Chronic Hepatitis C Virus (HCV) Infection:

Treatment Considerations from the Department of Veterans Affairs National Hepatitis C Resource Center Program and the Office of Public Health

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I. Summary Table and Summary Figure

This document is intended to supplement 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 treatment decisions based on the existing PBM Criteria For Use documents. The following treatment considerations are based on available medical evidence and represent the opinion of an expert panel of VA HCV clinicians. The purpose of this document is to provide a detailed algorithmic approach to assist in clinical decision-making on HCV treatment considerations based on specific patient characteristics including genotype, treatment history, presence of cirrhosis, and interferon eligibility. 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. 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	IFN Eligibility	Preferred Regimen	Alternative Regimen	Defer for Future Treatment
1	Naïve	Non-cirrhotic or Cirrhotic	Eligible	Sofosbuvir + PEG-IFN/RBV x 12 weeks	Simeprevir x 12 weeks + PEG-IFN/RBV x 24 weeks *(Do not use in GT1a with Q80K polymorphism)*	Reasonable to defer if non-cirrhotic and no significant extra-hepatic disease
		Non-cirrhotic	Ineligible	Sofosbuvir + RBV x 24 weeks OR Sofosbuvir + Simeprevir ± RBV x 12 weeks; **NOT FDA approved**		
		Cirrhotic	Ineligible	Sofosbuvir + Simeprevir ± RBV x 12 weeks; **NOT FDA approved**		
	Experienced	Non-cirrhotic	Eligible	Sofosbuvir + PEG-IFN/RBV x 12 weeks	Simeprevir x 12 weeks + PEG-IFN/RBV x 24 weeks (relapsers) or 48 weeks (prior partial or null responders) *(Do not use in GT1a with Q80K polymorphism or previous failure of boceprevir- or telaprevir-based therapy)*	Reasonable to defer if no significant extra-hepatic disease
	Experienced	Cirrhotic	Eligible	Sofosbuvir + PEG-IFN/RBV x 12 weeks	PEG-IFN/RBV null responders: Sofosbuvir + Simeprevir ± RBV x 12 weeks **NOT FDA approved**	
		Non-cirrhotic or Cirrhotic	Ineligible	Sofosbuvir + Simeprevir ± RBV x 12 weeks **NOT FDA approved**		Reasonable to defer if non-cirrhotic and no significant extra-hepatic disease
2	Naïve	Non-cirrhotic or Cirrhotic	Either	Sofosbuvir + RBV x 12 weeks		Reasonable to defer if non-cirrhotic and no significant extra-hepatic disease

HCV Genotype	Treatment History	Cirrhosis Status	IFN Eligibility	Preferred Regimen	Alternative Regimen	Defer for Future Treatment
	Experienced	Non-cirrhotic or Cirrhotic	Eligible	Sofosbuvir + RBV x 12-16 weeks OR Sofosbuvir + PEG-IFN/ RBV x 12 weeks; **NOT FDA approved**		Reasonable to defer if non-cirrhotic and no significant extra-hepatic disease
			Ineligible	Sofosbuvir + RBV x 12-16 weeks		
3	Naïve	Non-cirrhotic or Cirrhotic	Eligible	Sofosbuvir + RBV x 24 weeks	Sofosbuvir + PEG-IFN/RBV x 12 weeks **NOT FDA approved**	Reasonable to defer if non-cirrhotic and no significant extra-hepatic disease
		Non-cirrhotic or Cirrhotic	Ineligible	Sofosbuvir + RBV x 24 weeks		
	Experienced	Non-cirrhotic	Either	Sofosbuvir + RBV x 24 weeks	Sofosbuvir + PEG-IFN/RBV x 12 weeks **NOT FDA approved**	Reasonable to defer if no significant extra-hepatic disease
		Cirrhotic	Eligible	Sofosbuvir + PEG-IFN/ RBV x 12 weeks **NOT FDA approved**		
			Ineligible	Sofosbuvir + RBV x 24 weeks		
1, 2, 3, or 4	Either	Hepatocellular carcinoma	Either	Sofosbuvir + RBV x 24-48 weeks or until liver transplant, whichever occurs first		

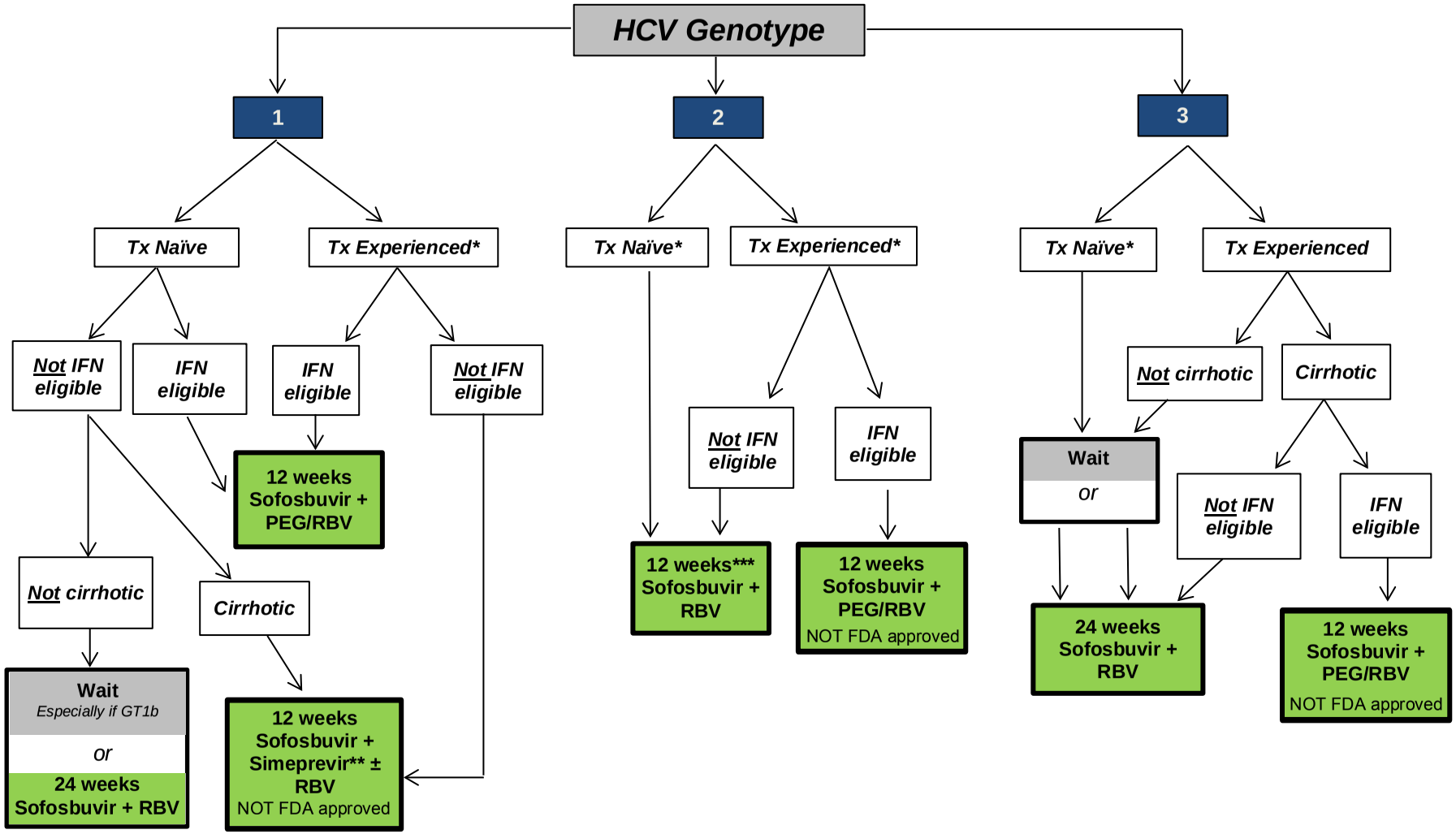
Abbreviations: PEG-IFN = peginterferon; RBV = ribavirin

Dosages: PEG-IFN alfa-2a 180 mcg subcutaneously weekly or PEG-IFN alfa-2b 1.5 mcg/kg subcutaneously weekly; RBV 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: Sofosbuvir or simeprevir should not be used as monotherapy or in reduced dosages; neither drug should be restarted if discontinued.

*** Interferon ineligible or intolerant criteria:** Platelet count <75,000/mm^3; Decompensated liver cirrhosis (Child-Turcotte-Pugh (CTP) Class B or C, CTP score ≥7); Severe mental health conditions that may be exacerbated by interferon and/or respond poorly to medical therapy (with risks of interferon use documented by Mental Health evaluation); Autoimmune diseases that may be exacerbated by interferon-mediated immune modulation; Inability to complete a prior treatment course due to documented interferon-related adverse effects (Table 5)

Summary Figure: Preferred Treatment Approach for HCV-Monoinfected and HIV/HCV-Coinfected Patients



Abbreviations: PEG-IFN = peginterferon; RBV = ribavirin; Tx = treatment

Dosages: PEG-IFN alfa-2a 180 mcg subcutaneously weekly or PEG-IFN alfa-2b 1.5 mcg/kg subcutaneously weekly; RBV 1,000 mg (<75 kg) or 1,200 mg (≥75 kg) orally daily (in two divided doses) with food; simeprevir 150 mg orally daily with food; sofosbuvir 400 mg orally daily

* Regardless of cirrhosis; ** GT1a with Q80K polymorphism may be associated with lower SVR; *** 16 weeks of sofosbuvir/ribavirin in treatment-experienced cirrhotics may improve SVR

Interferon (IFN) ineligible or intolerant criteria: Platelet count <75,000/mm^3; Decompensated liver cirrhosis (Child-Turcott-Pugh (CTP) Class B or C, CTP score ≥7); Severe mental health conditions that may be exacerbated by interferon and/or respond poorly to medical therapy (with risks of interferon use documented by Mental Health evaluation); Autoimmune diseases that may be exacerbated by interferon-mediated immune modulation; Inability to complete a prior treatment course due to documented interferon-related adverse effects (Table 5).

I. Introduction

Successful antiviral treatment of chronic hepatitis C virus (HCV) infection is defined as a sustained virological response (SVR), and achieving an SVR significantly decreases the risk of disease progression to 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, safety, and costs. Providing appropriate treatment to Veterans requires time, expertise including coordination with other services (e.g., Primary Care, Mental Health, Pharmacy, Social Work), and funding.

The following treatment considerations summarize the current best practices in the management and treatment of chronic hepatitis C virus (HCV) infection within the VHA, including the use of interferon-based and interferon-free regimens. These considerations are based on an extensive review of published data, American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) Recommendations for Testing, Managing, and Treating Hepatitis C (www.hcvguidelines.org), publicly available reviews from the U.S. Food and Drug Administration (FDA) data that are currently in abstract form, and input from VHA thought leaders involved in the care of Veterans with HCV infection.

Limitations: There are important limitations in the design of most studies of direct acting antiviral (DAA) agents in the treatment of hepatitis C. These limitations include: 1) small sample sizes, with resultant wide confidence intervals for sustained virologic response (SVR); 2) inclusion of few patients with cirrhosis, especially advanced cirrhosis; 3) lack of a control arm in most studies; 4) lack of head-to-head trials of DAA regimens; 5) many studies were open-label and no studies were double blinded; 6) most trials excluded 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 use; 7) studies do not yet have follow up data to report on long-term virologic and clinical outcomes from DAAs. Finally, much of the existing data is from abstracts and not published in peer-reviewed publications. With the limitations mentioned above, the committee weighs the strength and weaknesses of the existing data, recognizes there are gaps in the evidence, yet often needs to make decisions based on suboptimal data. The content in the document will change as new data become available. Some of the limitations of studies are noted in the "Comments" column in the tables. Overall, caution about the application of preliminary data should be exercised until detailed complete results 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 U.S. Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* (Table 1). Each panel member participated in the preparation and review of the draft recommendations and the committee approved, with the consensus statements reflected in the final document. The final recommendations were reviewed and endorsed by the VHA Office of Public Health. Additional resources pertaining to the care of the HCV-infected patient are available at www.hepatitis.va.gov.

Table 1. Grading System

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

Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Department of Health and Human Services. Available at aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Page A-3, Table 2. Accessed March 25, 2014.

Clinical benefit of achieving SVR (i.e., cure): SVR, defined as undetectable HCV RNA levels 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 SVR12 and SVR24, respectively) with reported positive and negative predictive values upward of 98% in boceprevir- and telaprevir-based studies. The agreement between SVR12 and SVR24 is related to the timing of virologic relapse and the finding that ≥98% of relapses occur within the first 12 weeks after treatment cessation. Based on these data, the FDA now recommends SVR at 12 weeks after completion of treatment as the primary endpoint for HCV clinical trials.[1,2,3]

Achieving an SVR with peginterferon/ribavirin treatment improves clinical outcomes, such as improving blood tests of liver function, lowering the risk of progressing to decompensated cirrhosis or HCC, and prolonging life. 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. Thus, there is compelling evidence that curing patients, including patients with cirrhosis, of HCV infection has clinically meaningful improvements in liver function and overall health.

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 with cirrhosis, and patients with serious extra-hepatic manifestations of HCV. Patients with mild liver disease (METAVIR F0-2) may consider waiting for additional FDA-approved, interferon-free regimens that are expected to attain high SVR with low adverse effect profile. Approval of such regimens is anticipated over the next 12 to 24 months. Decisions regarding deferral of treatment also should take into account the lack of data regarding the real-world safety and effectiveness of recently approved DAAs.

Patient adherence: Evaluating a patient's adherence to medical recommendations and the prescribed regimen is crucial to the patient selection process. Factors that may complicate adherence, such as active substance abuse, 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	Consider waiting until better treatments are available. Future treatments are likely to have fewer side effects, shorter duration, higher efficacy, and lower pill burden.	B-III
Compensated cirrhosis	Treatment is recommended for appropriate patients with compensated cirrhosis. Refer to Table 13, "Diagnosis of Compensated Cirrhosis for the Purpose of Identifying Treatment Candidates," for guidance on diagnosis of cirrhosis.	B-III
Decompensated cirrhosis, defined by one of the following: CTP score ≥7, ascites, hepatic encephalopathy, variceal bleeding or jaundice	Treatment options are limited and the risk versus benefits of treatment must be carefully considered. 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 with cirrhosis	Risk versus benefits of treatment must be carefully considered. Consult a specialist with experience in management of HCV.	A-II
Patients with serious extra-hepatic manifestations of HCV	Patients with serious extra-hepatic manifestations of HCV, such as leukocytoclastic vasculitis, membranoproliferative glomerulonephritis, or symptomatic cryoglobulinemia despite mild liver disease should receive treatment as soon as possible. Consult a specialist with experience in management of HCV.	A-III

CTP = Child-Turcotte-Pugh

Deciding when a patient should wait for future treatment: Deferral of HCV treatment may be considered in some patients until newer therapies are available that might further optimize the chance of treatment success and reduce the potential for treatment-related adverse effects (Table 3). Such patients include those without cirrhosis. Patients who have cirrhosis generally are recommended for treatment sooner rather than later, to reduce their risk of decompensation or development of HCC.

Table 3. Factors to Consider in Deciding to Treat Chronic HCV or Wait for Availability of Newer Therapies

Factor	Comment
Stage of liver fibrosis	Patients with mild liver fibrosis (METAVIR F0 – F2) are unlikely to develop decompensated liver disease in the subsequent few years and might benefit from waiting for approval of additional safe and effective interferon-free regimens.
Intolerance or contraindications to interferon	Future interferon-free regimens are expected to have fewer adverse events, be less complex to administer, and have high SVR rates. Interferon-free regimens are expected to receive FDA approval in late 2014.
Intolerance or contraindication to ribavirin	Ribavirin-free regimens have achieved high SVR rates in Phase II and Phase III trials and may be approved by the FDA in late 2014 for treatment of HCV genotype 1 infection.
Adherence	Future treatments may be less complex (e.g., one or a few pills per day), potentially increasing adherence.
Treatment duration	Future treatment duration is likely to be 12 weeks or less for most patients.
SVR	Future therapies may result in higher SVR rates in select groups (e.g., cirrhotics, patients who failed boceprevir- or telaprevir-based therapy).
Lack of adequate data	Key groups (e.g., patients who have failed boceprevir- or telaprevir-based therapy, decompensated cirrhotics) have not been well studied, and SVR rates in selected patient groups are based on modeling.

Future treatments: Multiple new drugs are being tested in patients with HCV, and preliminary evidence from several Phase II and III trials suggest excellent efficacy (>90% SVR for all genotypes), excellent safety profile, and interferon-free regimens for all genotypes. Thus, a variety of treatment options are expected to become available for HCV patients in the foreseeable future. When new drugs gain adequate evidence and/or receive FDA approval, preferred treatment regimens may change. The contents of this documentwill be updated as new treatments become available. Informing Veterans that a variety of highly effective, well-tolerated, interferon-free treatments with short treatment durations will be available relatively soon should be a priority.

Patient identification: A population health-based approach for selection of patients for treatment should be considered. The HCV Clinical Case Registry (CCR) (vaww.vistau.med.va.gov/VistaU/ccr/default.htm) is available at each VA facility and is accessible to selected clinicians by request. Using the CCR, providers can generate facility specific reports on the numbers and names of patients with HCV stratified by cirrhosis (determined fibrosis markers such as by platelet count, FIB-4, APRI), 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 in urgent need of treatment.

Pre-treatment evaluation: Before initiating antiviral therapy in a patient with chronic HCV, the information listed in Table 4 should be assessed.

Table 4. Pre-Treatment Evaluation

Essential pre-treatment information*
• HCV genotype (including subtype, e.g. 1a or 1b) - Q80K polymorphism IF genotype 1a AND considering simeprevir/peginterferon/ribavirin therapy • Clinical assessment of cirrhosis or no-cirrhosis • If cirrhotic, exclusion of hepatocellular carcinoma based on imaging study within the past 6 months • Previous HCV treatment history and outcome • Interferon eligibility (see Table 5 below) • HIV status and if HIV +, current antiretroviral regimen and degree of viral suppression • Documented use of 2 forms of birth control in patient and sexual 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)

Interferon eligibility: Although clinical trial data for new HCV treatment regimens that include both peginterferon and ribavirin are more robust, some patients are not able to tolerate interferon or are ineligible and should be considered for treatment with an interferon-free regimen. The following criteria should be used to determine whether a patient is considered to be interferon ineligible or intolerant (Table 5).

Table 5. Interferon Ineligible or Intolerant Criteria

• Platelet count <75,000/mm^3 • Decompensated liver cirrhosis (Child-Turcotte-Pugh Class B or C, CTP score ≥7) • Severe mental health conditions that may be exacerbated by interferon or respond poorly to medical therapy (with risks of interferon use documented by Mental Health evaluation) • Autoimmune diseases that may be exacerbated by interferon-mediated immune modulation • Inability to complete a prior treatment course due to documented interferon-related adverse effects

III. Chronic HCV Genotype 1 Infection

Table 6. Genotype 1, Interferon Eligible: Preferred Regimens and SVR Rates from Supporting Data

Regimens with optimal efficacy, favorable tolerability and toxicity profile, and ease of use.

Treatment Considerations					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	Sofosbuvir + PEG-IFN + RBV	12 weeks	A-II	89% (261/292)[a] Stratified by GT: GT1a: 92% (206/225)[a] GT1b: 82% (54/66)[a] (represents non-cirrhotic and cirrhotic patients; 1 patient had GT 1a/1b)	Reasonable to defer for future treatment if no significant extra-hepatic disease.
	Cirrhotic	Sofosbuvir + PEG-IFN + RBV	12 weeks	A-II	80% (43/54)[a]	SVR in cirrhotics was not stratified by GT1a and GT1b.
Experienced GT1a or 1b	Non-cirrhotic	Sofosbuvir + PEG-IFN + RBV	12 weeks	A-III	No data; estimated to be 71%-78%[b]	Reasonable to defer for future treatment if no significant extra-hepatic disease. **SVR estimates based on FDA modeling in treatment-naïve patients with poor predictors.**
	Cirrhotic	Sofosbuvir + PEG-IFN + RBV	12 weeks	A-III	No data; estimated to be 71%[b]	**SVR estimates based on FDA modeling in treatment-naïve patients with poor predictors.**

[a] NEUTRINO[4]

[b] www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204671Orig1s000SumR.pdf;

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 1, Interferon Ineligible or Intolerant*: Preferred Regimens and SVR Rates from Supporting Data

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.

Treatment Considerations					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	Sofosbuvir + RBV	24 weeks	B-I	24-week duration: 53% (10/19)[a] 90% (9/10)[b] 12-week duration: 47% (9/19)[a] 84% (21/25)[c]	Reasonable to defer for future treatment if no significant extra-hepatic disease, especially in GT1b-infected patients. The largest clinical trial to date of sofosbuvir/ribavirin therapy was conducted in 114 patients with HIV/HCV coinfection. Among GT1b-infected patients with HIV/HCV coinfection, SVR was achieved in 54% (13/24) as compared with 82% (74/90) with GT1a infection.[d] There is wide variability in SVR rates (53-90% with 24 weeks of treatment) based on small studies in HCV-monoinfected patients.[a,b,c]
		Sofosbuvir + Simeprevir ± RBV **NOT FDA approved**	12 weeks	B-III	Data not available	Reasonable to defer treatment if no significant extra-hepatic disease. Preferred regimen based on data in treatment-naïve METAVIR F3/F4 patients, in which 100% (19/19) of patients achieved SVR4.[e] GT1a: Q80K polymorphism may theoretically increase risk of relapse and thus, reduce achievement of SVR.

Treatment Considerations					Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	**Comments**
	Cirrhotic	Sofosbuvir + Simeprevir ± RBV **NOT FDA approved**	12 weeks	B-II	SVR4: 100% (12/12, +RBV)[e] [95% CI: 74-100] SVR4: 100% (7/7, -RBV)[e] [95% CI: 59-100] With Q80K polymorphism: SVR4: 91% (10/11)[e] (includes treatment-naïve and treatment-experienced patients) [95% CI: 59-100]	Small sample size, preliminary data. **DO NOT USE sofosbuvir + ribavirin in cirrhotics due to insufficient data.**
Experienced GT1a or 1b	Non-cirrhotic	Sofosbuvir + Simeprevir ± RBV **NOT FDA approved**	12 weeks	B-II	96% (26/27, +RBV)[e] [95% CI: 81-100] 93% (13/14, -RBV)[e] [95% CI: 66-100] Null responders with Q80K polymorphism: 89% (24/27)[e] [95% CI: 71-98]	Small sample size. Reasonable to defer for future treatment if no significant extrahepatic disease. **DO NOT USE sofosbuvir + ribavirin in treatment-experienced patients due to insufficient data**
	Cirrhotic	Sofosbuvir + Simeprevir ± RBV **NOT FDA approved**	12 weeks	B-II	SVR4: 93% (14/15, +RBV)[e] [95% CI: 68-100] SVR4: 100% (7/7, -RBV)[e] [95% CI: 59-100] With Q80K polymorphism: SVR4: 91% (10/11)[e] (includes treatment-naïve and treatment-experienced patients) [95% CI: 59-100]	Small sample size, preliminary data. Preferred regimen based on data in null responders with METAVIR F3/F4. **DO NOT USE sofosbuvir + ribavirin in treatment-experienced patients due to insufficient data.**

SVR4 = undetectable HCV RNA levels at 4 weeks posttreatment; 95% CI: 95% confidence interval for binomial proportion
[a] QUANTUM[11], [b] NIH-SPARE[10], [c] ELECTRON[12], [d] PHOTON-1[9], [e] COSMOS[8]; RBV = 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. Sofosbuvir or simeprevir should not be used as monotherapy or in reduced dosages; neither drug should be restarted if discontinued.
***Interferon ineligible or intolerant criteria:** See Table 5.

Table 8. Genotype 1, Interferon Eligible: Alternative Regimens and SVR Rates from Supporting Data

Regimens may be effective and tolerable, but have potential disadvantages when compared with preferred regimens. SVR rates cannot be compared between trials.

Treatment Considerations				Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**	**Evidence grade**	**SVR% (N/N)**	**Comments**
Naïve GT1a *without Q80K* Or GT1b	Non-cirrhotic	Simeprevir x 12 weeks + PEG-IFN/RBV x 24 weeks	B-I	84% (317/378)[a] Stratified by GT: GT1a: w/o Q80K: 84% (138/165)[a] with Q80K: 58% (49/84)[a] GT1b: 85% (228/267)[a]	Reasonable to defer for future treatment if no significant extrahepatic disease. *Screen for Q80K polymorphism prior to treatment.* **DO NOT USE simeprevir/PEG-IFN/RBV in GT1a patients who have the Q80K polymorphism.**
	Cirrhotic	Simeprevir x 12 weeks + PEG-IFN/RBV x 24 weeks	C-I	68% (89/130)[a] F3: 73% (60/82)[a] F4: 60% (29/48)[a]	*Screen for Q80K polymorphism prior to treatment.* **DO NOT USE simeprevir/PEG-IFN/RBV in GT1a patients who have the Q80K polymorphism.**
Experienced GT1a *without Q80K* Or GT1b	Non-cirrhotic	***PEG-IFN/RBV Relapsers:*** Simeprevir x 12 weeks + PEG-IFN/ RBV x 24 weeks ***PEG-IFN/RBV Partial and Null Responders:*** Simeprevir x 12 weeks + PEG-IFN/ RBV x 48 weeks	B-I	Relapsers: 82% (137/167)[b] Partial Responders: 65% (15/23)[c] GT1a: 56% (14/25) GT1b: 88% (38/43) Nulls: 53% (9/17)[c] GT1a:42% (11/26) GT1b: 58% (14/24)	Reasonable to defer for future treatment if no significant extrahepatic disease, or if **PEG-IFN/RBV partial or null responder.** *Screen for Q80K polymorphism prior to treatment.* **DO NOT USE simeprevir/PEG-IFN/RBV in GT1a patients who have the Q80K polymorphism.** **DO NOT USE if *previously failed a boceprevir- or telaprevir-based regimen.***
	Cirrhotic	***PEG-IFN/RBV Relapsers:***	B-I	Relapsers: 74% (29/39)[b]	*Screen for Q80K polymorphism prior to*

Treatment Considerations				Supporting Information	
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**	**Evidence grade**	**SVR% (N/N)**	**Comments**
		Simeprevir x 12 weeks + PEG-IFN/RBV x 24 weeks ***PEG-IFN/RBV Partial and Null Responders:*** Simeprevir x 12 weeks + PEG-IFN/RBV x 48 weeks		Partial Responders: 82% (9/11)[c] Nulls: 31% (4/13)[c]	*treatment.* **DO NOT USE simeprevir/PEG-IFN/RBV in GT1a patients who have the Q80K polymorphism.** **DO NOT USE in cirrhotic null responders OR in patients who have previously failed a boceprevir- or telaprevir-based regimen.**
	Cirrhotic	***PEG-IFN/RBV Null Responders:*** Sofosbuvir + Simeprevir ± RBV x 12 weeks **NOT FDA approved**	B-II	SVR4: 93% (14/15,+RBV)[d] [95% CI: 68-100] SVR4: 100% (7/7, –RBV)[d] [95% CI: 59-100] Null responders with Q80K polymorphism: SVR4: SVR 91% (10/11)[d] [95% CI: 69-100]	Small sample size, preliminary data. Preferred regimen based on data in null responders with METAVIR F3/F4.

95% CI: 95% confidence interval for binomial proportion; [a] QUEST 1 & 2[5], [b] PROMISE[6], [c] ASPIRE[7], [d] COSMOS[8]; 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; Simeprevir 150 mg orally daily with food. Simeprevir should not be used as monotherapy or in reduced dosages; it should not 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).

Interferon-Containing Regimens in Genotype 1 – Sofosbuvir

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 is FDA approved for treatment-naïve and treatment-experienced patients with chronic HCV genotype 1 or 4 infection. (See Table 6.)

The high SVR rates demonstrated or expected (based on FDA modeling) in the GT1 population irrespective of baseline characteristics, ease of use, and short treatment duration provide sufficient evidence to recommend sofosbuvir/peginterferon/ribavirin for 12 weeks as the preferred treatment regimen for HCV GT1 infection.

Sofosbuvir has been evaluated in a Phase III, open-label, single-arm clinical trial of monoinfected, treatment-naïve GT1-infected patients in combination with peginterferon and ribavirin for 12 weeks (NEUTRINO, n=327). No comparator arm with only peginterferon plus ribavirin was included in this study; rather, superiority of the sofosbuvir regimen was determined from historical response rates. SVR rates were 92% for GT1a, 82% for GT1b, 92% in those without cirrhosis, 80% in those with cirrhosis, 87% in blacks, 91% in non-blacks, 98% in those with IL28B CC, and 87% in those with IL28B non-CC alleles.[4] In those with multiple baseline factors traditionally associated with a lower treatment response (METAVIR F3/F4 fibrosis, IL28B non-CC, and HCV RNA >800,000IU/mL), SVR rates were 71%. Clinical trials of sofosbuvir were not conducted in treatment-experienced GT1-infected patients. Nevertheless, the FDA approved sofosbuvir/peginterferon/ribavirin for 12 weeks for treatment-experienced patients based on modeling that suggested an SVR rate of 71-78% in this group (www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204671Orig1s000SumR.pdf).

The 12-week treatment duration for sofosbuvir/peginterferon/ribavirin is significantly shorter than that for other regimens available at this time, and it is expected to be better tolerated with a more favorable adherence profile. Furthermore, sofosbuvir is associated with fewer side effects and fewer drug interactions, though DAAs have not been compared head-to-head in any clinical trials at this time. Sofosbuvir also is active against NS3/4A protease inhibitor-, NS5B non-nucleoside inhibitor- and NS5A inhibitor-resistant variants.

Interferon-Containing Regimens in Genotype 1 – Simeprevir

Simeprevir (150 mg/day with food) for 12 weeks in combination with peginterferon/ribavirin (1,000 mg/day if <75 kg and 1,200 mg/day if ≥75 kg with food, in divided doses) for 24 weeks is FDA approved for treatment-naïve patients and treatment-experienced relapsers with chronic HCV genotype 1 infection. (See Table 8.)

Simeprevir (150 mg/day with food) for 12 weeks in combination with peginterferon/ribavirin for 48 weeks is FDA approved for treatment-experienced partial and null responders with chronic HCV genotype 1 infection. (See Table 8.)

Simeprevir is an acceptable alternative treatment for GT1-infected patients without the baseline Q80K polymorphism in the HCV NS3/4a polymerase. From clinical studies with simeprevir plus peginterferon/ribavirin, 48% of U.S.-enrolled patients with GT1a harbored the Q80K polymorphism at baseline, which was associated with reduced SVR rates in these patients. Screening for the Q80K polymorphism prior to treatment is strongly recommended for patients infected with GT1a, and simeprevir plus peginterferon/ribavirin therapy should not be used in those with the Q80K polymorphism. For patients who will receive simeprevir/sofosbuvir therapy, Q80K polymorphism testing prior to treatment is strongly recommended but not required.

Simeprevir has been evaluated in clinical trials of treatment-naïve patients and treatment-experienced patients (relapsers and partial and null responders to peginterferon/ribavirin). In treatment-naïve patients, SVR rates were higher with simeprevir/peginterferon/ribavirin in those with GT1b versus GT1a

(85% vs 75%), IL28b CC versus CT or TT (95% vs 78% or 61%, respectively), and non-cirrhotics versus cirrhotics (84% vs 60-65%, respectively). SVR rates were lower in GT1a-infected patients who had the Q80K polymorphism at baseline compared with those without it (58% and 84%, respectively).[5] Among peginterferon/ribavirin relapsers, SVR rates with simeprevir-based therapy were 82% in those with METAVIR F0-2 (compared with 41% in those receiving peginterferon/ribavirin) and 73% with METAVIR F3-4 (compared with 41% and 24% in those receiving peginterferon/ribavirin, respectively).[6] Among peginterferon/ribavirin partial responders receiving simeprevir plus peginterferon/ribavirin for 12 weeks followed by peginterferon/ribavirin for an additional 36 weeks, the SVR rate was 65% (15/23). The SVR rates from pooled simeprevir duration groups in partial responders with GT1a and GT1b subtypes were 56% (14/25) and 88% (38/43), respectively. Simpeprevir-based therapy in cirrhotic, peginterferon/ribavirin partial responders achieved an SVR in 82% (9/11). In peginterferon/ribavirin null responders receiving simeprevir plus peginterferon/ribavirin for 12 weeks followed by peginterferon and ribavirin for an additional 36 weeks, the SVR rate was 53% (9/17). The SVR rates from pooled simeprevir duration groups in null responders with GT1a and GT1b subtypes were 42% (11/26) and 58% (14/24), respectively. Simeprevir-based therapy in cirrhotic, peginterferon/ribavirin null responders attained SVR in 31% (4/13).[7]

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).

The pharmacology (drug-drug interactions, food requirement), resistance profile, and more complicated regimen, which involves a longer duration of peginterferon/ribavirin treatment (24-48 weeks depending on baseline patient characteristics), makes this regimen more complicated and less desirable.

Interferon-Free Regimens in Genotype 1 – Sofosbuvir/Simeprevir and Sofosbuvir/Ribavirin

Based on limited data with sofosbuvir/simeprevir, and lower SVR rates with sofosbuvir/ribavirin, an interferon-free regimen should be used only to urgently treat Veterans with documented interferon ineligibility or intolerance in whom delaying therapy would have a high likelihood of resulting in morbidity and mortality. (See Table 7.)

Based on preliminary data, sofosbuvir/simeprevir may be considered as the preferred regimen in GT1-infected patients who are interferon ineligible or intolerant and as an alternative regimen in interferon eligible, cirrhotic null responders to prior peginterferon/ribavirin. This combination currently is not approved by the FDA.

Sofosbuvir/Simeprevir

The combination of sofosbuvir/simeprevir ± ribavirin has been evaluated in a limited population of GT1-infected patients in an ongoing open-label, Phase IIa trial (COSMOS); data from COSMOS have not been audited or reviewed by FDA. In 41 null responders with METAVIR F0-F2, SVR rates were 96% and 93% with 12 weeks of sofosbuvir/simeprevir with and without ribavirin, respectively. In patients with METAVIR F3-F4, SVR4 rates in 22 null responders were 93% and 100% with 12 weeks of sofosbuvir/simeprevir with and without ribavirin, respectively, and the SVR4 rate in 19 treatment-naïve patients was 100%. All relapses occurred in patients with GT1a and the Q80K polymorphism; relapse occurred in 3 null responders with METAVIR F0-F2 and 1 patient in the cohort with METAVIR F3/F4.[8]

Sofosbuvir/Ribavirin

FDA labeling identifies sofosbuvir/ribavirin (without peginterferon) for 24 weeks as a potential consideration for GT1-infected patients who are ineligible to receive an interferon-based regimen; however, limited data exist for GT1 treatment-experienced patients and those with cirrhosis. SVR rates for this regimen were extrapolated from several clinical trials. The largest trial of sofosbuvir/ribavirin was a Phase III study (PHOTON-1) of 114 treatment-naïve, GT1-infected patients with HIV/HCV coinfection. SVR rates were 82% in those with GT1a, 54% in those with GT1b, 80% in those with IL28B CC, and 75% in those with IL28B non-CC alleles. Relapse accounted for the majority of treatment failures. Of note, only 4% of GT1-infected patients in PHOTON-1 had cirrhosis.[9] In a small National Institutes of Health study of an inner-city population consisting of 10 treatment-naïve GT1-infected patients without cirrhosis who received sofosbuvir and weight-based ribavirin for 24 weeks, SVR was achieved in 90% (9/10); in the same study, among 25 treatment-naïve patients with unfavorable traditional predictors of treatment response and any stage of liver fibrosis, SVR was achieved in 68% (17/25; 1 patient dropped out at week 3 of treatment).[10] Another small study of mostly white, IL28B-CC, treatment-naïve patients without cirrhosis and normal body mass index, SVR was achieved in 84% (21/25) with a 12-week sofosbuvir/ribavirin regimen. An evaluation of a 12- and 24-week sofosbuvir/ribavirin regimen in 50 mostly non-CC, treatment-naïve patients of mixed ethnicity reported SVR rates of 56% (14/25) and 52% (13/25), respectively.[11] The only available data for sofosbuvir/ribavirin in treatment-experienced patients are from 10 null responders who were treated for 12 weeks in a comparator arm of the ELECTRON trial, which reported an SVR of 10% (1/10).[12] Based on modest SVR rates along with the lack of data in cirrhotics and treatment-experienced patients in these studies, sofosbuvir/ribavirin use is not recommended for cirrhotics and treatment-experienced patients.

Genotype 1-Infected Patients Who Failed Treatment with a Boceprevir- or Telaprevir-Based Regimen

There are insufficient data on the use of sofosbuvir- or simeprevir-based therapy in patients who have failed treatment with boceprevir- or telaprevir-based therapy. Due to concerns of potential cross-resistance, a simeprevir-based regimen should be avoided in patients who have previously failed a boceprevir- or telaprevir-based regimen due to lack of virologic response.

IV. Chronic HCV Genotype 2 Infection

Table 9. Genotype 2: Preferred Regimens in HCV Monoinfection and HIV/HCV Coinfection, and SVR Rates from Supporting Data

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

Treatment Considerations					Supporting Information	Comments
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR (N/N)**	
Naïve GT2	Non-cirrhotic	Sofosbuvir + RBV	12 weeks	A-I	97% (59/61)[a] 92% (85/92)[b] 97% (29/30)[c]	Reasonable to defer for future treatment if no significant extrahepatic disease.
	Cirrhotic	Sofosbuvir + RBV	12 weeks	A-II	83% (10/12)[a] 94% (16/17)[b] 100% (2/2)[c]	
Experienced GT2	Non-cirrhotic	Sofosbuvir + RBV	12 weeks	A-II	91% (30/33)[c] Relapsers: 86% (25/29)[d] Nonresponders: 70% (7/10)[d]	Reasonable to defer for future treatment if no significant extrahepatic disease.
			16 weeks	B-II	Relapsers: 89% (24/27)[d] Nonresponders: 88% (7/8)[d]	**NOT FDA approved**
		Sofosbuvir + PEG-IFN + RBV **NOT FDA approved**	12 weeks	B-II	100% (9/9)[f]	If interferon eligible
	Cirrhotic	Sofosbuvir + RBV	12 weeks	A-II	88% (7/8)[c] 60% (6/10)[d]	
			16 weeks	B-II	78% (7/9)[d]	**NOT FDA approved**
		Sofosbuvir + PEG-IFN + RBV **NOT FDA approved**	12 weeks	B-II	93% (13/14)[e]	If interferon eligible
Naïve or Experienced GT2 HIV/HCV Co-infection	Non-cirrhotic or Cirrhotic	Sofosbuvir + RBV	12 weeks	A-I	88% (23/26)[f]	Reasonable to defer for future treatment if non-cirrhotic and no

Treatment Considerations					Supporting Information	Comments
Treatment history and HCV genotype (GT)	Cirrhosis status	Regimen and duration		Evidence grade	SVR (N/N)	
						significant extrahepatic disease. In treatment-experienced patients, sofosbuvir/ribavirin x 12-16 weeks or sofosbuvir/PEG-IFN/RBV x 12 weeks (not FDA-approved) is preferred based on SVR rates in HCV-monoinfected patients.

[a] FISSION[4], [b] POSITRON[16], [c] VALENCE[15], [d] FUSION[16], [e] LONESTAR-2[13], [f] PHOTON-1[9]; 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 10. Genotype 2: Alternative Regimens in HCV Monoinfection and HIV/HCV Coinfection, and SVR Rates from Supporting Data

Regimens may be effective and tolerable, but have potential disadvantages when compared with preferred regimens. SVR rates cannot be compared between trials.

Treatment Considerations					Supporting Information
Treatment history and HCV genotype (GT)	Cirrhosis status	Regimen and duration		Evidence grade	SVR (N/N)
Naïve GT2	Non-cirrhotic	Peginterferon + RBV	24 weeks	B-I	82%[a]

[a] Ghany et al. [14]; 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 in Genotype 2

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 is FDA approved for treatment-naïve and treatment-experienced patients with chronic HCV genotype 2 infection. (See Table 9.)

The preferred treatment regimen for chronic HCV GT2 infection is supported by the results of four Phase III studies.[4,15,16] 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 non-cirrhotics and 88% (7/8) of cirrhotics with sofosbuvir/ribavirin treatment for 12 weeks.[15] In the FUSION study, a statistically insignificant increase in SVR rates was seen with extending sofosbuvir/ribavirin therapy from 12 to 16 weeks in prior nonresponders without cirrhosis (70% [7/10] vs. 88% [7/8], respectively) and in treatment-experienced cirrhotics (60% [6/10] vs. 78% [7/9], respectively).[16] Based on results from this small study, sofosbuvir and ribavirin 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 non-cirrhotics and cirrhotics from the LONESTAR-2 study, SVR was achieved in 100% (9/9) and 93% (13/14), respectively, with the addition of peginterferon to sofosbuvir/ribavirin therapy for 12 weeks.[13] This regimen is not FDA approved.

Among treatment-naïve, non-cirrhotic and interferon-tolerant populations, an alternative regimen for treatment of HCV GT2 is peginterferon and ribavirin 800 mg daily for 24 weeks.[14] Pretreatment characteristics of GT2 patients who achieve a high rate of SVR (>75%) with this regimen include a low baseline HCV RNA (≤800,000 IU/mL) and absence of bridging fibrosis or cirrhosis, absence of prior treatment failure, and absence of other factors related to poor interferon responsiveness (e.g., African American ethnicity, obesity, IL28 non-CC genotype).[14] Use of weight-based ribavirin (i.e., 1,000 mg if <75 kg or 1,200 mg if ≥75 kg daily) may improve treatment outcomes or allow for a shorter treatment duration.

V. Chronic HCV Genotype 3 Infection

Table 11. Genotype 3: Preferred Regimens in HCV Monoinfection and HIV/HCV Coinfection, and SVR Rates from Supporting Data

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

Treatment Considerations					Supporting Information	Comments
Treatment history and HCV genotype (GT)	Cirrhosis status	Regimen and duration		Evidence grade	SVR% (N/N)	
Naïve GT3	Non-cirrhotic	Sofosbuvir + RBV	24 weeks	A-I	94% (86/92)[a]	Reasonable to defer for future treatment if no significant extrahepatic disease.

Treatment Considerations					Supporting Information	Comments
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	
	Cirrhotic	Sofosbuvir + RBV	24 weeks	A-I	92% (12/13)[a]	
Experienced GT3	Non-cirrhotic	Sofosbuvir + RBV	24 weeks	A-I	87% (87/100)[a]	Reasonable to defer for future treatment if no significant extrahepatic disease.
	Cirrhotic, Interferon-eligible	Sofosbuvir + PEG-IFN + RBV **NOT FDA approved**	12 weeks	A-II	83% (10/12)[b]	
	Cirrhotic, Interferon ineligible or intolerant*	Sofosbuvir + RBV	24 weeks	A-I	60% (27/45)[a]	
Naïve or Experienced GT3 HIV/HCV Coinfection	Non-cirrhotic or Cirrhotic	Sofosbuvir + RBV	24 weeks	A-II	92% (12/13) [c]	Reasonable to defer for future treatment if non-cirrhotic and no significant extrahepatic disease. In treatment-experienced cirrhotics who are IFN eligible, sofosbuvir/PEG-IFN/RBV x 12 weeks (not FDA approved) is preferred based on SVR rates in HCV-monoinfected patients.

[a] VALENCE[15], [b] LONESTAR-2[13], [c] PHOTON-1[9]; 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.

***Interferon ineligible or intolerant criteria:** See Table 5.

Table 12. Genotype 3: Alternative Regimens in HCV Monoinfection and HIV/HCV Coinfection (Interferon-Eligible Patients), and SVR Rates from Supporting Data

Regimens may be effective and tolerable, but have potential disadvantages when compared with preferred regimens. SVR rates cannot be compared between trials.

Treatment Considerations					Supporting Information	Comments
Treatment history and HCV genotype (GT)	**Cirrhosis status**	**Regimen and duration**		**Evidence grade**	**SVR% (N/N)**	
Naïve GT3	Non-cirrhotic	Sofosbuvir + PEG-IFN + RBV **NOT FDA approved**	12 weeks	A-II	92% (23/25)[a]; represents combined GT2 and GT3 data	Reasonable to defer for future treatment if no significant extrahepatic disease.
	Cirrhotic	Sofosbuvir + PEG-IFN + RBV **NOT FDA approved**	12 weeks	A-III	Data not available	
Experienced GT3	Non-cirrhotic	Sofosbuvir + PEG-IFN + RBV **NOT FDA approved**	12 weeks	A-II	83% (10/12)[b]	Reasonable to defer for future treatment if no significant extrahepatic disease.

[a] PROTON[17], [b] LONESTAR-2[13]; 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.

Sofosbuvir for Genotype 3

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 is FDA approved for treatment-naïve and treatment-experienced patients with chronic HCV genotype 3 infection.

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). In treatment-naïve patients, SVR was achieved in 94% (86/92) of non-cirrhotics and 92% (12/13) of cirrhotics. In treatment-experienced patients, SVR was attained in 87% (87/100) of non-cirrhotics and 60% (27/45) of cirrhotics.[15] In other studies, shorter treatment duration (12-16 weeks) with sofosbuvir and ribavirin resulted in lower SVR rates (21-68%).[4,9,16]

A Phase II, open-label study (PROTON) with sofosbuvir, peginterferon, and ribavirin for 12 weeks in treatment-naïve, non-cirrhotic patients achieved SVR in 92%; however, these results represent combined GT2 and GT3 data.[17] 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 non-cirrhotics and 83% (10/12) of cirrhotics.[13] This regimen is not FDA approved.

VI. Identifying Treatment Candidates Based on Liver Disease Stage

HCV is a slowly progressive disease, usually requiring more than 20-40 years to progress to cirrhosis, but it may progress sooner in some patients, particularly among those who drink alcohol regularly. In non-cirrhotic patients, the short-term risk of developing a liver-related complication is low. Once a patient develops advanced cirrhosis, there is a higher likelihood of developing decompensated cirrhosis, including HCC, although the actual risk remains modest (<5% per year). Achieving SVR among patients with compensated cirrhosis reduces the risk of developing decompensated cirrhosis or HCC.

Patients with decompensated cirrhosis (Child-Turcotte-Pugh Class B or C; CTP score ≥7) have increased mortality, with median survival of 24 months or less. However, treatment options are limited for patients with decompensated cirrhosis. Treatment risks with interferon include infection and worsening hepatic function. The safety and efficacy data for sofosbuvir-based regimens among patients with decompensated cirrhosis are lacking. Since peginterferon is not recommended and no dosage recommendation can be given for simeprevir (if its use in combination with sofosbuvir were considered) in patients with decompensated cirrhosis, at the present time, the decision to treat and treatment follow-up of patients with decompensated cirrhosis should be made by an experienced and knowledgeable specialist.

Table 13. Diagnosis of Compensated Cirrhosis for the Purpose of Identifying Treatment Candidates

Method	Comment
Clinical Findings	• Physical exam findings (palpable left lobe, splenomegaly, palmar erythema) AND • Low platelet count (<100,000/mm^3)* AND • Abdominal imaging findings (see below)
Abdominal Imaging • Ultrasound • Computed tomography (CT) • Magnetic resonance imaging (MRI)	• Surface abnormalities (e.g., nodularity, and left lobe/caudate lobe hypertrophy) are suggestive of cirrhosis. • Features of portal hypertension (e.g., splenomegaly, recanalization of umbilical vein, collaterals) and ascites also are suggestive of cirrhosis.
Liver Fibrosis Imaging • Vibration-controlled transient elastography (Fibroscan®) • Acoustic radiation force impulse imaging (ARFI)	• Both elastography and ARFI are FDA-approved, ultrasound-based techniques for estimating the extent of liver fibrosis. • Fibroscan value of >12.5 kilopascals has been associated with histologic cirrhosis. • ARFI value of >1.75 meters/second has been associated with histologic cirrhosis.
Serum Markers of Fibrosis/Cirrhosis • APRI	• APRI and FIB-4 scores are easily calculated using standard clinical labs. • APRI >1.5 has been associated with advanced fibrosis (METAVIR F3);

Method	Comment
• FIB-4 • HALT-C cirrhosis score • Fibrosure, Fibrotest, Fibrospect	APRI >2.0 has been associated with cirrhosis (METAVIR F4) in the setting of chronic HCV infection. • FIB-4 >3.25 has been associated with advanced fibrosis (METAVIR F3-F4) in the setting of chronic HCV infection. • HALT-C cirrhosis score predicts likelihood of having cirrhosis based on standard clinical data. • Fibrosure, Fibrotest, and Fibrospect are proprietary, costly serum fibrosis assays that are not recommended for routine use in the diagnosis of cirrhosis.
Liver Biopsy	• Liver biopsy may be considered, but it is invasive and limited by potential sampling error. • METAVIR or Batts-Ludwig stage 4 fibrosis (on a scale from 0 to 4) or Ishak stage 5 or 6 fibrosis (on a scale from 0 to 6) confirms the diagnosis of cirrhosis.

Abbreviations: APRI = [(AST/upper limit of normal AST) x 100]/platelet count (10^9/L); FIB-4 = [Age (years) x AST]/platelet count (10^9/L) x $ALT^{1/2}$; HALT-C cirrhosis score (see www.haltctrial.org/cirrhosis.html)

* A low platelet count in the context of chronic HCV infection is predictive of histologic cirrhosis.

Diagnosis of Compensated Cirrhosis for the Purpose of Identifying Treatment Candidates (see Table 13): Noninvasive and invasive methods to determine the presence and stage of cirrhosis are continually evolving. Cirrhosis determination can be made using a histologic assessment of liver biopsy tissue. However, several limitations exist, namely, not all facilities offer this procedure, the quality of tissue is dependent upon the equipment and 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 13). Similarly, the Ghany HALT-C score (www.haltctrial.org/cirrhosis.html) uses standard clinical data to predict the likelihood of a patient having cirrhosis. A score of >0.6 (i.e., >60%) is generally considered as an indication of cirrhosis. A Lok HALT-C HCC score greater than 3.25 (www.haltctrial.org/hccform.html) is associated with increased risk of developing hepatocellular carcinoma in the subsequent 3-5 years.

Platelet counts are an additional noninvasive tool to identify cirrhotic patients with more advanced cirrhosis. In the absence of hematopoietic disorders, patients with platelet counts of <150,000/mm^3 have increased risk of developing HCC, whereas patients with platelet counts of <100,000/mm^3 have an even higher risk of developing HCC.

Imaging: Findings of nodular liver or splenomegaly (>13 cm) on imaging (e.g., ultrasound, CT scan or MRI) suggest cirrhosis. Recently, the FDA approved two specialized ultrasound-based evaluations, vibration-controlled transient elastography 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.

Hepatocellular carcinoma: The following is based on expert opinion, given that minimal data are available. Achieving an SVR is likely to improve outcome among patients in whom treatment is expected to remove/ablate the entire tumor (i.e., "curative intent") (e.g., transplant, surgical resection, and, potentially, radiofrequency ablation or TACE of small HCC). Thus, sofosbuvir/ribavirin treatment (possibly in combination with peginterferon) in these patients is reasonable, particularly for those awaiting liver transplantation and for those with a CTP score <7, given the available clinical trial data in this population and FDA labeling. 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.

VII. Laboratory Monitoring

Table 14. Discontinuing HCV Treatment Based on Lack of Virologic Response

Treatment Monitoring Considerations
• Patients receiving a sofosbuvir-based regimen should have HCV RNA assessed at week 4 of treatment; if the HCV RNA is detectable* at week 4 or at any timepoint thereafter, reassess HCV RNA in 2 weeks. If HCV RNA increases at any timepoint or if the 8-week HCV RNA is detectable*, discontinuation of all treatment should be strongly considered. (A-III) • Patients receiving a simeprevir-peginterferon-ribavirin regimen should have HCV RNA levels assessed at weeks 4, 12 and 24; if the HCV RNA is ≥25 IU/mL at any of these time points, all treatment should be discontinued. (A-I)

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

Periodic laboratory monitoring of hemoglobin, hematocrit, white blood cell count with differential, platelet count, and liver enzymes is necessary in all patients receiving HCV antiviral therapy. Consider checking laboratory tests every 2 weeks initially for the first month, and then at least monthly thereafter, depending upon patient tolerability. HCV RNA levels should be assessed at 12 weeks after the end-of-treatment to determine if SVR was achieved. HCV RNA at 24 weeks after the end-of-treatment is suggested but optional. For further guidance on laboratory monitoring, refer to the *2012 Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office* (www.hepatitis.va.gov/provider/guidelines/2012HCV-supplement.asp, Supplemental Table 1).

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.[14] 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.

If the week 4 HCV RNA is detectable while on sofosbuvir-based therapy, HCV RNA should be reassessed in 2 weeks. If the repeated HCV RNA level has increased (i.e., >1 $\log_{10}$ IU/mL from nadir) **OR** if the HCV RNA is ≥25 IU/mL at week 8 of therapy, discontinuation of all therapy should be strongly considered (adapted from NEUTRINO study criteria for treatment discontinuation[4]).

The following criteria were used in the NEUTRINO protocol to define on-treatment virologic failure (note, HCV RNA levels were checked at least every 2 weeks using an assay with an LLOQ of ≤25 IU/mL), and provide more detailed information about specific situations where discontinuation of sofosbuvir-based therapy should be strongly considered[4]:

- HCV RNA is ≥LLOQ (confirmed on at least one repeat test) after having previously had HCV RNA <LLOQ while on treatment
- >1 $\log_{10}$ IU/ml increase in HCV RNA (confirmed on at least one repeat test) from nadir while on treatment
- HCV RNA persistently ≥LLOQ through 8 weeks of treatment

VIII. Adverse Effects

Sofosbuvir[21]

The most common adverse events with sofosbuvir in combination with peginterferon and ribavirin were fatigue (59%), headache (36%), nausea (34%) and insomnia (25%). Approximately 10% of patients treated with sofosbuvir and ribavirin experienced a hemoglobin level of <10 g/dL and <1% developed a hemoglobin level of <8.5 g/dL. Neutropenia (absolute neutrophil count [ANC] <750/mm^3) and thrombocytopenia (platelet counts of <50,000/mm^3) were not observed. In studies with peginterferon, ribavirin, and sofosbuvir, 20% of patients developed a hemoglobin level of <10 g/dL and 2% developed a hemoglobin level of <8.5 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[22]

The most common adverse effects of simeprevir, peginterferon and ribavirin 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 simeprevir, peginterferon, and ribavirin 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 simeprevir 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, simeprevir should be discontinued. Consider urgent medical care and dermatological consultation if needed. Patients should be monitored until the rash has resolved.

Dyspnea
In clinical trials of simeprevir, peginterferon, and ribavirin, 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 simeprevir-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 simeprevir discontinuation. Bilirubin elevations generally were not associated with elevations in liver transaminases.

Sulfa Allergy
Simeprevir 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.

IX. Proper Use

Drug-Drug Interactions[21,22]
Sofosbuvir is not metabolized by the cytochrome P450 (CYP) system of enzymes but is a substrate of P-glycoprotein (P-gp); P-gp inducers may decrease sofosbuvir plasma concentrations.

- Sofosbuvir should not be coadministered with any of the following: St. John's wort, anticonvulsants (e.g., carbamazepine, phenytoin, phenobarbital, oxcarbazepine), antimycobacterials (e.g., rifabutin, rifampin, rifapentine), or tipranavir/ritonavir.
- No dosage adjustment is needed for concomitant administration with the following: cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, methadone, raltegravir, rilpivirine, tacrolimus, or tenofovir.

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 should not be coadministered with any of the following: milk thistle, St. John's wort, HIV protease inhibitors (with or without ritonavir), efavirenz, etravirine, nevirapine, antiretroviral agents containing cobicistat, antimycobacterials (rifabutin, rifampin, rifapentine), macrolides, azole antifungals, ketolides, dexamethasone, anticonvulsants (e.g., carbamazepine, phenytoin, phenobarbital, oxcarbazepine).
- No dosage adjustment is needed for concomitant administration with the following: cyclosporine, tacrolimus, ethinyl estradiol, norethindrone, methadone, omeprazole, rilpivirine, raltegravir, or tenofovir.

Refer to full prescribing information for a complete list of potential drug-drug interactions and dosage adjustments of concomitantly prescribed medications.

Sofosbuvir package insert: www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf

Simeprevir package insert: www.olysio.com/shared/product/olysio/prescribing-information.pdf

Storage and Stability[21,22]

Sofosbuvir and simeprevir tablets 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 was stable for 45 days in an open petri dish at 77°F with 60-75% relative humidity.

Missed Doses[21,22]

Patients should be instructed to take a missed sofosbuvir dose as soon as possible that day and to take the next sofosbuvir 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.

X. Groups with Special Considerations for Therapy

Table 15. HIV/HCV Coinfection, Genotypes 1 and 4: Preferred Regimens and SVR Rates from Supporting Data

Regimens with optimal efficacy, favorable tolerability and toxicity profile, and ease of use.

Treatment Considerations						Supporting Information	
HCV Genotype (GT) and Treatment Status	**Interferon Eligibility**	**Cirrhosis Status**	**Regimen and Duration**		**Evidence Grade**	**SVR% (N/N)**	**Comments**
GT1 or GT4, Treatment naïve or treatment experienced	Eligible	Non-cirrhotic or Cirrhotic	Sofosbuvir + PEG-IFN + RBV	12 weeks	A-II/lll	90% (18/20) in treatment-naïve, non-cirrhotics[a]	Single-center, single-arm, open label study
GT1 or GT4, Treatment naïve	Ineligible or intolerant*	Non-cirrhotic	Sofosbuvir + RBV	24 weeks	B-I	76% (87/114) in GT1 treatment-naïve with 4%, cirrhotics[b] Stratified by GT: GT1a: 82% (74/90) GT1b: 54% (13/24) (represents non-cirrhotic and cirrhotic patients)[b]	Reasonable to defer for future treatment if no significant extrahepatic disease, especially in GT1b-infected patients. The largest clinical trial to date of sofosbuvir/ ribavirin therapy was conducted in 114 patients with HIV/HCV coinfection. Among GT1b-infected patients with HIV/HCV co-infection, SVR was achieved in 54% (13/24) as compared with 82% (74/90) with GT1a infection.[b] **Consult with an ID/HIV specialist on treatment options.**
		Cirrhotic	*For consideration:* Sofosbuvir+ Simeprevir ± RBV **NOT FDA approved**	12 weeks	B-III	Data not available	**Treatment options are limited. The risk versus benefits of treatment must be carefully considered along with drug-drug interactions.** **Consult with an ID/HIV specialist on treatment options.** **The FDA does not address the use of simeprevir in**

Treatment Considerations						Supporting Information	
HCV Genotype (GT) and Treatment Status	**Interferon Eligibility**	**Cirrhosis Status**	**Regimen and Duration**		**Evidence Grade**	**SVR% (N/N)**	**Comments**
							HIV/HCV-coinfected patients. **DO NOT USE sofosbuvir + ribavirin in cirrhotics due to insufficient data.**
GT1 or GT4, Treatment experienced	Ineligible or intolerant*	Non-cirrhotic or Cirrhotic	*For consideration:* Sofosbuvir+ Simeprevir ± RBV **NOT FDA approved**	12 weeks	B-III	Data not available	**Treatment options are limited. The risk versus benefits of treatment must be carefully considered.** **Consult with an ID/HIV specialist on treatment options.** **The FDA does not address the use of simeprevir in HIV/HCV-coinfected patients.** **DO NOT USE sofosbuvir + ribavirin in treatment-experienced patients due to insufficient data.**

[a] Rodriguez-Torres et al. [19], [b] PHOTON-1[9]; 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.

***Interferon ineligible or intolerant criteria:** See Table 5.

For HCV genotype 2 or 3 treatment considerations in HIV/HCV coinfection, refer to Tables 9-12.

HIV/HCV coinfection

Sofosbuvir (400 mg/day) in combination with ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) and peginterferon for 12 weeks is FDA approved for chronic HCV genotype 1 or 4 infection in treatment-naïve and treatment-experienced patients with HIV/HCV coinfection. (See Table 15.)

Sofosbuvir combined with weight-based ribavirin is FDA-approved for treatment-naïve and treatment-experienced HCV GT2-infected patients for 12 weeks and in HCV GT3-infected patients for 24 weeks with HIV/HCV coinfection. (See Tables 9-12.)

The preferred treatment for chronic HCV in HIV/HCV-coinfected patients is sofosbuvir plus peginterferon/ribavirin for 12 weeks or sofosbuvir/ribavirin for 24 weeks, because of improved tolerance and diminished potential for drug-drug interactions.

While there are few data on the use of simeprevir in HIV/HCV-coinfected individuals, the use of sofobuvir plus simeprevir (+/– ribavirin) for 12 weeks can be considered in IFN ineligible or intolerant GT1-infected patients, particularly those who are HCV treatment experienced. However, attention to drug-drug interactions between HIV and HCV drugs is needed. This regimen is not FDA approved.

The open-label Phase III clinical trial, PHOTON-1, examined the safety and efficacy of 12 and 24 weeks of sofosbuvir and ribavirin in HIV/HCV-coinfected patients with HCV GT1 (treatment naïve), 2, and 3 infection (treatment naïve and experienced). The mean CD4 count of study participants was >500 cells/mm^3. For all genotypes, response rates observed in HIV/HCV-coinfected patients were similar to response rates observed in HCV-monoinfected patients (Tables 9-12, 15). SVR12 and SVR24 rates were similar. For treatment-naïve GT1-infected patients, SVR12 and 24 rates to sofosbuvir and ribavirin for 24 weeks were 76% (87/114) and 75% (86/114), respectively. There was no difference in the SVR12 and 24 rates in those with GT2 infection and those with GT3 infection. For treatment-naïve patients, SVR rates to sofosbuvir and ribavirin for 12 weeks were 88% (23/26) in GT2-infected patients, and 67% (28/42) in GT3-infected patients. For treatment-experienced patients, SVR rates to sofosbuvir and ribavirin for 24 weeks were 92% (22/24) in GT2-infected patients and 88% (15/17) in GT3-infected patients. When GT1-infected patients were stratified by subtype, SVR12 rates were noted to be 82% (74/90) in those with GT1a infection and 54% (13/24) in those with GT1b infection. Only 4% of GT1- and GT2-infected patients, and 14% of GT3-infected patients had documented cirrhosis.[9,18]

A Phase II, single-center, open-label, single-arm trial evaluated 23 treatment-naïve, non-cirrhotic, GT1-4 HCV/HIV coinfected patients who received sofosbuvir, peginterferon, and ribavirin (1,000 or 1,200 mg/day) for 12 weeks. 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% of GT4-infected patients.[19]

Simeprevir use in HIV/HCV-coinfected individuals is not addressed in the FDA labeling. In an open-label study of 106 patients, simeprevir for 12 weeks plus peginterferon/ribavirin for 24 or 48 weeks was evaluated in treatment-naïve or treatment-experienced GT1 patients with HIV/HCV coinfection. The overall SVR12 rate was 79% in treatment-naïve patients, 87% in relapsers to peginterferon/ribavirin, 70% in partial responders, and 57% in null responders to peginterferon/ribavirin. Protease-inhibitor or efavirenz-based regimens were not permitted in this study. F3-F4 disease was present in 21% of patients and SVR rates in this population ranged from 64% to 80%.[20]

Treatment options are limited in treatment-experienced, interferon-ineligible or interferon-intolerant HIV/HCV-coinfected patients with cirrhosis, and the risk versus benefits of treatment must be carefully considered. Consult with an ID/HIV specialist on treatment options. In interferon-ineligible or interferon-intolerant GT1 HIV/HCV-coinfected individuals, sofobuvir plus simeprevir (+/– ribavirin) for 12 weeks can be considered, particularly in HCV treatment-experienced cirrhotic patients. Although this regimen has

not been studied in HIV/HCV-coinfected individuals and is not FDA approved, preliminary data (SVR4) in HCV-monoinfected patients suggests this may be a reasonable treatment option in HIV/HCV-coinfected patients. Furthermore, there are insufficient data with sofosbuvir plus ribavirin in treatment-experienced and cirrhotic HIV/HCV-coinfected populations to be able to recommend this regimen. Thus, for HIV/HCV-coinfected patients who are interferon ineligible or intolerant and for whom urgent treatment is required, consultation with an ID/HIV/ID expert is strongly recommended and, if sofosbuvir plus simeprevir (+/– ribavirin) is considered, a complete and thorough evaluation of potential drug-drug interactions is required.

HIV/HCV Drug-Drug Interactions[21,22]

Sofosbuvir has no significant interactions with antiretroviral drugs recommended for the treatment of HIV, including emtricitabine, tenofovir, efavirenz, darunavir (+/– ritonavir), rilpivirine, and raltegravir. Sofosbuvir and tipranavir (+/– ritonavir) should not be coadministered as this may diminish the therapeutic effect of sofosbuvir. Increased rates of hyperbilirubinemia were observed when sofosbuvir was coadministered with HIV regimens containing atazanavir (see "Adverse Effects in HIV/HCV Coinfection," below).

Simeprevir should not be coadministered with the following HIV medications: HIV protease inhibitors (+/– ritonavir), efavirenz, etravirine, nevirapine, or antiretroviral agents containing cobicistat.

Use of zidovudine and didanosine with ribavirin is not recommended.

Adverse Effects in HIV/HCV Coinfection[21]

The most commonly reported adverse effects in HIV/HCV-coinfected patients treated with sofosbuvir and ribavirin were fatigue (30-38%), headache (24-30%), nausea (13-22%), and insomnia (15-16%). Hyper-bilirubinemia (total bilirubin >2.5 mg/dL) was observed in 22/114 (20%) of HIV/HCV patients treated with sofosbuvir and ribavirin 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 a 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.

Selecting Patients for Treatment

Patients should be managed in collaboration with an ID/HIV specialist. Patients with uncontrolled HIV infection and advanced immunosuppression should begin HIV antiretrovirals before considering therapy for HCV. Optimal candidates for HCV treatment are patients who are on a stable regimen for HIV (HIV viral load <50 copies/mL) for at least 8 weeks and have an absolute CD4 count of >200 cells/mm^3.

Laboratory Monitoring[21,22]

In addition to the laboratory tests performed for HCV-monoinfected patients receiving 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*.[23]

Renal Insufficiency or Hepatic Impairment

Table 16. Modification of Drug Use in Patients with Renal Insufficiency or Hepatic Impairment

Treatment Considerations			
Condition	**Treatment**	**Comment**	**Grade**
Renal Insufficiency	Simeprevir	Has not been studied in HCV-infected patients with CrCl <30 mL/min. However, no dosage adjustment 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	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-l
	Peginterferon	Should not be used in patients with moderate or severe hepatic impairment (Child-Turcotte-Pugh Class B or C; CTP score ≥7).	A-l

CTP = Child-Turcotte-Pugh

Sofosbuvir[21]

Sofosbuvir and its major metabolites are eliminated primarily via renal clearance. No dosage adjustment is required for patients with mild or moderate renal impairment (CrCl ≥30 mL/min). However, the safety and efficacy of sofosbuvir are not established in patients with severe renal impairment (CrCl <30 mL/min). Hemodialysis removes 18% of the dose. Until additional data are available, sofosbuvir should not be used in patients with severe renal impairment (CrCl <30 mL/min) or end-stage renal disease requiring dialysis.

Because peginterferon 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 ≥7), the safety and efficacy of sofosbuvir in combination with these agents have not been established. Collaboration with an experienced hepatologist is necessary to carefully consider the risks versus benefits of sofosbuvir-based treatment in patients with decompensated cirrhosis.

Simeprevir[22]

Simeprevir does not require dosage adjustment for mild, moderate, or severe renal impairment. No clinically significant differences in pharmacokinetics were observed in HCV-noninfected volunteers with mild, moderate, or severe renal impairment. Creatinine clearance was not identified as a significant covariate of simeprevir population pharmacokinetics in HCV-infected patients.

Simeprevir does not require dosage adjustment in patients with mild hepatic impairment (Child-Turcotte-Pugh Class A). In HCV-uninfected patients, the mean steady-state AUC of simeprevir 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 simeprevir have not been established in HCV-infected patients with Child-Turcotte-Pugh Class B or C. Due to higher simeprevir exposure and potentially increased adverse reactions, no dosage recommendation can be given for simeprevir 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 17. 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 for Patients with HCC	GT1, 2, 3, or 4	Sofosbuvir + RBV (combination with PEG-IFN may be considered but is not FDA approved)	24-48 weeks	B-II	64% (25/39)[a]	Close collaboration with the transplant center is necessary prior to and during treatment. Patients had HCC with compensated liver disease (CTP score <7).
Post-Liver Transplant	GT1, 2, 3, or 4	Sofosbuvir + RBV (PEG-IFN may be considered) **NOT FDA**	24 weeks	B-III	77% (31/40)[b] 60% (19/32)[c] 50% (6/12)[c] with PEG-IFN	Close collaboration with the transplant center is necessary prior to and during treatment. Among patients with severe post-transplant HCV, 34% (15/44) mortality due to progressive liver disease and

Treatment Considerations					Supporting Information	
Transplant status	HCV genotype (GT)	Regimen and duration		Evidence grade	SVR % (N/N)	Comments
		APPROVED				were not related to sofosbuvir/ribavirin therapy.
Post-Other Solid Organ Transplant (Kidney, Heart, or Lung)	GT1, 2, 3, or 4	Discuss with transplant center. **DO NOT USE (peg)interferon-containing regimens in these populations.** **Sofosbuvir has not been studied in non-liver transplant recipients.**				

CTP = Child-Turcotte-Pugh

[a] Curry MP et al. [24]; [b] Charlton MR et al. [25]; [c] Forns X et al. [26]

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.

Sofosbuvir (400 mg/day) in combination with ribavirin (1,000 mg/day if <75 kg and 1,200 mg/day if ≥75 kg, in divided doses) is FDA approved for HCV-infected patients with hepatocellular carcinoma meeting Milan criteria who are awaiting *liver transplantation, for a duration of up to 48 weeks or until the time of transplantation, whichever occurs first. (See Table 17.)*

Close collaboration with the patient's transplant center is necessary to determine the timing of treatment initiation (e.g., treatment once patient is listed for transplant). Sofosbuvir plus ribavirin treatment shows promise with evidence that the longer duration of viral negativity (i.e., >30 days) prior to transplant, the less likely virologic recurrence will occur. Among 61 patients with HCC awaiting liver transplant (median MELD of 8, CTP score <7) treated for up to 48 weeks, 41 had undetectable HCV RNA at the time of transplant.[24] 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.

Sofosbuvir and simeprevir are currently not approved by the FDA for use in post-transplant patients. (See Table 17.)

Sofosbuvir plus ribavirin has been evaluated in two Phase II trials of post-transplant HCV. Charlton and colleagues treated 40 patients with post-transplant HCV 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.[25] In a compassionate use program, Forns and colleagues treated 44 patients with severe recurrence of HCV following liver transplantation, including fibrosing cholestatic hepatitis, 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 and ribavirin and 50% for sofosbuvir, peginterferon

plus ribavirin. Because of the severity of the HCV disease in the patients at the time of treatment initiation, 15 patients died of progressive liver disease during the treatment period. No deaths were attributed to sofosbuvir and ribavirin treatment. Liver function tests (e.g., bilirubin, INR) improved with treatment.[25] Although these trials were small, they are consistent in suggesting that sofosbuvir plus ribavirin may be safe and effective treatment for post-transplant HCV. Larger studies are needed to better evaluate safety and efficacy.

Sofosbuvir has not been studied in non-liver transplant settings. 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 therapy would likely benefit from receiving future therapies that are more evidence-based.

Extra-hepatic manifestations of HCV

Table 18. Treatment of Patients with Extra-Hepatic HCV

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

Mental Health and Substance-Use Disorders

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) or CAGE (www.hepatitis.va.gov/products/video-alcohol-brief-counseling.asp). 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. There are no published data supporting a minimum length of abstinence as an inclusion criterion for HCV antiviral treatment. Patients with active substance- or alcohol-use disorders should be considered for therapy on a case-by-case basis and care should be coordinated with substance-use treatment specialists.

East Asian Ancestry[21]

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

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