setting**

In a study of post-transplant patients with HCV, 223 patients were randomized to LDV/SOF+ RBV for 12 or 24 weeks.<sup>22</sup> Ribavirin dosing was weight-based for patients without cirrhosis and CTP A; in CTP B and C patients, ribavirin was initiated at 600mg/day and increased as tolerated. In this study, 112 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, complications of cirrhosis and progressive multifocal leukoencephalitis. 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 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.

### **Sofosbuvir and Simeprevir in the Post-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. 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 a RBV-containing regimen, all required RBV dose 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, given the potential drug-drug interaction between SMV and cyclosporine (see below and Appendix, Table 3), SMV is contraindicated in patients receiving cyclosporine.

Sofosbuvir plus ribavirin has 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 subjects 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.<sup>30</sup> In a compassionate use program, 44 patients with severe recurrence of HCV following liver transplantation, including fibrosing cholestatic hepatitis, were treated with sofosbuvir plus ribavirin 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 was 60% for sofosbuvir plus ribavirin and 50% for sofosbuvir, peginterferon plus ribavirin. 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 sofosbuvir plus ribavirin treatment. Liver function tests (e.g., bilirubin, INR) improved with treatment.<sup>30</sup> Although these trials are small, they are consistent in suggesting that sofosbuvir plus ribavirin is safe and effective in the treatment of HCV post-transplant.

Sofosbuvir 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 therapy would likely benefit from receiving future therapies that are more evidence-based. No clinically significant drug-drug interaction was observed with co-administration of LDV or SOF and cyclosporine and tacrolimus. However, concomitant use of simeprevir with cyclosporine results in significantly increased simeprevir concentrations (approximately 6-fold) due to inhibition of OATP1B1, P-gp and CYP3A; simeprevir should not be coadministered with cyclosporine. Although concomitant use of simeprevir with tacrolimus resulted in increased simeprevir concentrations (approximately 2-fold) due to inhibition of OATP1B1, no dose adjustment is required for either drug. Routine monitoring of tacrolimus levels is recommended since tacrolimus levels can be reduced when coadministered with SMV.

## Extra-hepatic manifestations of HCV

**Table 12. Treatment of Patients with Extra-Hepatic Manifestations of HCV**

Treatment Considerations
<ul style="list-style-type: none"><li>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)</li></ul>

### Mental Health and Substance-Use 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:** 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](http://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 is 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<sup>25</sup>

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

<p>Pamela S. Belperio, PharmD, BCTPS, AAHIVE National Public Health Clinical Pharmacist VA Office of Public Health / Population Health</p> <p>Conflicts of interest: None</p>	<p>Timothy R. Morgan, MD Chief, Hepatology VA Long Beach Healthcare System Professor of Medicine, University of California, Irvine</p> <p>Conflicts of interest: Clinical Trials: Bristol-Myers Squibb, Genentech, Gilead, Merck Data Analysis: AbbVie Speakers' Bureau: None Advisory Boards: None</p>
<p>Mary Jane Burton, MD Clinical Director, Viral Hepatitis Clinics, G.V. Sonny Montgomery VA Medical Center Associate Professor of Medicine, University of Mississippi Medical Center</p> <p>Conflicts of interest: None</p>	<p>Catherine Rongey, MD, MSHS Staff Physician, Gastroenterology and Hepatology, San Francisco VA Medical Center Adjunct Assistant Professor, University of California, San Francisco Viral Hepatitis National Public Health Clinical Lead</p> <p>Conflicts of interest: None</p>
<p>Maggie Chartier, PsyD, MPH National Public Health Clinical Psychologist, HIV, Hepatitis, and Public Health Pathogens Programs Office of Public Health/Clinical Public Health Staff Psychologist, San Francisco VA Medical Center, Mental Health Service</p> <p>Conflicts of interest: None</p>	<p>David Ross, MD, PhD, MBI Director, HIV, Hepatitis, and Public Health Pathogens Programs Office of Public Health/Clinical Public Health</p> <p>Conflicts of interest: None</p>
<p>Rena K. Fox, MD Medical Editor, VA National Hepatitis Website Professor of Clinical Medicine, University of California, San Francisco</p> <p>Conflicts of interest:</p>	<p>Phyllis Tien, MD Staff Physician, San Francisco VA Medical Center Professor of Medicine, University of California, San Francisco</p> <p>Conflicts of interest: Advisory Boards: AbbVie, Bristol-Myers Squibb</p>
<p>Alexander Monto, MD Director, Liver Clinic, San Francisco VA Medical Center Associate Professor of Clinical Medicine</p>	<p>Helen S. Yee, PharmD Clinical Pharmacy Specialist, San Francisco VA Medical Center Associate Clinical Professor of Pharmacy,</p>

University of California, San Francisco Conflicts of interest: None	University of California, San Francisco Adjunct Professor, University of the Pacific Conflicts of interest: None
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Interim Treatment Considerations: next update will be in January 2015

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Interim Treatment Considerations: next update will be in January 2015

## 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, %)
<b>ION-1<sup>1</sup></b>			
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)
<b>ION-3<sup>3</sup></b>			
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
<b>ELECTRON-2<sup>6</sup></b>			
LDV/SOF x 12 weeks	Naïve	Not studied	13/20 (65) (all were CTP Class B)
<b>ERADICATE<sup>7</sup></b>			
LDV/SOF x 12 weeks	Naïve, HCV/HIV coinfectd	10/10 (100, ARV untreated) SVR4: 22/22 (100, ARV treated)	Not studied
<b>COSMOS<sup>4</sup></b>			
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, %)
<b>ION-2<sup>2</sup></b>			
LDV/SOF ± RBV x 12 weeks	Experienced (PegIFN + 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 (PegIFN + RBV ± BOC or TVR)	86/87 (99, -RBV) 88/89 (99, +RBV)	22/22 (100, -RBV) 22/22 (100, +RBV)
<b>SYNERGY<sup>5</sup></b>			
LDV/SOF x 12 weeks	Experienced (SOF + RBV relapsers)	7/7 (100)	7/7 (100)
<b>ELECTRON-2<sup>6</sup></b>			
LDV/SOF + RBV x 12 weeks	Experienced (SOF + RBV ± DAA)	19/19 (100)	Not studied
<b>COSMOS<sup>4</sup></b>			
SOF/SMV ± RBV x 12 weeks	Experienced (PegIFN + RBV)	13/14 (93, -RBV) 26/27 (93, +RBV)	4/4 (100, -RBV) 4/5 (80, +RBV)
SOF/SMV ± RBV x 24 weeks	Experienced (PegIFN + RBV)	14/15 (93, -RBV) 19/24 (79, +RBV)	4/4 (100, -RBV) 9/9 (100, +RBV)

**Table 3: Drug-Drug Interactions with HCV Antiviral Agents** <sup>23-25, 32-34</sup>

Selected drugs	HCV Direct-Acting Antiviral Agents		
	NS5A/NS5B Inhibitor	NS5B Inhibitor	Protease Inhibitors
	Ledipasvir (LDV)/ Sofosbuvir (SOF)	Sofosbuvir (SOF)	Simeprevir (SMV)
<b>Analgesic</b>			
buprenorphine	?	?	✓
methadone	✓	✓	✓
<b>Antacids</b>			
Aluminum and magnesium hydroxide*	Separate dose by 4 hrs (↓LDV concentration)*	?	?
<b>Antiarrhythmics</b>			
digoxin	use caution and monitor closely (may ↑ digoxin concentration)	?	use caution and monitor closely (may ↑ concentration of antiarrhythmic)
amiodarone, disopyramide, flecanide, mexiletine, propafenone, quinidine	?	?	use caution and monitor closely (may ↑ concentration of antiarrhythmic)
<b>Anticonvulsants</b>			
carbamazepine, phenytoin, phenobarbital, oxcarbazepine	✗ (may ↓ LDV/SOF concentration)	✗ (may ↓SOF concentration)	✗ (may ↓SMV concentration)
<b>Antifungals</b>			
itraconazole, ketoconazole, posaconazole	?	?	✗ (may ↑SMV concentration)
<b>Antiinfectives</b>			
clarithromycin, erythromycin, telithromycin	?	?	✗ (may ↑SMV concentration)
<b>Antimycobacterials</b>			
ribabutin, rifampin, rifapentine	✗ (may ↓ LDV/SOF concentration)	✗ (may ↓SOF concentration)	✗ (may ↓SMV concentration)
<b>Calcium Channel Blockers (CCB)</b>			
amlodipine, diltiazem, felodipine, nicardipine, nifedipine	?	?	use caution and monitor closely (may ↑ CCB concentration)
verapamil	✓	?	use caution and monitor closely (may ↑ CCB concentration)
<b>Corticosteroids</b>			
dexamethasone (systemic)	?	?	✗ (may ↓SMV concentration)
budesonide, fluticasone, methylprednisone,	?	?	✓

	HCV Direct-Acting Antiviral Agents		
Selected drugs	NS5A/NS5B Inhibitor	NS5B Inhibitor	Protease Inhibitors
	Ledipasvir (LDV)/ Sofosbuvir (SOF)	Sofosbuvir (SOF)	Simeprevir (SMV)
prednisone			
<b>H<sub>2</sub>-Receptor Antagonists</b>	Do not exceed famotidine 40mg twice daily; administer simultaneously or 12 hours apart	Do not exceed famotidine 40mg twice daily	✓
<b>HCV drug</b>			
<b>Simeprevir</b>	✗ (↑ LDV/SOF concentration)	✓	
<b>Herbal supplements</b>			
St. John's Wort (Hypericum perforatum)	✗ (may ↓ LDV/SOF concentration)	✗	✗ (may ↓ SMV concentration)
Milk Thistle	?	?	✗ (may ↑ SMV concentration)
<b>HIV ARVs</b>	For a complete listing of drug-interactions associated with HIV antiretrovirals, refer to <b>Appendix Table 4: Drug-Drug Interactions with HIV Antiretrovirals</b>		
<b>HMG CO-A Reductase Inhibitors</b>			
rosuvastatin	✗ (may ↑ rosuvastatin concentration)	?	✓ Initiate at 5mg once daily; dose not to exceed 10mg daily
atorvastatin	?	?	✓ Dose not to exceed 40mg once daily
simvastatin, lovastatin, pitavastatin	?	?	✓ Use lowest necessary dose, titrate carefully; monitor closely for potential ↑ statin concentration
pravastatin	✓	?	✓ Use lowest necessary dose, titrate carefully; monitor closely for potential ↑ statin concentration
fluvastatin	?	?	✓
<b>Immunosuppressants</b>			
cyclosporine	✓	✓	✗ (may ↑ SMV & cyclosporine concentrations)
tacrolimus	✓	✓	No dose adjustment; use caution and monitor closely (potential ↑ SMV &/or ↓ tacrolimus concentrations)
sirolimus	?	?	use caution and monitor closely (potential ↑ SMV &/or ↓/↑ sirolimus concentrations)

Selected drugs	HCV Direct-Acting Antiviral Agents		
	NS5A/NS5B Inhibitor	NS5B Inhibitor	Protease Inhibitors
	Ledipasvir (LDV)/ Sofosbuvir (SOF)	Sofosbuvir (SOF)	Simeprevir (SMV)
<b>Opioid Antagonist</b>			
naloxone	?	?	✓
<b>Oral Contraceptive</b>			
ethinyl estradiol, norgestimate products, norethindrone	✓	?	?
<b>PDE-5 Inhibitors</b>			
sildenafil, tadalafil, vardenafil	?	?	use caution and monitor closely (may ↑ concentration of PDE-5 inhibitor)
<b>Proton Pump Inhibitors (PPI)</b>			
omeprazole	✓ Max dose 20mg once daily; administer simultaneously under fasted conditions	?	✓
Other PPI	✓ PPI doses comparable to omeprazole 20 mg once daily or lower can be administered simultaneously under fasted conditions	?	✓
<b>Sedatives/Anxiolytics</b>			
oral midazolam, triazolam	?	?	use caution and monitor closely (may ↑ concentration of sedative)
<b>Stimulant</b>			
methylphenidate	?	?	✓
<b>SSRI</b>			
escitalopram	?	?	✓

✓ = drug that can be used concomitantly

✗ = drug not recommended

? = data limited or not available on PK interactions

No dosage adjustment is needed for concomitant administration with the following: escitalopram, ethinyl estradiol, norethindrone, methadone, omeprazole, rilpivirine, raltegravir, or tenofovir. No clinically relevant interactions are expected with the following: antacids, budesonide, fluticasone, methylprednisolone, prednisone, fluvastatin, H<sub>2</sub>-receptor antagonists, buprenorphine and naloxone, NRTIs (such as abacavir, didanosine, emtricitabine, lamivudine, stavudine, zidovudine), maraviroc, methylphenidate, and proton pump inhibitors.

**Table 4: Drug-Drug Interactions with HIV Antiretrovirals**<sup>23-25, 32-34</sup>

(Adapted from U.S. Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*

<http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/26/hiv-hcv>)<sup>1</sup>

	HCV Direct-Acting Antiviral Agents		
	Co-Formulated NS5A/NS5B Inhibitors	NS5B Inhibitor	Protease Inhibitor
Selected HIV drugs	Ledipasvir (LDV)/SOF	Sofosbuvir (SOF)	Simeprevir (SMV)
<b>Nucleoside Reverse Transcriptase Inhibitors</b>			
FTC	✓	✓	✓
3TC	✓	✓	✓
ABC	✓	✓	✓
TDF	✓ <sup>a</sup>	✓	✓
ZDV*	✓	✓	✓
<b>HIV Protease Inhibitors</b>			
DRV/r or DRV/cobi	✓ <sup>a</sup>	✓	✗
ATV or ATV/r or ATV/cobi	✓ <sup>a</sup>	✓	✗
LPV/r	✓ <sup>a</sup>	✓	✗
TPV/r	✗	✗	✗
SQV/r	✓ <sup>a</sup>	✓	✗
FPV or FPV/r	✓ <sup>a</sup>	✓	✗
<b>Non-Nucleoside Reverse Transcriptase Inhibitors</b>			
EFV	✓	✓	✗
EFV/TDF/FTC	✓ Monitor for TDF-associated AEs		✗
RPV	✓	✓	✓
ETR	✓	✓	✗
NVP	✓	✓	✗
<b>Integrase Strand Transfer Inhibitors</b>			
RAL	✓	✓	✓
DTG	✓	✓	✓
EVG/cobi/ TDF/ FTC	✗	✓	✗
EVG + (PI/r without coBI)	Refer to recommendations for specific ritonavir-boosted PI		
<b>CCR5 Antagonist</b>			
MVC	✓	✓	✓ ↓ MVC dose to 150mg twice daily

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV/r = atazanavir/ritonavir; ATV/cobi = atazanavir/cobicistat; coBI = cobicistat; DAA = direct-acting antiviral agents; DRV/r = darunavir/ritonavir; DRV/cobi = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; 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 Fumerate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

✓ = ARV agents that can be used concomitantly

✗ = ARV agents not recommended

? = data limited or not available on PK interactions with ARV drug

<sup>a</sup> Regimens containing TDF and a HIV protease inhibitor/ritonavir [or ATV/cobi or DRV/cobi] coadministration, consider alternative HCV or ARV therapy to avoid increases in TDF exposures. If coadministration is necessary, monitor for tenofovir-associated adverse reactions

\*Should not be administered concomitantly with ribavirin or Peg-IFN.

Refer to full prescribing information for a complete list of potential drug-drug interactions and dosage adjustments of concomitantly prescribed medications.<sup>23-25</sup>

Ledipasvir/Sofosbuvir package insert

Sofosbuvir package insert: [www.gilead.com/~media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi\\_pi.pdf](http://www.gilead.com/~media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf)

Simeprevir package insert: [www.olyzio.com/shared/product/olyzio/prescribing-information.pdf](http://www.olyzio.com/shared/product/olyzio/prescribing-information.pdf)