

Therapeutic Class Overview Hepatitis C Polymerase Inhibitors

Therapeutic Class

- Overview/Summary:** Included in this review is sofosbuvir (Sovaldi[®]), a once-daily nucleotide analog inhibitor of hepatitis C virus (HCV) nonstructural protein 5B ribonucleic acid polymerase, which is essential for viral replication. The efficacy of sofosbuvir has been established in patients with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/human immunodeficiency virus (HIV)-1 co-infection. The safety and efficacy of sofosbuvir have not been established in post-liver transplant patients or those who have previously failed therapy with a treatment regimen that includes HCV nonstructural protein 3/4A protease inhibitor. Sofosbuvir must be administered in combination with ribavirin or peginterferon alfa and ribavirin. Because of this, warnings and precautions that are associated with these agents are applicable to polymerase inhibitor combination treatment.¹

Several treatment guidelines were recently updated to include recommendations on the use of sofosbuvir in the treatment of HCV infection.²⁻⁵ The consensus guidelines from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) prefer sofosbuvir-based combination therapy for most patients with chronic HCV genotype 1 through 6 infection. Telaprevir- and boceprevir-containing regimens are considered inferior to the preferred and alternative regimens and are no longer recommended for the treatment of HCV genotype 1 infection.² Clinical trials have demonstrated significant improvements in the sustained virologic response rates when sofosbuvir is added to ribavirin or peginterferon alfa and ribavirin.^{1,6-11}

Table 1. Current Medications Available in Therapeutic Class¹

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Sofosbuvir (Sovaldi [®])	Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin; treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with ribavirin alone (without peginterferon alfa) in patients who are ineligible to receive an interferon-based regimen; treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin; treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin; prevention of post-transplant HCV reinfection in combination with ribavirin in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection	Tablet: 400 mg	-

HCV=hepatitis C virus, HIV=human immunodeficiency virus

Evidence-based Medicine

- The Food and Drug Administration (FDA) approval of the polymerase inhibitor sofosbuvir was based on the results of six clinical trials consisting of 1,947 patients who were treatment-naïve or had not responded to previous treatment with peginterferon alfa and ribavirin (treatment-experienced), including patients with hepatitis C virus (HCV) and human immunodeficiency virus co-infection. In

addition, sofosbuvir was effective in patients who were not eligible for an interferon-based treatment regimen and in patients with hepatocellular carcinoma awaiting liver transplantation, addressing unmet medical needs in these populations.^{1,6-8}

- The addition of sofosbuvir to standard therapy (i.e., ribavirin or peginterferon alfa and ribavirin) resulted in significantly higher sustained virologic response rates compared to standard therapy alone in adults with chronic HCV genotype 1, 2, 3 and 4 infections.^{1,6-8}
- Several regimens not currently approved by the FDA are being evaluated in clinical trials. These include evaluation of sofosbuvir plus ribavirin in patients with recurrent HCV infection (any genotype) after liver transplantation; sofosbuvir plus peginterferon alfa and ribavirin in treatment-experienced patients with genotype 2 or 3 HCV infection; and sofosbuvir plus simeprevir in difficult to treat groups of hepatitis C patients (prior null responders and treatment-naïve patients with advanced liver disease). The results of interim analyses from these studies are available.¹⁰⁻¹⁴
- The most commonly reported adverse events in clinical studies of sofosbuvir and ribavirin were fatigue and headache. In patients treated with sofosbuvir, ribavirin and peginterferon alfa, the most commonly reported adverse events included fatigue, headache, nausea, insomnia, and anemia.^{1,6-8}

Key Points within the Medication Class

- According to Current Clinical Guidelines:²⁻⁵
 - The most efficacious therapy for the treatment of hepatitis C virus (HCV) genotype 1 through 6 is the use of sofosbuvir-based combination therapy.
 - Simeprevir, peginterferon alfa, and ribavirin triple therapy regimen is generally recommended as an alternative, rather than a preferred regimen.
 - The use of sofosbuvir plus simeprevir (with or without ribavirin) off-label regimen is recommended in genotype 1 HCV infected patients who are either peginterferon alfa ineligible, prior null or partial responders to peginterferon alfa and ribavirin dual therapy, or liver transplant recipients.
 - In the treatment of HCV genotype 1 infection, telaprevir- and boceprevir-containing regimens are considered inferior to the preferred and alternative regimens and are either no longer recommended or are reserved for patients who are not candidates for the preferred and alternative regimens.
 - No one peginterferon alfa or ribavirin product is preferred or recommended over another.
- Other Key Facts:
 - Sofosbuvir is available as a 400 mg tablet and is dosed 400 mg once daily.¹
 - The standard drug regimen for chronic hepatitis C requires 24 to 48 weeks of treatment, with self-injections of peginterferon alfa which is associated with a number of side effects including nausea, mood swings and severe flu-like symptoms. Sofosbuvir combination therapy shortens the treatment duration to only 12 week in genotype 1, 2 and 4 HCV infections and offers an interferon-free regimen in genotype 2 and 3 HCV infections.^{1,2}
 - When added to standard therapy, sofosbuvir has been found to be well tolerated with no significant side effects beyond what is observed with peginterferon alfa and ribavirin.¹
 - Sofosbuvir is a substrate of P-glycoprotein (P-gp). Thus, coadministration of potent P-gp inducers such as rifampin and St. John's wort should be avoided. Nevertheless, there are fewer drug interactions with sofosbuvir compared to the HCV protease inhibitors.^{1,15-17}
 - Compared to combination therapy with HCV protease inhibitors for the treatment of genotype 1 HCV infection, sofosbuvir combination therapy offers potential for improved efficacy, shorter duration of treatment that is not response-guided, no viral resistance, favorable safety profile, reduced pill burden, and fewer drug-drug interactions (no CYP450 hepatic metabolism).^{1,15-17}

References

1. Sovaldi® [package insert on the internet]. Foster City (CA): Gilead Sciences, Inc.; 2013 Dec.
2. American Association for the Study of Liver Diseases (AASLD), Infectious Diseases Society of America (IDSA), International Antiviral Society-USA (IAS-USA). Recommendations for testing, managing, and treating hepatitis C [guideline on the Internet]. Alexandria (VA): AASLD/IDSA/IAS-USA 2014 Apr [cited 2014 Jun 1]. Available at: <http://www.hcvguidelines.org>.

3. European Association for the Study of the Liver (EASL): Treatment of Hepatitis [guideline on the Internet]. Geneva (Switzerland): EASL 2014 Apr [cited 2014 Jun 1]. Available at: <http://files.easl.eu/easl-recommendations-on-treatment-of-hepatitis-C.pdf>.
4. Department of Veteran Affairs National Hepatitis C Resource Center Program and the Office of Public Health. Chronic hepatitis C Virus (HCV) infection: Treatment considerations [guideline on the Internet]. Washington (DC): VA 2014 May [cited 2014 Jun 1]. Available at: <http://www.hepatitis.va.gov/pdf/2014hcv.pdf>.
5. World Health Organization (WHO). Guidelines for the screening, care and treatment of persons with hepatitis C infection [guideline on the Internet]. Geneva (Switzerland): WHO 2014 Apr [cited 2014 Jun 1]. Available at: <http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/>.
6. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013 May 16;368(20):1878-87.
7. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013 May 16;368(20):1867-77.
8. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med*. 2014 May 22;370(21):1993-2001.
9. Gilead Announces Phase 3 Results for an All-Oral, Sofosbuvir-Based Regimen for the Treatment of Hepatitis C in Patients Co-Infected with HIV [press release on the Internet]. Washington (DC): Gilead Sciences Inc.; 2013 Nov 2 [cited 2014 Jun 1]. Available from: http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-newsArticle_Print&ID=1871556.
10. Charlton M, Gane E, Manns MP, Brown RS, Curry MP, Kwo P, et al. Sofosbuvir and Ribavirin for the Treatment of Established Recurrent Hepatitis C Infection After Liver Transplantation: Preliminary Results of a Prospective, Multicenter Study. 64th Annual Meeting of the American Association for the Study of Liver Diseases. Washington, DC. November 1-5. 2013. Abstract LB-2.
11. Lawitz E, Poordad F, Brainard DM, Hyland RH, An D, Symonds WT, et al. Sofosbuvir in Combination With PegIFN and Ribavirin for 12 Weeks Provides High SVR Rates in HCV-Infected Genotype 2 or 3 Treatment Experienced Patients with and without Compensated Cirrhosis: Results from the LONESTAR-2 Study. 64th Annual Meeting of the American Association for the Study of Liver Diseases. Washington, DC. November 1-5. 2013. Abstract LB-4.
12. Jacobson IM, Ghalib RH, Rodriguez-Torres M, Younossi ZM, Corregidor A, Sulkowski MS et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: The COSMOS study. American Association for the Study of Liver Diseases (AASLD). Washington. November 1-5, 2013. Abstract 1840610.
13. Results from the COSMOS study with Simeprevir and Sofosbuvir in cirrhotic and non-cirrhotic HCV genotype 1 patients presented at AASLD [press release on the Internet]. Stockholm, Sweden: Medivir AB; 2013 Nov 4 [cited 2014 Jun 1]. Available from: <http://www.medivir.se/v5/en/uptodate/pressrelease.cfm?releaseid=4E7105B904E97096&year=2013>.
14. Lawitz E, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, Sulkowski MS, et al. Simeprevir plus sofosbuvir with/without ribavirin in HCV genotype 1 prior null-responder/treatment-naïve patients (Cosmos study): primary endpoint (SVR12) results in patients with METAVIR F3-4 (Cohort 2). European Association for the Study of the Liver (EASL). London. April 9-13, 2014. Abstract 165.
15. Victrelis® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2014 Apr.
16. Incivek® [package insert]. Cambridge (MA): Vertex Pharmaceuticals Incorporated; 2013 Oct.
17. Olysio® [package insert]. Titusville (NJ): Janssen Therapeutics; 2013 Nov.

Therapeutic Class Review Hepatitis C Polymerase Inhibitors

Overview/Summary

The hepatitis C virus (HCV) is an enveloped ribonucleic acid virus that is transmitted through exposure with infected blood. It causes chronic infection in 70 to 85% of infected persons and the Centers for Disease Control and Prevention estimates 3.2 million persons are chronically infected. Chronic HCV infection can lead to the development of active liver disease, and accounts for up to 40% of all patients undergoing liver transplantation.^{1,2} There are seven genotypes of HCV (genotypes 1 to 7), with genotype 1 being the most common in the United States, followed by genotypes 2 and 3.^{2,3} The goal of hepatitis C treatment is HCV eradication in order to prevent complications and death. Genotyping is helpful in the clinical management of patients with hepatitis C for determining the choice of therapy. Assessment of liver disease severity is also recommended for predicting prognosis and determining the timing of therapy.^{4,5} Due to the slow evolution of chronic infection, it is difficult to demonstrate if treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virological parameters. Sustained virologic response (SVR), defined as the absence of HCV ribonucleic acid (RNA) 24 weeks following discontinuation of treatment, has historically been the most important primary endpoint in clinical trials. Recently, SVR 12 (undetectable HCV RNA 12 weeks after the end of therapy) has also been accepted as a primary endpoint for regulatory approval in the US due to concordance with SVR 24.⁴ Prior to the availability of direct-acting antiviral agents, combination of peginterferon alfa and ribavirin has been the standard of care for the treatment of chronic hepatitis C.²⁻¹⁰ The newly approved direct-acting antiviral agents include the nonstructural protein 3 protease inhibitors, boceprevir, telaprevir, and simeprevir as well as nonstructural protein 5B polymerase inhibitor, sofosbuvir.¹¹⁻¹⁴ Several other direct-acting antiviral agents are in the final stages of development that aim to improve efficacy, ease of administration, tolerability and patient adherence, as well as to shorten treatment duration.⁴ The consensus guidelines from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) give preference to sofosbuvir-based combination therapy for most patients with chronic HCV genotype 1 through 6 infection. The choice of treatment regimen is primarily determined by HCV genotype, response to prior treatment (in any), the stage of liver disease, as well as patient's ability to tolerate and be adherent treatment.⁵

In the treatment of chronic HCV genotype 1 infection, the AASLD/IDSA consensus guidelines consider telaprevir- and boceprevir-containing regimens to be markedly inferior to the preferred and alternative regimens due to higher rates of serious adverse events, longer treatment duration, high pill burden, numerous drug-drug interactions, frequency of dosing, intensity of monitoring for continuation and stopping of therapy, and dietary requirements.⁵ Treatment guidelines do not give preference to one specific peginterferon alfa or ribavirin product over another.²⁻¹⁰

Included in this review is sofosbuvir (Sovaldi[®]), a nucleotide analog inhibitor of HCV nonstructural protein 5B RNA polymerase, which is essential for viral replication the hepatitis C. The efficacy of sofosbuvir has been established in patients with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/human immunodeficiency virus (HIV)-1 co-infection. Prescribing information does not restrict sofosbuvir use to either treatment-naïve or experienced patients, and the specific Food and Drug Administration-approved indications are outlined in Table 2.¹⁴ Compared to combination therapy with HCV protease inhibitors for the treatment of HCV genotype 1 infection, sofosbuvir combination therapy offers potential for improved efficacy, shorter duration of treatment that is not response-guided, no viral resistance, favorable safety profile, reduced pill burden, and fewer drug-drug interactions (no CYP450 hepatic metabolism).¹¹⁻¹⁴

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Sofosbuvir (Sovaldi [®])	Hepatitis C virus NS5B polymerase inhibitor	-

Indications

Table 2. Food and Drug Administration Approved Indications¹⁴

Indication	Sofosbuvir
Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin; treatment in combination with ribavirin alone (without peginterferon alfa) can be considered for hepatitis C patients with genotype 1 infection who are ineligible to receive an interferon-based regimen	✓
Treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin	✓
Treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin	✓
Prevention of post-transplant HCV reinfection in combination with ribavirin in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection	✓

HCV=hepatitis C virus, HIV=human immunodeficiency virus

There are additional factors that should be considered when initiating treatment with sofosbuvir. Sofosbuvir should be used in combination with ribavirin or peginterferon alfa and ribavirin; it should not be used as monotherapy for the treatment of chronic hepatitis C. Treatment regimen and duration are dependent on both viral genotype and patient population. Treatment response varies based on baseline host and viral factors. The safety and efficacy of sofosbuvir have not been established in post-liver transplant patients or those who have previously failed therapy with a treatment regimen that includes hepatitis C virus (HCV) nonstructural protein 3/4A protease inhibitors. Available data is insufficient for dosing recommendations for patients with HCV genotype 5 or 6 infection.¹⁴

Pharmacokinetics

Table 3. Pharmacokinetics¹⁵

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Sofosbuvir	Not reported	80	GS-461203	0.4

Clinical Trials

The Food and Drug Administration approval of sofosbuvir was based on the results of five Phase 3 trials (N=1,724) in hepatitis C virus (HCV) mono-infected patients with HCV genotypes 1 to 6 and one Phase 3 trial (N=223) HCV/human immunodeficiency virus (HIV)-1 co-infected subjects with HCV genotype 1, 2 or 3 infection. Sofosbuvir dose was 400 mg daily, ribavirin dose was weight-based at 1,000 to 1,200 mg daily in two divided doses when given with sofosbuvir, and the peginterferon alfa dose was 180 µg weekly. Treatment duration was fixed in each trial and was not guided by patients' HCV ribonucleic acid (RNA) levels. Sustained virologic response (SVR), the primary endpoint, was defined as HCV RNA below the lower limit of quantification at 12 weeks after the end of treatment.¹⁴

NEUTRINO (N=327) was an open-label, single-arm Phase 3 trial that evaluated a 12-week regimen of sofosbuvir plus peginterferon alfa and ribavirin in treatment-naïve patients with HCV genotype 1, 4, 5, or 6 (of whom 98% had genotype 1 or 4). In this study, 90% of patients treated with sofosbuvir combination therapy achieved a SVR₁₂ as compared to an adjusted historical response rate of 60% (P<0.001) observed in studies of telaprevir and boceprevir. Rates of SVR₁₂ did not differ greatly according to the HCV genotype. The rate of SVR was 92% among patients without cirrhosis and 80% among those with cirrhosis. A SVR occurred in 98% of patients with the CC genotype of IL28B (a marker for improved immune response to HCV), as compared to 87% of patients with the non-CC IL28B genotype.¹⁶

While sofosbuvir was not specifically studied in treatment-experienced patients with HCV genotype 1 infection, the estimated response rate in patient who previously failed treatment with peginterferon alfa and ribavirin is 71% according to the prescribing information. This is based on the observed response rate in NEUTRINO subjects with multiple baseline factors associated with a lower response to interferon-based treatment (i.e., IL28B non-C/C alleles, HCV RNA >800,000 IU/mL and F3 to F4 fibrosis).¹⁴

FISSION (N=499) was a randomized, open-label noninferiority Phase 3 trial that compared treatment with sofosbuvir plus ribavirin for 12 weeks to peginterferon alfa plus ribavirin for 24 weeks in treatment-naïve patients with HCV genotype 2 or 3. A SVR12 was achieved in 67% of patients in both groups. Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with HCV genotype 3 than among those with HCV genotype 2 (56 vs 97%). Among patients with cirrhosis at baseline, 47% of patients receiving sofosbuvir plus ribavirin had a SVR compared to 38% of those receiving peginterferon alfa plus ribavirin.¹⁶

No resistance-associated mutations were detected among patients in either NEUTRINO or FISSION trials who received sofosbuvir and had a relapse after virological suppression; the precise reason for relapse is unknown.¹⁶

POSITRON (N=278) was a randomized, double-blinded Phase 3 trial that compared 12 weeks of treatment with sofosbuvir and ribavirin to placebo in patients with HCV genotype 2 or 3 who were interferon intolerant, ineligible or unwilling. A SVR was achieved in 78% of patients treated with sofosbuvir and ribavirin compared to 0% of those receiving placebo (P<0.001). Response rates in patients receiving sofosbuvir and ribavirin were lower among patients with HCV genotype 3 than among those with HCV genotype 2 (61 vs 93%). Among patients with HCV genotype 3 receiving sofosbuvir and ribavirin, 21% of patients with cirrhosis achieved a SVR compared to 68% without cirrhosis. Among patients with HCV genotype 2 receiving sofosbuvir and ribavirin, 94% of patients with cirrhosis achieved a SVR compared to 92% without cirrhosis.¹⁷

FUSION (N=201) was a randomized, double-blinded Phase 3 trial that evaluated 12 or 16 weeks of treatment with sofosbuvir and ribavirin in patients with HCV genotype 2 or 3 who did not achieve SVR with prior interferon-based treatment (relapsers and nonresponders). Treatment with sofosbuvir and ribavirin resulted in higher rates of SVR in the 12-week (50%) and 16-week groups (73%) compared to historical control rate of 25%. Patients receiving 16 weeks of treatment had a significantly higher SVR rate than patients receiving 12 weeks of treatment (difference, +23%; P<0.001). SVR in patients with HCV genotype 2 who received 12 weeks of treatment were lower than among those who received 16 weeks of treatment (86 vs 94%; difference of -8%; 95% confidence interval [CI], -24 to 9); however, the difference was not statistically significant. SVR rates in patients with HCV genotype 3 who received 12 weeks of treatment were significantly lower than among those who received 16 weeks of treatment (difference, -32%; 95% CI, -48 to -15). Among patients with cirrhosis who received 12 weeks of treatment, the SVR was 31% (60% with HCV genotype 2 and 19% with HCV genotype 3) compared to 61% among patients without cirrhosis (96% with HCV genotype 2 and 37% with HCV genotype 3). Among patients with cirrhosis who received 16 weeks of treatment, the SVR was 66% (78% with HCV genotype 2 and 61% with HCV genotype 3) as compared to 76% among patients without cirrhosis (100% with HCV genotype 2 and 63% with HCV genotype 3).¹⁷

VALENCE (N=419) was a placebo-controlled Phase 3 study that initially evaluated 12 weeks of treatment with sofosbuvir and ribavirin or placebo in treatment-naïve and treatment-experienced patients with HCV genotype 2 and 3. The treatment duration was subsequently extended to 24 weeks for patients with genotype 3 (N=250). In the sofosbuvir groups, SVR was achieved by 93% (95% CI, 85 to 98) of patients with HCV genotype 2 receiving 12 weeks of therapy and 85% (95% CI, 80 to 89) of patients with HCV genotype 3 receiving 24 weeks of therapy. SVR rates were >90% in treatment-naïve patients, regardless of HCV genotype or liver fibrosis. Among treatment-experienced patients with cirrhosis, the SVR was lower in patients with genotype 3 compared to genotype 2 (61.7 vs 77.8%).¹⁸

PHOTON-1 (N=223) is an unpublished open-label Phase 3 trial evaluating 12- or 24 weeks of treatment with sofosbuvir and ribavirin in treatment-naïve patients with genotype 1 and treatment-naïve and treatment-experienced patients with genotype 2 or 3 HCV who were all co-infected with HIV.¹⁴ In this trial, 95% of

patients were receiving antiretroviral therapy for their HIV infection. The most common HIV treatment regimens included emtricitabine/tenofovir administered with efavirenz, atazanavir/ritonavir, darunavir/ritonavir or raltegravir.¹⁹ In this trial, SVR was achieved by 76% (87/114) of treatment-naïve patients with HCV genotype 1 receiving 24 weeks of therapy, 88% of treatment-naïve patients with HCV genotype 2 receiving 12 weeks of therapy, and 92% of treatment-experienced patients with HCV genotype 3 receiving 24 weeks of therapy. HIV rebound occurred in two patients (0.9%) on antiretroviral therapy.¹⁴

An unpublished open-label Phase 2 clinical trial evaluated sofosbuvir plus ribavirin in patients with HCV genotypes 1 to 6 and hepatocellular carcinoma prior to undergoing liver transplantation. Patients meeting the MILAN criteria (a single tumor ≤ 5 cm in diameter or ≤ 3 tumors each ≤ 3 cm in diameter and no extra hepatic manifestations of the cancer or evidence of vascular invasion of tumor) were treated for 24 to 48 weeks or until the time of liver transplantation. The post-transplant virologic response (pTVR) rate was 64% in the 36 evaluable patients who have reached the 12 week post-transplant time point. The safety profile of sofosbuvir and ribavirin was similar to that observed in Phase 3 clinical trials.¹⁴

An unpublished, ongoing, single-arm, open-label interferon-free Phase 2 pilot study is evaluating 24-week regimen of sofosbuvir plus ribavirin in naïve and treatment-experienced patients with recurrent HCV infection (any genotype) after liver transplantation. The interim SVR4 rate was 80.8% (21/26). There were no episodes of acute or chronic rejection. No drug interaction dose adjustments of immunosuppression have been required.²⁰

LONESTAR-2 is an unpublished, ongoing open-label Phase 2 study evaluating a 12-week regimen of sofosbuvir 400 mg once daily added to peginterferon alfa (180 μ g/week) and weight-based ribavirin twice daily (1,000 or 1,200 mg/day) among 47 treatment-experienced patients with HCV genotype 2 or 3 infection. In this study 55% of patients had cirrhosis. SVR12 occurred in 83% (20/24) of genotype 3 patients achieved and 96% (22/23) of HCV genotype 2 patients.²¹

The COSMOS trial is an unpublished, randomized, open-label, Phase 2a trial evaluating a once daily combination of simeprevir 400 mg and sofosbuvir 150 mg with and without ribavirin for 12 and 24 weeks in HCV genotype 1 patients. The four-point score METAVIR scale was used to quantify the degree of inflammation and fibrosis of the liver. Cohort 1 (N=80) included prior null responders with METAVIR scores F0 to F2 and Cohort 2 (N=87) included prior null responders and treatment-naïve patients with METAVIR scores F3 to F4.²²

In the Cohort 1, SVR12 was achieved by 96% (26/27) of patients receiving a 12-week simeprevir added to sofosbuvir and ribavirin regimen and 93% (13/14) of patients receiving a 12-week simeprevir and sofosbuvir regimen without ribavirin. In the Cohort 2, SVR12 was achieved by 93% (25/27) of patients receiving a 12-week simeprevir added to sofosbuvir and ribavirin regimen and 93% (13/14) of patients receiving simeprevir and sofosbuvir regimen without ribavirin. Treatment was found to be generally safe and well tolerated. There was little to no benefit from adding ribavirin in this difficult to treat groups of hepatitis C patients and 12 week treatment provided similar clinical benefit to 24 week treatment.²²⁻²⁴

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Genotype 1, 2, 3, 4, 5, and 6 Chronic Hepatitis: Treatment-Naïve Patients				
<p>Lavitz et al¹⁶ (NEUTRINO and FISSION)</p> <p>NEUTRINO: Sofosbuvir 400 mg once daily for 12 weeks</p> <p>and</p> <p>peginterferon alfa-2a 180 µg once weekly for 12 weeks</p> <p>and</p> <p>ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks</p> <p>FISSION: Sofosbuvir 400 mg once daily for 12 weeks</p> <p>and</p> <p>ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks</p> <p>vs</p> <p>peginterferon alfa-2a 180 µg once weekly for 24 weeks</p> <p>and</p>	<p>NEUTRINO: MC, OL, SG</p> <p>Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 1, 4, 5, or 6), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV infection</p> <p>FISSION: AC, MC, OL, R</p> <p>Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV</p>	<p>NEUTRINO: N=327</p> <p>12 weeks</p> <p>FISSION: N=499</p> <p>24 weeks</p>	<p>NEUTRINO: Primary: SVR12*</p> <p>Secondary: Not reported</p> <p>FISSION: Primary: SVR12*</p> <p>Secondary: Not reported</p>	<p>NEUTRINO: Primary: Treatment with sofosbuvir added to peginterferon alfa-2a and ribavirin achieved a SVR12 in 90% of patients (95% CI, 87 to 93). In addition, this regimen was found to be more effective in achieving a SVR12 compared to an adjusted historical response rate of 60% (P<0.001) observed in studies of telaprevir and boceprevir.</p> <p>The rate of SVR12 was 92% (95% CI, 89 to 95) among patients without cirrhosis and 80% (95% CI, 67 to 89) among those with cirrhosis. A SVR12 occurred in 98% of patients with the CC genotype of IL28B, as compared to 87% of patients with the non-CC IL28B genotype.</p> <p>Rates of SVR12 were similar among various HCV genotypes: 89% for patients with genotype 1 (92% for genotype 1a and 82% for genotype 1b) and 96% for those with genotype 4. The single patients with genotype 5 and all six patients with genotype 6 achieved SVR12.</p> <p>Secondary: Not reported</p> <p>FISSION: Primary: A SVR12 was achieved in 67% of patients in both sofosbuvir plus ribavirin group and peginterferon alfa-2a plus ribavirin group.</p> <p>Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (56 vs 97%).</p> <p>Among patients with cirrhosis at baseline, 47% of patients receiving sofosbuvir plus ribavirin had a SVR12 compared to 38% of those receiving peginterferon alfa-2a plus ribavirin.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ribavirin 800 mg/day in two divided doses for 24 weeks	infection			Secondary: Not reported
Treatment of Genotype 2 and 3 Chronic Hepatitis: Treatment-Naïve and Experienced Patients				
<p>Jacobson et al¹⁷ (POSITRON and FUSION)</p> <p>POSITRON: Sofosbuvir 400 mg once daily for 12 weeks</p> <p>and</p> <p>ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks</p> <p>vs</p> <p>placebo</p> <p>FUSION: Sofosbuvir 400 mg once daily for 12 weeks</p> <p>and</p> <p>ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight of ≥75 kg) for 12 weeks</p> <p>vs</p> <p>sofosbuvir 400 mg once daily for 16 weeks</p>	<p>POSITRON: DB, MC, PC, R</p> <p>Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who are not candidates for interferon therapy</p> <p>FUSION: AC, DB, MC, R</p> <p>Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who</p>	<p>POSITRON: N=278</p> <p>12 weeks</p> <p>FUSION: N=201</p> <p>12 to 16 weeks</p>	<p>POSITRON: Primary: SVR12*</p> <p>Secondary: Not reported</p> <p>FUSION: Primary: SVR12*</p> <p>Secondary: Not reported</p>	<p>POSITRON: Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 78% of patients (95% CI, 72 to 83) compared to 0% among those receiving placebo (P<0.001).</p> <p>Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (61 vs 93%).</p> <p>Among patients with genotype 3 infection receiving sofosbuvir plus ribavirin, 21% of patients with cirrhosis achieved a SVR12 compared to 68% without cirrhosis.</p> <p>Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, 94% of patients with cirrhosis achieved a SVR12 compared to 92% without cirrhosis.</p> <p>Secondary: Not reported</p> <p>FUSION: Primary: Treatment with sofosbuvir plus ribavirin resulted in higher rates of SVR12 in the 12-week group (50%; 95% CI, 40 to 60) and 16-week group (73%; 95% CI, 63 to 81) compared to historical control rate of 25%.</p> <p>Patients receiving 16 weeks of treatment had a significantly higher rate of SVR than patients receiving 12 weeks of treatment (difference, -23%; 95% CI, -35 to -11; P<0.001).</p> <p>Response rates in patients with genotype 2 infection who received 12 weeks</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>and</p> <p>ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight of ≥75 kg) for 16 weeks</p>	<p>have previously not responded to treatment with an interferon containing regimen</p>			<p>of treatment were lower than among those who received 16 weeks of treatment (86 vs 94%; difference of -8%; 95% CI, -24 to 9); however, the difference was not statistically significant.</p> <p>Response rates in patients with genotype 3 infection who received 12 weeks of treatment were significantly lower than among those who received 16 weeks of treatment (difference, -32%; 95% CI, -48 to -15).</p> <p>Among patients with cirrhosis who received 12 weeks of treatment, the rate of response was 31% (60% with HCV genotype 2 infection and 19% with HCV genotype 3 infection), as compared to 61% among patients without cirrhosis (96% with HCV genotype 2 infection and 37% with HCV genotype 3 infection).</p> <p>Among patients with cirrhosis who received 16 weeks of treatment, the rate of response was 66% (78% with HCV genotype 2 infection and 61% with HCV genotype 3 infection) as compared to 76% among patients without cirrhosis (100% with HCV genotype 2 infection and 63% with HCV genotype 3 infection).</p> <p>Secondary: Not reported</p>
<p>Zeuzem et al¹⁸ (VALENCE)</p> <p>Sofosbuvir 400 mg once daily for 12 weeks</p> <p>and</p> <p>ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks</p> <p>vs</p>	<p>DB, MC, PC, R</p> <p>Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3) and serum HCV RNA levels of ≥10,000 IU/mL during screening</p>	<p>N=419</p> <p>12 weeks (genotype 2) or 24 weeks (genotype 3)</p>	<p>Primary: SVR12*</p> <p>Secondary: Not reported</p>	<p>Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 93% (95% CI, 85 to 98) of patients with HCV genotype 2 receiving 12 weeks of therapy and 85% (95% CI, 80 to 89) of patients with HCV genotype 3 receiving 24 weeks of therapy.</p> <p>Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (96.7%; 95% CI, 82.8 to 99.9), treatment-naïve cirrhotics (100%; 95% CI, 15.8 to 100), and treatment-experienced non-cirrhotics (93.8%; 95% CI, 79.2 to 99.2), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 2 infection (77.8%; 40.0 to 97.2).</p> <p>Similarly, among patients with genotype 3 infection receiving sofosbuvir plus</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>placebo</p> <p>After study initiation, on the basis of emerging data from phase 3 trials, the study was unblinded, treatment for all patients with genotype 3 infection was extended to 24 weeks, the placebo group was terminated, and the goals of the study were redefined to be descriptive and not include hypothesis testing.</p>				<p>ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (94.6%; 95% CI, 86.3 to 97.6), treatment-naïve cirrhotics (92.3%; 95% CI, 64.0 to 99.8), and treatment-experienced non-cirrhotics (86.7%; 95% CI, 78.4 to 92.7), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 3 infection (61.7%; 46.4 to 75.5).</p> <p>Secondary: Not reported</p>

*SVR12 was defined as HCV RNA level below the lower limit of quantification at 12 weeks after the end of treatment.

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, R=randomized, SG=single-group

Miscellaneous abbreviations: HCV=hepatitis C virus, RNA=ribonucleic acid, SVR=sustained virologic response

Special Populations**Table 5. Special Populations**¹⁴

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Sofosbuvir	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. No dosage adjustment required in the elderly. Safety and efficacy in children <18 years of age have not been established.	No dosage adjustment required in mild or moderate renal impairment. Safety and efficacy have not been established in severe renal impairment (eGFR <30 mL/minute) or ESRD requiring hemodialysis; no dose recommendation can be given.	No dosage adjustment required. Safety and efficacy have not been established in patients with decompensated cirrhosis.	B*	Unknown; use with caution.

eGFR=estimated glomerular filtration rate, ESRD=end stage renal disease

*Ribavirin has a pregnancy category of X. Sofosbuvir must be used in combination with ribavirin or in combination with peginterferon alfa and ribavirin.

Adverse Drug Events

The safety of sofosbuvir is based on pooled Phase 3 clinical trial data (N=1,639) including patients who received sofosbuvir in combination with ribavirin (with or without peginterferon alfa) and patients who received peginterferon alfa and ribavirin combination therapy, or placebo alone. Table 6 below summarizes adverse events reported in ≥15% patients in any treatment arm.¹⁴

Table 6. Adverse Drug Events (%)¹⁴

Adverse Event(s)	Sofosbuvir
Fatigue	30* to 59 [†]
Headache	24 [‡] to 36 [†]
Nausea	13* to 34 [†]
Pruritus	11 [‡] to 27*
Insomnia	15 [‡] to 25 [†]
Anemia	6* to 21 [†]
Asthenia	5 [†] to 21*
Rash	8 [‡] to 18 [†]
Decreased appetite	6* [‡] to 18 [†]
Pyrexia	4* [‡] to 18 [†]
Chills	2* [‡] to 17 [†]
Neutropenia	<1* [‡] to 17 [†]
Influenza like illness	3 [‡] to 16 [†]
Myalgia	6 [‡] to 14 [†]
Irritability	10* [‡] to 13 [†]
Diarrhea	9 [‡] to 12* [†]

*Sofosbuvir plus weight-based ribavirin for 24 weeks treatment regimen.

[†]Sofosbuvir plus peginterferon alfa and weight-based ribavirin for 12 weeks treatment regimen.[‡]Sofosbuvir plus weight-based ribavirin for 12 weeks treatment regimen.

Contraindications/Precautions

When sofosbuvir is used in combination with peginterferon alfa or ribavirin, contraindications to and precautions with those agents are applicable to combination therapies (Black Box Warnings associated with these agents are outlined below).¹⁴

Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Sofosbuvir combination treatment is contraindicated in women who are pregnant or may become pregnant and men whose female partners are pregnant.¹⁴

Drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of sofosbuvir. Rifampin and St. John's wort should not be used with sofosbuvir.¹⁴

Black Box Warning for Pegasys® (peginterferon alfa-2a) and Peg Intron® (peginterferon alfa-2b)^{25,26}

WARNING
Alfa interferon, including peginterferon alfa-2a and alfa-2b, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping peginterferon alfa-2a or alfa-2b therapy.
Use with ribavirin: ribavirin may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease.

Black Box Warnings for Copegus® (ribavirin), Rebetol® (ribavirin) and Ribasphere®/Ribasphere® RibaPak® (ribavirin)²⁷⁻²⁹

WARNING
Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication.
The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin.
Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as six months. Therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for six months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the six month post treatment follow up period.

Drug Interactions

Table 7. Drug Interactions (Not All Inclusive)³⁰

Generic Name	Interacting Medication or Disease	Potential Result
Sofosbuvir	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to loss of therapeutic effect of sofosbuvir. Coadministration is not recommended.

Generic Name	Interacting Medication or Disease	Potential Result
Sofosbuvir	Rifampin, rifabutin, rifapentine	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.
Sofosbuvir	St. John's wort (<i>Hypericum perforatum</i>)	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.
Sofosbuvir	Tipranavir/ritonavir	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.

Dosage and Administration

Table 8. Dosing and Administration¹⁴

Generic Name	Adult Dose	Pediatric Dose	Availability
Sofosbuvir	<p><u>Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin; treatment in combination with ribavirin alone (without peginterferon alfa) can be considered for hepatitis C patients with genotype 1 infection who are ineligible to receive an interferon-based regimen:</u> Tablet: 400 mg once daily for 12 weeks (with peginterferon alfa and ribavirin) or 24 weeks (with ribavirin alone in patients ineligible to receive an interferon-based regimen)</p> <p><u>Treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin:</u> Tablet: 400 mg once daily for 12 weeks</p> <p><u>Treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin:</u> Tablet: 400 mg once daily for 12 weeks (genotype 2) or 24 weeks (genotype 3)</p> <p><u>Prevention of post-transplant HCV reinfection in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection:</u> Tablet: 400 mg once daily for up to 48 weeks or until liver transplantation, whichever occurs first</p>	Safety and efficacy in children have not been established.	Tablet: 400 mg

HCV=hepatitis C virus, HIV=human immunodeficiency virus

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases, Infectious Diseases Society of	<ul style="list-style-type: none"> Current consensus guidelines provide guidance regarding optimal hepatitis C virus (HCV) treatment assuming that the decision to treat has already been made; guidance regarding in whom and when to initiate treatment will be

Clinical Guideline	Recommendation(s)
<p>America, and International Antiviral Society-USA: Recommendations for testing, managing, and treating hepatitis C (2014)⁵</p>	<p>provided in a future consensus guideline update.</p> <ul style="list-style-type: none"> • It may be advisable to delay treatment for some patients with documented early fibrosis stage (F0 to 2), because waiting for future highly effective, pangenotypic, direct-acting antiviral combinations in interferon-free regimens may be prudent. Potential advantages of waiting to begin treatment will be provided in a future consensus guideline update. • A regimen is classified as either "recommended" when it is favored for most patients or "alternative" when optimal in a particular subset of patients in that category. When a treatment is clearly inferior or is deemed harmful, it is classified as "not recommended." • Recommendations for peginterferon alfa and ribavirin relapsers are the same as for treatment-naïve persons as described below. • Interferon ineligible criteria: <ul style="list-style-type: none"> ○ Intolerance to interferon alfa. ○ Autoimmune hepatitis and other autoimmune disorders. ○ Hypersensitivity to peginterferon alfa or any of its components. ○ Decompensated hepatic disease. ○ Major uncontrolled depressive illness. ○ A baseline neutrophil count below 1,500/μL, a baseline platelet count below 90,000/μL, or baseline hemoglobin below 10 g/dL. ○ A history of preexisting cardiac disease. <p><u>Treatment of HCV genotype 1 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u></p> <ul style="list-style-type: none"> • Recommended treatments: <ul style="list-style-type: none"> ○ Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. ○ Interferon ineligible: sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: <ul style="list-style-type: none"> ○ Interferon eligible: simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present). ○ Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: <ul style="list-style-type: none"> ○ Boceprevir or telaprevir plus peginterferon alfa and ribavirin for 24 or 48 weeks. ○ Peginterferon alfa and ribavirin for 48 weeks. ○ Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <p><u>Treatment of HCV genotype 2 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u></p> <ul style="list-style-type: none"> • Recommended treatments: <ul style="list-style-type: none"> ○ Sofosbuvir plus ribavirin for 12 weeks. • Alternative treatments: <ul style="list-style-type: none"> ○ None. • Treatments that are not recommended: <ul style="list-style-type: none"> ○ Peginterferon alfa and ribavirin for 24 weeks. ○ Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. ○ Any regimen with boceprevir, telaprevir, or simeprevir.

Clinical Guideline	Recommendation(s)
	<p><u>Treatment of HCV genotype 3 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u></p> <ul style="list-style-type: none"> • Recommended treatments: <ul style="list-style-type: none"> ○ Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: <ul style="list-style-type: none"> ○ Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Treatments that are not recommended: <ul style="list-style-type: none"> ○ Peginterferon alfa and ribavirin for 24 to 48 weeks. ○ Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. ○ Any regimen with boceprevir, telaprevir, or simeprevir. <p><u>Treatment of HCV genotype 4 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u></p> <ul style="list-style-type: none"> • Recommended treatments: <ul style="list-style-type: none"> ○ Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. ○ Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: <ul style="list-style-type: none"> ○ Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 to 48 weeks. • Treatments that are not recommended: <ul style="list-style-type: none"> ○ Peginterferon alfa and ribavirin for 48 weeks. ○ Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. ○ Any regimen with boceprevir or telaprevir. <p><u>Treatment of HCV genotype 5 or 6 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u></p> <ul style="list-style-type: none"> • Recommended treatments: <ul style="list-style-type: none"> ○ Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: <ul style="list-style-type: none"> ○ Peginterferon alfa and ribavirin for 48 weeks. • Treatments that are not recommended: <ul style="list-style-type: none"> ○ Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. ○ Any regimen with boceprevir or telaprevir. <p><u>Recommendations for patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin</u></p> <ul style="list-style-type: none"> • Recommended treatments: <ul style="list-style-type: none"> ○ Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: <ul style="list-style-type: none"> ○ Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 12 to 24 weeks. ○ Sofosbuvir plus ribavirin for 24 weeks. ○ Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present). • Treatments that are not recommended: <ul style="list-style-type: none"> ○ Boceprevir or telaprevir plus peginterferon alfa and ribavirin. ○ Monotherapy with peginterferon alfa, ribavirin, or a direct-acting

Clinical Guideline	Recommendation(s)
	<p style="text-align: center;">antiviral.</p> <p><u>Recommendations for patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin plus either boceprevir or telaprevir</u></p> <ul style="list-style-type: none"> • Recommended treatments: <ul style="list-style-type: none"> ○ Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 12 to 24 weeks. • Alternative treatments: <ul style="list-style-type: none"> ○ Interferon eligible: Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks. ○ Interferon ineligible: Sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: <ul style="list-style-type: none"> ○ Boceprevir, simeprevir, or telaprevir plus peginterferon alfa and ribavirin. ○ Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. ○ A recommendation for simeprevir use for patients with previous telaprevir or boceprevir exposure has not been provided due to potential risk of preexistent resistance to protease inhibitor treatment. <p><u>Recommendations for patients with HCV genotype 2 with prior null or partial response to peginterferon alfa and ribavirin</u></p> <ul style="list-style-type: none"> • Recommended treatments: <ul style="list-style-type: none"> ○ Sofosbuvir plus ribavirin for 12 weeks; <ul style="list-style-type: none"> ▪ In treatment-experienced cirrhotics only, the decision to extend therapy to 16 weeks should be made on a case-by-case basis. • Alternative treatments: <ul style="list-style-type: none"> ○ Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (cirrhotics only) • Treatments that are not recommended: <ul style="list-style-type: none"> ○ Boceprevir or telaprevir plus peginterferon alfa and ribavirin. ○ Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <p><u>Recommendations for patients with HCV genotype 3 with prior null or partial response to peginterferon alfa and ribavirin</u></p> <ul style="list-style-type: none"> • Recommended treatments: <ul style="list-style-type: none"> ○ Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: <ul style="list-style-type: none"> ○ Sofosbuvir plus ribavirin for 16 weeks (cirrhotics only). ○ Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Treatments that are not recommended: <ul style="list-style-type: none"> ○ Peginterferon alfa and ribavirin with or without protease inhibitor. ○ Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <p><u>Recommendations for patients with HCV genotype 4 with prior null or partial response to peginterferon alfa and ribavirin</u></p> <ul style="list-style-type: none"> • Recommended treatments: <ul style="list-style-type: none"> ○ Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: <ul style="list-style-type: none"> ○ Sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended:

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ Peginterferon alfa and ribavirin with or without protease inhibitor ○ Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <p><u>Recommendations for patients with HCV genotype 5 or 6 with prior null or partial response to peginterferon alfa and ribavirin</u></p> <ul style="list-style-type: none"> ● Recommended treatments: <ul style="list-style-type: none"> ○ Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. ● Alternative treatments: <ul style="list-style-type: none"> ○ None. ● Treatments that are not recommended: <ul style="list-style-type: none"> ○ Peginterferon alfa and ribavirin with or without protease inhibitor. ○ Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <p><u>Initial treatment of human immunodeficiency virus (HIV)/HCV co-infected patients with HCV genotype 1 who are treatment-naïve or prior peginterferon alfa and ribavirin relapsers</u></p> <ul style="list-style-type: none"> ● Recommended treatments: <ul style="list-style-type: none"> ○ Interferon eligible: sofosbuvir plus peginterferon and ribavirin for 12 weeks. ○ Interferon ineligible: <ul style="list-style-type: none"> ▪ Sofosbuvir plus ribavirin for 24 weeks. ▪ Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. ● Alternative treatments: <ul style="list-style-type: none"> ○ Interferon eligible: simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present). ○ Interferon ineligible: none. ● Treatments that are not recommended: <ul style="list-style-type: none"> ○ Boceprevir or telaprevir plus peginterferon alfa and ribavirin for 24 or 48 weeks. ○ Peginterferon alfa and ribavirin for 48 weeks. ○ Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 48 weeks. ● Allowable antiretroviral therapy: <ul style="list-style-type: none"> ○ For sofosbuvir use: all except didanosine, zidovudine, or tipranavir. ○ For simeprevir use: limited to raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir. <p><u>Recommendations for HIV/HCV co-infected patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin</u></p> <ul style="list-style-type: none"> ● Recommended treatments: <ul style="list-style-type: none"> ○ Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. ● Alternative treatments: <ul style="list-style-type: none"> ○ Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. ○ Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. ● Treatments that are not recommended: same as for treatment-naïve or prior peginterferon alfa and ribavirin relapsers above. ● Allowable antiretroviral therapy: same as for treatment-naïve or prior peginterferon alfa and ribavirin relapsers above.

Clinical Guideline	Recommendation(s)
	<p><u>Treatment of HIV/HCV co-infected patients with HCV genotype 2</u></p> <ul style="list-style-type: none"> • Recommended treatments (regardless of treatment history): <ul style="list-style-type: none"> ○ Sofosbuvir plus ribavirin for 12 weeks. • Alternative treatments: <ul style="list-style-type: none"> ○ Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (only in prior nonresponders to peginterferon alfa and ribavirin eligible for peginterferon alfa). • Treatments that are not recommended: <ul style="list-style-type: none"> ○ Peginterferon alfa and ribavirin for 24 to 48 weeks. ○ Any regimen with boceprevir, telaprevir, or simeprevir. ○ Allowable antiretroviral therapy: same as above. <p><u>Treatment of HIV/HCV co-infected patients with HCV genotype 3</u></p> <ul style="list-style-type: none"> • Recommended treatments (regardless of treatment history): <ul style="list-style-type: none"> ○ Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: <ul style="list-style-type: none"> ○ Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (only in prior nonresponders to peginterferon alfa and ribavirin eligible for peginterferon alfa). • Treatments that are not recommended: <ul style="list-style-type: none"> ○ Peginterferon alfa and ribavirin for 24 to 48 weeks. ○ Any regimen with boceprevir, telaprevir, or simeprevir. ○ Allowable antiretroviral therapy: same as above. <p><u>Treatment of HIV/HCV co-infected patients with HCV genotype 4</u></p> <ul style="list-style-type: none"> • Recommended treatments (regardless of treatment history): <ul style="list-style-type: none"> ○ Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. ○ Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: <ul style="list-style-type: none"> ○ None. • Treatments that are not recommended: <ul style="list-style-type: none"> ○ Peginterferon alfa and ribavirin for 48 weeks. ○ Any regimen with boceprevir, telaprevir, or simeprevir. ○ Allowable antiretroviral therapy: same as above. <p><u>Treatment of HIV/HCV co-infected patients with HCV genotype 5 or 6</u></p> <ul style="list-style-type: none"> • Recommended treatments (regardless of treatment history): <ul style="list-style-type: none"> ○ Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: <ul style="list-style-type: none"> ○ None. • Treatments that are not recommended: <ul style="list-style-type: none"> ○ Peginterferon alfa and ribavirin for 48 weeks. ○ Any regimen with boceprevir, telaprevir, or simeprevir. ○ Allowable antiretroviral therapy: same as above. <p><u>Treatment of patients with cirrhosis</u></p> <ul style="list-style-type: none"> • Treatment-naïve patients with compensated cirrhosis, including those with hepatocellular carcinoma, should receive the same treatment as recommended for patients without cirrhosis. • Patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Recommended regimen for patients with any HCV genotype who have decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C) who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. <ul style="list-style-type: none"> ○ Sofosbuvir plus weight-based ribavirin (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks. ○ This regimen should be used only by highly experienced HCV provider. • The following regimens are not recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C): <ul style="list-style-type: none"> ○ Any interferon-based therapy. ○ Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. ○ Telaprevir, boceprevir, or simeprevir-based regimens. <p><u>Treatment of patients who develop recurrent HCV infection post-liver transplant</u></p> <ul style="list-style-type: none"> • Recommended regimen for treatment-naïve patients with HCV genotype 1 in the allograft liver, including those with compensated cirrhosis. <ul style="list-style-type: none"> ○ Sofosbuvir plus simeprevir with or without dose-adjusted ribavirin for 12 to 24 weeks. • Alternate regimen for treatment-naïve patients with genotype 1 HCV in the allograft liver, including those with compensated cirrhosis. <ul style="list-style-type: none"> ○ Sofosbuvir and dose-adjusted ribavirin (with consideration of the patient's creatinine clearance and hemoglobin level), with or without peginterferon alfa, for 24 weeks. • Recommended regimen for treatment-naïve patients with HCV genotype 2 or 3 in the allograft liver, including those with compensated cirrhosis. <ul style="list-style-type: none"> ○ Sofosbuvir plus dose-adjusted ribavirin (with consideration for creatinine clearance and hemoglobin level) for 24 weeks. • Treatment-naïve patients with decompensated allograft HCV infection should receive the same treatment as recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C).
<p>Department of Veterans Affairs National Hepatitis C Resource Center Program and the Office of Public Health: HCV Infection: Treatment Considerations (2014)⁷</p>	<p><u>Treatment considerations</u></p> <ul style="list-style-type: none"> • 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 treatment should be considered in patients with advanced cirrhosis, selected patients with hepatocellular carcinoma awaiting liver transplant, post-transplant recipients with cirrhosis, and patients with serious extra-hepatic manifestations of HCV. • Patients with mild liver disease (F0 to F2) may consider waiting until newer therapies are available that may improve the chance of treatment success and reduce treatment-related adverse effects; approval is anticipated over the next 12 to 24 months. • Factors that may complicate adherence, such as active substance abuse, neurocognitive disorders, and lack of social support, should be addressed before initiating medications. • 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: <ul style="list-style-type: none"> ○ Platelet count <75,000/mm³.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ Decompensated liver cirrhosis (Child Turcotte Pugh class B or C). ○ Severe mental health conditions that may be exacerbated by interferon or may respond poorly to medical therapy. ○ 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. <ul style="list-style-type: none"> ● Treatment of patients with HCV/HIV co-infection is similar to that of HCV mono-infected patients. Drug-drug interactions must be carefully considered. <p><u>Treatment of HCV genotype 1 in treatment-naïve, non-cirrhotic or cirrhotic interferon eligible patients</u></p> <ul style="list-style-type: none"> ● Preferred regimen: <ul style="list-style-type: none"> ○ Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. ● Alternative regimen: <ul style="list-style-type: none"> ○ Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (do not use in genotype 1a with Q80K polymorphism). <p><u>Treatment of HCV genotype 1 in treatment-naïve, non-cirrhotic interferon ineligible patients</u></p> <ul style="list-style-type: none"> ● Preferred regimens: <ul style="list-style-type: none"> ○ Sofosbuvir plus ribavirin for 24 weeks. ○ Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. ● Alternative regimen: <ul style="list-style-type: none"> ○ None. <p><u>Treatment of HCV genotype 1 in treatment-naïve, cirrhotic interferon ineligible patients</u></p> <ul style="list-style-type: none"> ● Preferred regimen: <ul style="list-style-type: none"> ○ Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. ● Alternative regimen: <ul style="list-style-type: none"> ○ None. <p><u>Treatment of HCV genotype 1 in treatment-experienced, non-cirrhotic interferon eligible patients</u></p> <ul style="list-style-type: none"> ● Preferred regimen: <ul style="list-style-type: none"> ○ Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. ● Alternative regimen: <ul style="list-style-type: none"> ○ Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (relapsers) or 48 weeks (prior partial or null responders); do not use in genotype 1a with Q80K polymorphism or previous failure of boceprevir- or telaprevir-based therapy. <p><u>Treatment of HCV genotype 1 in treatment-experienced, cirrhotic interferon eligible patients</u></p> <ul style="list-style-type: none"> ● Preferred regimen: <ul style="list-style-type: none"> ○ Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. ● Alternative regimen (peginterferon alfa and ribavirin null responders only): <ul style="list-style-type: none"> ○ Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. <p><u>Treatment of HCV genotype 1 in treatment-experienced, non-cirrhotic or cirrhotic interferon ineligible patients</u></p> <ul style="list-style-type: none"> ● Preferred regimen: <ul style="list-style-type: none"> ○ Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Alternative regimen: <ul style="list-style-type: none"> ○ None. <p><u>Treatment of HCV genotype 2 in treatment-naïve patients</u></p> <ul style="list-style-type: none"> • Preferred regimen: <ul style="list-style-type: none"> ○ Sofosbuvir plus ribavirin for 12 weeks. • Alternative regimen: <ul style="list-style-type: none"> ○ None. <p><u>Treatment of HCV genotype 2 in treatment-experienced patients</u></p> <ul style="list-style-type: none"> • Preferred regimens: <ul style="list-style-type: none"> ○ Sofosbuvir plus ribavirin for 12 to 16 weeks. ○ Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only). • Alternative regimen: <ul style="list-style-type: none"> ○ None. <p><u>Treatment of HCV genotype 3 in treatment-naïve patients</u></p> <ul style="list-style-type: none"> • Preferred regimens: <ul style="list-style-type: none"> ○ Sofosbuvir plus ribavirin for 24 weeks. • Alternative regimen: <ul style="list-style-type: none"> ○ Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only). <p><u>Treatment of HCV genotype 3 in treatment-experienced cirrhotic patients</u></p> <ul style="list-style-type: none"> • Preferred regimens: <ul style="list-style-type: none"> ○ Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only). • Alternative regimen: <ul style="list-style-type: none"> ○ Sofosbuvir plus ribavirin for 24 weeks (interferon ineligible only). <p><u>Treatment of HCV genotype 1, 2, 3, or 4 in patients with hepatocellular carcinoma</u></p> <ul style="list-style-type: none"> • Preferred regimens: <ul style="list-style-type: none"> ○ Sofosbuvir plus ribavirin for 24 to 48 weeks or until liver transplant, whichever occurs first. • Alternative regimen: <ul style="list-style-type: none"> ○ None. <p><u>Treatment of patients with HCV genotype 1, 2, 3, or 4 infection post-liver transplant</u></p> <ul style="list-style-type: none"> • Sofosbuvir plus ribavirin with or without peginterferon for 24 weeks <p><u>Treatment of patients with HCV genotype 1, 2, 3, or 4 infection post-other solid organ transplant (kidney, heart, or lung)</u></p> <ul style="list-style-type: none"> • Discuss with transplant center. Do not use peginterferon-containing regimens. Sofosbuvir has not been studied in non-liver transplant recipients. <p><u>Discontinuing HCV treatment based on lack of virologic response</u></p> <ul style="list-style-type: none"> • Patients receiving sofosbuvir-based regimen should have HCV ribonucleic acid (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 the repeated HCV RNA 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 treatment should be strongly considered.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> Patients receiving simeprevir plus peginterferon and ribavirin regimen should have HCV RNA levels assessed at week 4, 12, and 24; if the HCV RNA is ≥ 25 IU/mL at any of these time points, all treatment should be discontinued. <p><u>Use in renal insufficiency</u></p> <ul style="list-style-type: none"> Sofosbuvir use is not recommended if creatinine clearance < 30 mL/min or end-stage renal disease due to insufficient safety and efficacy data. No simeprevir dose adjustment is needed if creatinine clearance < 30 mL/min. Peginterferon alfa-2a dosage should be reduced to 135 μg/week once weekly for creatinine clearance < 30 mL/min, including hemodialysis. Peginterferon alfa-2b dosage should be reduced by 25% for creatinine clearance 30 to 50 mL/min and by 50% for creatinine clearance < 30 mL/min, including hemodialysis. Ribavirin should be dosed at 200 mg daily alternating with 400 mg daily for creatinine clearance 30-50 mL/min and 200 mg daily for creatinine clearance < 30 mL/min, including hemodialysis. <p><u>Use in hepatic impairment</u></p> <ul style="list-style-type: none"> No simeprevir dosage recommendation can be provided in moderate to severe hepatic impairment (Turcotte Pugh Class B or C) due to higher simeprevir exposures. No sofosbuvir dosage adjustment is required for patients with any degree of renal impairment. Peginterferon alfa use is not recommended in patients with moderate or severe hepatic impairment (Turcotte Pugh Class B or C). <p><u>Mental health and substance-use disorders</u></p> <ul style="list-style-type: none"> Patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder) who are engaged in mental health treatment should be considered for therapy on a case-by-case basis; interferon use may worsen these conditions. <p><u>Substance or alcohol use</u></p> <ul style="list-style-type: none"> 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 per month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. There are no published data supporting minimal 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 specialist.
<p>European Association for the Study of the Liver: Treatment of Hepatitis (2014)⁴</p>	<p><u>Goals and endpoints of HCV therapy</u></p> <ul style="list-style-type: none"> The goal of therapy is to eradicate HCV infection, to prevent hepatic cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma, and death. The endpoint of therapy is SVR, defined by undetectable HCV RNA 12 and 24 weeks after the end of treatment; SVR usually equates to cure of infection in more than 99% of patients. Both SVR 12 and SVR 24 have been accepted in the US and Europe, given that their concordance is 99%. <p><u>Indications for treatment</u></p> <ul style="list-style-type: none"> All treatment-naïve and -experienced patients with compensated disease due to HCV should be considered for therapy.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Treatment should be prioritized for patients with significant fibrosis (F3 to F4). • Treatment is justified in patients with moderate fibrosis (F2). • In patients with no or mild disease (F0 to F1), the indication for and timing of therapy can be individualized. • Patients with decompensated cirrhosis who are on the transplant list should be considered for interferon-free, ideally ribavirin-free therapy. <p><u>Treatment considerations for HIV/HCV-coinfection</u></p> <ul style="list-style-type: none"> • Indications for HCV treatment and treatment regimens in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection. • The use of cobicistat-based regimens, efavirenz, delavirdine, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir, is not recommended in HIV-infected patients receiving simeprevir. • Daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz. • No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs. <p><u>Treatment options for HCV genotype 1 infection</u></p> <ul style="list-style-type: none"> • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. <ul style="list-style-type: none"> ○ The most efficacious and the easiest to use interferon alfa-containing option, without the risk of selecting resistant viruses in case of treatment failure. • Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (in treatment-naïve and prior relapsers, including cirrhotics) or 48 weeks (in prior partial and null responders, including cirrhotics). <ul style="list-style-type: none"> ○ Not recommended for HCV genotype 1a with Q80K polymorphism. ○ HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥ 25 IU/mL at week 4, 12 or 24. • Daclatasvir plus peginterferon alfa and ribavirin for 24 weeks (HCV genotype 1b only). <ul style="list-style-type: none"> ○ Not recommended for HCV genotype 1a given the preliminary data available, pending results of on-going large-scale studies. ○ Daclatasvir should be given for 12 weeks in combination with peginterferon alfa and ribavirin. Daclatasvir, in combination with peginterferon alfa and ribavirin, should be continued for an additional 12 weeks (24 weeks total) in patients who do not achieve an HCV RNA level < 25 IU/mL at week 4 and undetectable at week 10. Peginterferon alfa and ribavirin should be continued alone between week 12 and 24 (24 weeks total) in patients who achieve an HCV RNA level < 25 IU/mL at week 4 and undetectable at week 10. • Sofosbuvir plus ribavirin for 24 weeks. <ul style="list-style-type: none"> ○ Due to suboptimal SVR rates, reserve for interferon alfa ineligible patients when no other interferon-free option is available. • Sofosbuvir plus simeprevir for 12 weeks. <ul style="list-style-type: none"> ○ The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. • Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced, including prior telaprevir or boceprevir failures). <ul style="list-style-type: none"> ○ The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.

Clinical Guideline	Recommendation(s)
	<p><u>Treatment options for HCV genotype 2 infection</u></p> <ul style="list-style-type: none"> • Sofosbuvir plus ribavirin for 12 weeks (or 16 to 20 weeks in cirrhotics, especially treatment-experienced). • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks is an option for cirrhotic and/or treatment-experienced patients. <p><u>Treatment options for HCV genotype 3 infection</u></p> <ul style="list-style-type: none"> • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks • Sofosbuvir plus ribavirin for 24 weeks <ul style="list-style-type: none"> ○ Suboptimal in treatment-experienced cirrhotics, who should be proposed an alternative treatment option. • Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced, pending data with 12 weeks of therapy). <ul style="list-style-type: none"> ○ The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. <p><u>Treatment options for HCV genotype 4 infection</u></p> <ul style="list-style-type: none"> • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (in treatment-naïve and prior relapsers, including cirrhotics) or 48 weeks (in prior partial and null responders, including cirrhotics). <ul style="list-style-type: none"> ○ HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥ 25 IU/mL at week 4, 12 or 24. • Daclatasvir plus peginterferon alfa and ribavirin for 24 weeks. <ul style="list-style-type: none"> ○ Daclatasvir should be given for 12 weeks in combination with peginterferon alfa and ribavirin. Daclatasvir, in combination with peginterferon alfa and ribavirin, should be continued for an additional 12 weeks (24 weeks total) in patients who do not achieve an HCV RNA level < 25 IU/mL at week 4 and undetectable at week 10. Peginterferon alfa and ribavirin should be continued alone between week 12 and 24 (24 weeks total) in patients who achieve an HCV RNA level < 25 IU/mL at week 4 and undetectable at week 10. • Sofosbuvir plus ribavirin for 24 weeks. <ul style="list-style-type: none"> ○ Should be reserved for interferon alfa intolerant or -ineligible patients. • Sofosbuvir plus simeprevir for 12 weeks. <ul style="list-style-type: none"> ○ The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. • Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced). <ul style="list-style-type: none"> ○ The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. <p><u>Treatment options for HCV genotype 5 or 6 infection</u></p> <ul style="list-style-type: none"> • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Sofosbuvir plus ribavirin for 24 weeks. <ul style="list-style-type: none"> ○ Should be reserved for interferon alfa intolerant or -ineligible patients. <p><u>Treatment monitoring</u></p> <ul style="list-style-type: none"> • A real-time polymerase chain reaction-based assay with a lower limit of detection of < 15 IU/mL should be used to monitor HCV RNA levels during and after therapy.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • In patients treated with sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks, HCV RNA should be measured at baseline and at weeks 4, 12, and 12 or 24 weeks after the end of therapy. • In patients treated with simeprevir for 12 weeks plus peginterferon alfa and ribavirin for an additional 24 or 48 weeks, HCV RNA should be measured at baseline, week 4, 12, 24 (end of treatment in treatment-naïve and prior relapsers), week 48 (end of treatment in prior partial and null responders), and 12 or 24 weeks after the end of therapy. • In patients treated with daclatasvir for 12 to 24 weeks plus peginterferon alfa and ribavirin for 24 weeks, HCV RNA should be measured at baseline, week 4, 10, and 24 (end of treatment), and 12 or 24 weeks after the end of therapy. • In patients treated with sofosbuvir plus simeprevir with or without ribavirin for 12 weeks; sofosbuvir plus daclatasvir with or without ribavirin for 12 or 24 weeks; and sofosbuvir plus ribavirin 12 or 24 weeks, HCV RNA should be measured at baseline, week 2 (assessment of adherence), week 4, week 12 or 24 (end of treatment), and 12 or 24 weeks after the end of therapy. <p><u>Stopping (futility) rules</u></p> <ul style="list-style-type: none"> • Treatment with simeprevir plus peginterferon alfa and ribavirin should be stopped if HCV RNA level is ≥ 25 IU/mL at treatment week 4, 12 or 24. • No futility rules have been defined for other treatment regimens. <p><u>Virological response-guided triple therapy</u></p> <ul style="list-style-type: none"> • With the triple combination of daclatasvir plus peginterferon alfa and ribavirin, patients who do not achieve an HCV RNA level < 25 IU/mL at week 4 and undetectable at week 10 should receive the three drugs for 24 weeks. • Patients who achieve an HCV RNA level < 25 IU/mL at week 4 and undetectable at week 10 should stop daclatasvir at week 12 and continue with peginterferon alfa and ribavirin dual therapy until week 24. • No response-guided therapy is used in other treatment regimens. <p><u>Measures to improve treatment adherence</u></p> <ul style="list-style-type: none"> • HCV treatment should be delivered within a multidisciplinary team setting, with experience in HCV assessment and therapy. • Counseling on the importance of adherence is recommended. • In persons who actively inject drugs, access to harm reduction programs is mandatory. • Patients should be counseled to abstain from alcohol during antiviral therapy; patients with on-going alcohol consumption during treatment should receive additional support during antiviral therapy. • HCV treatment can be considered also for patients actively using drugs if they wish to receive treatment and are able and willing to maintain regular appointments. <p><u>Retreatment of non-sustained virological responders</u></p> <ul style="list-style-type: none"> • Patients who failed on a regimen containing sofosbuvir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only), or a combination of sofosbuvir and daclatasvir (all genotypes). • Patients who failed on a regimen containing simeprevir, telaprevir or boceprevir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and daclatasvir. • Patients who failed on a regimen containing daclatasvir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and

Clinical Guideline	Recommendation(s)
	<p>simeprevir (HCV genotypes 1 or 4 only).</p> <ul style="list-style-type: none"> • Patients who failed on a regimen containing sofosbuvir and simeprevir can be retreated with a combination of sofosbuvir and daclatasvir. • Patients who failed on a regimen containing sofosbuvir and daclatasvir can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only). • Alternatively, patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir can wait until new treatment combinations are available if they do not need urgent therapy. • The utility of HCV resistance testing prior to retreatment in patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir is unknown. <p><u>Treatment of patients with severe liver disease</u></p> <ul style="list-style-type: none"> • Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short- to mid-term complications; interferon-free regimens are preferred. • If a 12 to 24 week interferon-based direct-acting antiviral regimen is considered tolerable in patients with compensated cirrhosis and good liver function and without cytopenia, these patients can be treated as recommended above across genotypes. • Patients with cirrhosis should undergo regular surveillance for hepatocellular carcinoma, irrespective of SVR. <p><u>Patients with an indication for liver transplantation</u></p> <ul style="list-style-type: none"> • In patients awaiting liver transplantation, antiviral therapy is indicated, because it prevents graft infection if HCV RNA has been undetectable at least 30 days prior to transplantation. • Patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma should be treated with sofosbuvir plus ribavirin until liver transplantation. • Patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma can also be treated with sofosbuvir, peginterferon alfa and ribavirin for 12 weeks. • In patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma, the addition of another direct acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant; therefore, patients awaiting liver transplantation with genotype 1 to 4 infection can be treated with sofosbuvir, daclatasvir and ribavirin for 12 weeks prior to transplantation. • Patients with decompensated cirrhosis awaiting liver transplantation (Child Pugh class B and C) can be treated with sofosbuvir plus ribavirin until liver transplantation in experienced centers under close monitoring. Interferon alfa is contraindicated in these patients. • The addition of another direct-acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant; therefore, patients with decompensated cirrhosis awaiting liver transplantation (Child Pugh class B and C) with genotype 1 to 4 infection should be treated with sofosbuvir, daclatasvir and ribavirin until liver transplantation in experienced centers under close monitoring. • Patients with decompensated cirrhosis not on transplant waiting list should only be offered an interferon-free regimen within a clinical trial, an expanded access program or within experienced centers, because the efficacy, safety and outcomes have not yet been established for this group.

Clinical Guideline	Recommendation(s)
	<p><u>Post-liver transplantation recurrence</u></p> <ul style="list-style-type: none"> • Patients with post-transplant recurrence of HCV infection should be considered for therapy. • Patients with HCV genotype 2 infection must sofosbuvir plus ribavirin for 12 to 24 weeks, pending more data in this population. • Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with sofosbuvir plus daclatasvir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • Patients with HCV genotype 1 or 4 infection can be treated with sofosbuvir plus simeprevir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • No dose adjustment is required for tacrolimus or cyclosporine with any of the above combinations. Careful monitoring is important in the absence of safety data in this population. <p><u>Hepatitis B virus (HBV) co-infection</u></p> <ul style="list-style-type: none"> • Patients should be treated with the same regimens, following the same rules as HCV mono-infected patients. • If HBV replicates at significant levels before, during or after HCV clearance, concurrent HBV nucleoside/nucleotide analogue therapy is indicated. <p><u>Hemodialysis patients</u></p> <ul style="list-style-type: none"> • Hemodialysis patients, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy. • Hemodialysis patients should receive an interferon alfa-free and ribavirin-free regimen. • Due to the lack of safety and efficacy data, the need for dose adjustments for sofosbuvir, simeprevir and daclatasvir is unknown. • Given the lack of data, extreme caution is recommended and sofosbuvir should not be administered to patients with an estimated glomerular filtration rate <30 mL/min/1.73 m² or with end-stage renal disease. <p><u>Non-hepatic solid organ transplant recipients</u></p> <ul style="list-style-type: none"> • HCV treatment before kidney transplantation may avoid liver-related mortality in the post-transplant patient, and may prevent HCV-specific causes of renal graft dysfunction. • Where possible, interferon-free and ribavirin-free antiviral regimen should be given to potential transplant recipients before listing for renal transplantation; however, no safety and efficacy data is available in this population. • Given the lack of data, extreme caution is recommended and sofosbuvir should not be administered to patients with an estimated glomerular filtration rate <30 mL/min/1.73 m² or with end-stage renal disease. • In non-hepatic solid organ transplant recipients, patients with an indication for anti-HCV therapy should receive an interferon-free regimen. • Patients with HCV genotype 2 infection must be treated with sofosbuvir plus ribavirin for 12 to 24 weeks, pending more data in this population. • Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with sofosbuvir plus daclatasvir for 12 to 24 weeks, with or without ribavirin, pending more safety data in this population. • Patients with HCV genotype 1 or 4 infection can be treated with sofosbuvir plus simeprevir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • No dose adjustment is required for tacrolimus or cyclosporine with any of

Clinical Guideline	Recommendation(s)
	<p>these combinations. Careful monitoring is important in the absence of safety data in this population.</p> <p><u>Active drug addicts and patients on stable maintenance substitution</u></p> <ul style="list-style-type: none"> • HCV treatment for people who inject drugs (PWIDs) should be considered on an individualized basis and delivered within a multidisciplinary team setting. • Sofosbuvir and simeprevir can be used in PWIDs on opioid substitution therapy. They do not require specific methadone and buprenorphine dose adjustment, but monitoring for signs of opioid toxicity or withdrawal should be undertaken. More data is needed with daclatasvir. • Consideration of interferon-containing or interferon-free therapy in PWIDs should be undertaken on an individualized basis, but those with early liver disease can be advised to await further data and/or potential development of improved therapies. • The regimens that can be used in PWIDs are the same as in non-PWIDs. • Awareness should be raised that liver transplantation is a therapeutic option in those with a history of injection drug use. • Opioid substitution therapy is not a contraindication for liver transplantation and individuals on opioid substitution should not be advised to reduce or stop therapy. <p><u>Treatment of acute hepatitis C</u></p> <ul style="list-style-type: none"> • Peginterferon alfa monotherapy for 24 weeks can be used in patients with acute hepatitis C, who will achieve SVR in as many as 90% of cases. • Peginterferon alfa plus ribavirin for 24 weeks is recommended in patients with acute hepatitis C who are HIV-coinfection. • Although no data is available yet, interferon-free regimens can theoretically be used in patients with acute hepatitis C and are expected to achieve high SVR rates. <p>Note: Daclatasvir is not currently Food and Drug Administration-approved in the United States.</p>
<p>World Health Organization: Guidelines for the Screening, Care and Treatment of Persons with Hepatitis C Infection (2014)⁸</p>	<p><u>Recommendations for treatment of HCV infection</u></p> <ul style="list-style-type: none"> • All adults and children with chronic HCV infection, including people who inject drugs, should be assessed for antiviral treatment. • Peginterferon alfa in combination with ribavirin is recommended for the treatment of chronic HCV infection rather than standard non-peginterferon alfa with ribavirin. • Where access to treatment for HCV infection is limited, priority for treatment should be given to patients with advanced liver disease (F3 and F4). • Treatment with the direct-acting antivirals telaprevir or boceprevir, given in combination with peginterferon alfa and ribavirin, is suggested for genotype 1 chronic HCV infection rather than peginterferon alfa and ribavirin alone. • In high-income settings, HCV treatment with peginterferon alfa and ribavirin and with boceprevir or telaprevir plus peginterferon alfa and ribavirin has been evaluated as being cost-effective. • Sofosbuvir, given in combination with ribavirin with or without peginterferon alfa (depending on the HCV genotype), is recommended in genotypes 1, 2, 3 and 4 HCV infection rather than peginterferon alfa and ribavirin alone (or no treatment for persons who cannot tolerate peginterferon alfa); recommendation made without taking resource use into consideration. • Simeprevir, given in combination with peginterferon alfa and ribavirin, is recommended for persons with genotype 1b HCV infection and for persons with genotype 1a HCV infection without the Q80K polymorphism rather than

Clinical Guideline	Recommendation(s)
	<p>peginterferon alfa and ribavirin alone; recommendation made without taking resource use into consideration.</p> <ul style="list-style-type: none"> • Absolute contraindications to peginterferon alfa: <ul style="list-style-type: none"> ○ Uncontrolled depression, psychosis, or epilepsy. ○ Uncontrolled autoimmune disease. ○ Decompensated cirrhosis (Child–Pugh \geq B7 or B6 in HCV/HIV coinfection). ○ Pregnancy or unwillingness to use contraception. ○ Breastfeeding women. ○ Severe concurrent medical disease including severe infections. ○ Poorly controlled hypertension, cardiac failure, or diabetes. ○ Solid organ transplant (except liver transplant recipients). ○ Chronic obstructive pulmonary disease. ○ Age <2 years old. • Relative contraindications to peginterferon alfa: <ul style="list-style-type: none"> ○ Abnormal hematological indices: <ul style="list-style-type: none"> ▪ Hb <13 g/dL in men or <12 g/dL in women. ▪ Neutrophil count <1.5x10⁹/L. ▪ Platelet count <90x10⁹/L. ○ Serum creatinine >1.5 mg/dL. ○ Hemoglobinopathies (sickle cell disease or thalassemia). ○ Significant coronary artery disease. ○ Untreated thyroid disease. • Treatment for HCV infection is both efficacious and cost-effective in PWID and is therefore recommended. • Specialist care needs to address the additional needs of special populations of patients, including PWID, persons coinfecting with (or at risk for infection with) HIV, children and adolescents, and those with cirrhosis. • The decision to initiate treatment for HCV/HIV-coinfection is more complex than in those with HCV monoinfection, as response rates are lower, risk of potential toxicities is higher and treatment is complicated by a high pill burden, overlapping toxicities, and interactions between drugs used for treating HCV and HIV.
<p>Centers for Disease Control and Prevention: Hepatitis ABC Fact Sheet (2012)⁹</p>	<p><u>Hepatitis C</u></p> <ul style="list-style-type: none"> • For acute hepatitis C, antivirals and supportive treatments are used. • Regular monitoring for signs of liver disease progression is required and some patients are treated with antiviral drugs.
<p>American Gastroenterological Association: Medical Position Statement on the Management of Hepatitis C (2006)¹⁰</p>	<ul style="list-style-type: none"> • The treatment of choice is peginterferon plus ribavirin. • Patients with genotypes 1 and 4 require 48 weeks of therapy with peginterferon and high daily doses of ribavirin (1,000 to 1,200 mg, depending on weight). • Patients with genotypes 2 and 3 can be treated for only 24 weeks with peginterferon and 800 mg of ribavirin daily, with the following exceptions: <ul style="list-style-type: none"> • A longer duration of therapy may be considered on an individual patient basis taking into account factors such as elevated viral level, cirrhosis, or delayed response to therapy. • Twelve weeks of therapy suffices in patients in whom HCV RNA levels are undetectable at week four. • Patients with genotype 3, with high levels of HCV RNA or advanced fibrosis on liver biopsy, may require treatment for 48 weeks.

Conclusions

Sovaldi® (sofosbuvir) is a novel once-daily nucleotide analog inhibitor of hepatitis C virus (HCV) nonstructural protein 5B ribonucleic acid (RNA) polymerase, which is essential for viral replication of HCV. The efficacy of sofosbuvir has been established in patients with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/human immunodeficiency virus-1 co-infection.¹⁴ The approval has changed the way in which hepatitis C is treated.

Similar to HCV protease inhibitors, sofosbuvir may be used in both treatment-naïve patients as well as those who have been previously treated with interferon-based treatment, including prior null responders, partial responders and relapsers.¹¹⁻¹⁴ Sofosbuvir must be administered in combination with ribavirin or peginterferon alfa and ribavirin. Because of this, warnings and precautions that are associated with these agents are applicable to polymerase inhibitor combination treatment. The safety and efficacy of sofosbuvir have not been established in post-liver transplant patients or those who have previously failed therapy with a treatment regimen that includes HCV nonstructural protein 3/4A protease inhibitors.¹⁴

The pivotal clinical trials demonstrate that treatment with sofosbuvir, in combination with ribavirin or peginterferon alfa and ribavirin, results in significantly higher sustained virologic response rates among adult patients with chronic hepatitis C genotype 1, 2, 3 and 4 infection compared to standard therapy alone.^{14,16-18} Several regimens not currently approved by the Food and Drug Administration are currently being evaluated in clinical trials. These include evaluation of sofosbuvir plus ribavirin in patients with recurrent HCV infection (any genotype) after liver transplantation; sofosbuvir plus peginterferon alfa and ribavirin in treatment-experienced patients with genotype 2 or 3 HCV infection; and sofosbuvir plus simeprevir in difficult to treat groups of hepatitis C patients (prior null responders and treatment-naïve patients with advanced liver disease).²⁰⁻²⁴

Compared to combination therapy with HCV protease inhibitors for the treatment of HCV genotype 1 infection, sofosbuvir combination therapy offers potential for improved efficacy, shorter duration of treatment that is not response-guided, no viral resistance, favorable safety profile, reduced pill burden, and fewer drug-drug interactions (no CYP450 hepatic metabolism).¹¹⁻¹⁴

The 2014 consensus guidelines from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) give preference to sofosbuvir-based combination therapy for most patients with chronic HCV genotype 1 through 6 infection. The use of telaprevir- and boceprevir-containing regimens is no longer recommended in the treatment of HCV genotype 1 infection.⁵ Treatment guidelines do not give preference to one specific peginterferon alfa or ribavirin product over another.²⁻¹⁰ To date, no head-to-head trials have been published to directly compare the efficacy of HCV polymerase inhibitor sofosbuvir and HCV protease inhibitors.

References

1. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010 Dec 17;59(RR-12):1-110.
2. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, Management and treatment of hepatitis C; An Update. 2009. *Hepatology* 2009; 49(4):1-40.
3. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. *J Hepatol*. 2013 Dec 4.
4. European Association for the Study of the Liver (EASL): Treatment of Hepatitis [guideline on the Internet]. Geneva (Switzerland): EASL 2014 Apr [cited 2014 Jun 1]. Available at: <http://files.easl.eu/easl-recommendations-on-treatment-of-hepatitis-C.pdf>.
5. American Association for the Study of Liver Diseases (AASLD), Infectious Diseases Society of America (IDSA), International Antiviral Society-USA (IAS-USA). Recommendations for testing, managing, and treating hepatitis C [guideline on the Internet]. Alexandria (VA): AASLD/IDSA/IAS-USA 2014 Apr [cited 2014 Jun 1]. Available at: <http://www.hcvguidelines.org>.
6. American Association for the Study of Liver Diseases (AASLD). An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection: 2011 Practice Guideline by the American Association for the Study of Liver Diseases [guideline on the internet]. Geneva, Switzerland: American Association for the Study of Liver Diseases; 2013 [cited 2014 Jun 1]. Available from: <http://www.aasld.org/practiceguidelines/Documents/AASLDUpdateTreatmentGenotype1HCV11113.pdf>.
7. Department of Veteran Affairs National Hepatitis C Resource Center Program and the Office of Public Health. Chronic hepatitis C Virus (HCV) infection: Treatment considerations [guideline on the Internet]. Washington (DC): VA 2014 May [cited 2014 Jun 1]. Available at: <http://www.hepatitis.va.gov/pdf/2014hcv.pdf>.
8. World Health Organization (WHO). Guidelines for the screening, care and treatment of persons with hepatitis C infection [guideline on the Internet]. Geneva (Switzerland): WHO 2014 Apr [cited 2014 Jun 1]. Available at: <http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/>.
9. Centers for Disease Control and Prevention. The ABCs of Hepatitis Fact Sheet [guideline on the Internet]. Atlanta (GA): CDC 2012 Aug [cited 2014 Jun 1]. Available at: <http://www.cdc.gov/hepatitis/resources/professionals/pdfs/abctable.pdf>.
10. Dienstag JL, McHutchison JG. American Gastroenterological Association Medical position statement on the management of hepatitis C. *Gastroenterology*. 2006;130(1):225-30.
11. Victrelis[®] [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2014 Apr.
12. Incivek[®] [package insert]. Cambridge (MA): Vertex Pharmaceuticals Incorporated; 2013 Oct.
13. Olysio[®] [package insert]. Titusville (NJ): Janssen Therapeutics; 2013 Nov.
14. Sovaldi[®] [package insert on the internet]. Foster City (CA): Gilead Sciences, Inc.; 2013 Dec.
15. Micromedex[®] Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Healthcare; Updated periodically [cited 2014 Jun 1]. Available from: <http://www.thomsonhc.com/>.
16. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013 May 16;368(20):1878-87.
17. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013 May 16;368(20):1867-77.
18. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med*. 2014 May 22;370(21):1993-2001.
19. Gilead Announces Phase 3 Results for an All-Oral, Sofosbuvir-Based Regimen for the Treatment of Hepatitis C in Patients Co-Infected With HIV [press release on the Internet]. Washington (DC): Gilead Sciences Inc.; 2013 Nov 2 [cited 2014 Jun 1]. Available from: http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-newsArticle_Print&ID=1871556.
20. Charlton M, Gane E, Manns MP, Brown RS, Curry MP, Kwo P, et al. Sofosbuvir and Ribavirin for the Treatment of Established Recurrent Hepatitis C Infection After Liver Transplantation: Preliminary Results of a Prospective, Multicenter Study. 64th Annual Meeting of the American Association for the Study of Liver Diseases. Washington, DC. November 1-5. 2013. Abstract LB-2.
21. Lawitz E, Poordad F, Brainard DM, Hyland RH, An D, Symonds WT, et al. Sofosbuvir in Combination With PegIFN and Ribavirin for 12 Weeks Provides High SVR Rates in HCV-Infected Genotype 2 or 3 Treatment Experienced Patients with and without Compensated Cirrhosis: Results from the LONESTAR-2 Study. 64th Annual Meeting of the American Association for the Study of Liver Diseases. Washington, DC.

- November 1-5, 2013. Abstract LB-4.
22. Jacobson IM, Ghalib RH, Rodriguez-Torres M, Younossi ZM, Corregidor A, Sulkowski MS et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: The COSMOS study. American Association for the Study of Liver Diseases (AASLD). Washington. November 1-5, 2013. Abstract 1840610.
 23. Results from the COSMOS study with Simeprevir and Sofosbuvir in cirrhotic and non-cirrhotic HCV genotype 1 patients presented at AASLD [press release on the Internet]. Stockholm, Sweden: Medivir AB; 2013 Nov 4 [cited 2013 Jun 1]. Available from: <http://www.medivir.se/v5/en/uptodate/pressrelease.cfm?releaseid=4E7105B904E97096&year=2013>.
 24. Lawitz E, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, Sulkowski MS, et al. Simeprevir plus sofosbuvir with/without ribavirin in HCV genotype 1 prior null-responder/treatment-naive patients (Cosmos study): primary endpoint (SVR12) results in patients with METAVIR F3–4 (Cohort 2). European Association for the Study of the Liver (EASL). London. April 9-13, 2014. Abstract 165.
 25. Pegasys® [package insert]. South San Francisco (CA): Genentech USA, Inc.; 2013 Jul.
 26. PegIntron® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2013 Dec.
 27. Copegus® [package insert]. South San Francisco (CA): Genentech, Inc.; 2013 Feb.
 28. Rebetol® [package insert]. Whitehouse Station (NJ): Schering-Plough Corporation; 2013 Nov.
 29. Ribasphere® [package insert]. Warrendale (PA): Kadmon Pharmaceuticals, LLC; 2012 Feb.
 30. Drug Facts and Comparisons [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2014 Jun]. Available from: <http://online.factsandcomparisons.com>.