2018 Update to the Consensus Statements on the Treatment of Hepatitis C

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Foreword

Four years ago, the Hepatology Society of the Philippines published the 2014 Consensus Statements on the Diagnosis and Treatment of Hepatitis C. Since then, a number of direct-acting antivirals (DAA) have been made available in the country. These agents have significantly improved the viral response rates of drug therapy for chronic hepatitis C and the resulting outcomes and prognosis of patients with chronic hepatitis C. Therefore, this document updates the consensus statements of the 2014 guidelines to include the scientific evidence supporting DAAs currently available in the Philippines.

These updated treatment recommendations categorized patients according to virus genotype, previous pharmacotherapy (i.e., treatment naive patients or those treated with pegylated interferon (Peg-IFN) and ribavirin), and the presence of cirrhosis and hepatic decompensation in defining the most appropriate antiviral regimens.

As emphasized in the previous consensus statements, the treatment for hepatitis C is fast growing and evolving. Hence, these statements may be amended as new data and treatments become available.

As of July 2018, velpatasvir is not yet commercially available. However, it is accessible to some patients through compassionate use and is expected to be commercially available soon.

Methods

This update was developed through the initiative of the Hepatology Society of the Philippines, which created a consensus core group composed of six hepatologists. The members of the core group performed a literature search for all available literature on the treatment of hepatitis C, with focus on the appropriate treatment according to HCV genotype. Efficacy and safety data of treatments were extracted and evaluated, and recommendations were developed for treatments with net benefit that were currently available in the Philippines. Recommendations were discussed and revised until consensus within the core group was achieved.

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Treatment of HCV Genotype 1a (HCV1a) and 1b (HCV1b) Infection

The first report of sustained virologic response (SVR) for HCV genotype 1 (HCV1) using an all-oral DAA combination therapy[1] was quickly followed within a few years by several other all-oral regimens with vastly superior efficacy and safety profile compared to peg-IFN–containing regimens. While all of the trials on DAA have defined SVR as 12 weeks (SVR12) after the end of treatment, as opposed to 24 weeks (SVR24) in earlier trials using Peg-IFN, SVR12 of DAAs is highly concordant (>97%) with SVR24.[2]

Genotype 1a and 1b, treatment-naive without liver cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) for 12 weeks
- Sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) for 12 weeks
- Sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) for 12 weeks

Genotype 1a and 1b, treatment-naive with compensated liver cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) for 12 weeks
- Sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) for 12 weeks

Alternative regimen:

- Sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) with or without weight-based ribavirin (1,000 mg OD for <75 kg; 1,200 mg OD for >75 kg) for 24 weeks

Summary of evidence

Sofosbuvir plus ledipasvir

The combination of sofosbuvir 400 mg and ledipasvir 90 mg is available as a fixed-dose combination tablet. The combination was evaluated in a phase III trial, where the combination was given using one of these four regimens: (1) once daily without ribavirin for 12 weeks and (2) for 24 weeks; and (3) with ribavirin for 12 weeks and (4) with ribavirin for 24 weeks.[3] Two-thirds of the patients had HCV1a infection and the rest had HCV1b. SVR rates were 97% to 99% for all four groups, with no significant differences between groups and between HCV1a and HCV1b patients. A subgroup analysis on patients with compensated cirrhosis showed that the SVR of 12 weeks of sofosbuvir plus ledipasvir were similar between patients with no cirrhosis and those with compensated cirrhosis (97% vs 100%, respectively).

A second phase III study reported a similar SVR rate (95%) in patients given sofosbuvir plus ledipasvir for 12 weeks.[4] While the study found that a shortened regimen (eight weeks) in non-cirrhotic patients was effective provided that they were of non-African ethnicity, were mono-infected, and had a baseline HCV RNA of <6 million IU/mL, relapse rates were relatively high (5%) compared with 12 weeks of treatment (1%) and is therefore not recommended.

These findings support the recommendation for sofosbuvir and ledipasvir once daily for 12 weeks for the treatment of HCV1a and HCV1b with or without compensated liver cirrhosis.

Sofosbuvir plus daclatasvir

A randomized controlled trial (RCT) demonstrated that sofosbuvir 400 mg plus daclatasvir 60 mg given for 12 or 24 weeks both had a 100% SVR12 in treatment-naïve patients without cirrhosis.[5] The addition of ribavirin to either 12- or 24-week regimen did not improve SVR rates.

The efficacy of the 12-week regimen was later confirmed in patients co-infected with HCV and human immunodeficiency virus (HIV).[6] In this study, the SVR rate of the 12-week regimen was 96.4% vs only 75.6% for the eight-week regimen.

Only around 10% of patients in the registration trials of this DAA combination had compensated cirrhosis, which are insufficient to form a recommendation for first-line therapy. However, real-world data in patients with compensated cirrhosis suggest that treatment extension to 24 weeks delivers higher SVR rates (95% to 97%) compared to 12 weeks (88%), and may be considered as an alternative regimen, with or without ribavirin.[7,8]

Sofosbuvir plus daclatasvir for 12 weeks is therefore a recommended treatment for treatment-naïve HCV1 patients without cirrhosis, while a 24-week regimen with or without with or without ribavirin may be given as an alternative treatment for treatment-naïve HCV1 patients with compensated cirrhosis.

Sofosbuvir plus velpatasvir

The combination of sofosbuvir and velpatasvir is recognized as the first pangenotypic (genotypes 1-6) anti-HCV regimen with high SVR rates. In a phase III study where 68% of patients were treatment naïve and 53% had HCV1 infection, 12 weeks of daily sofosbuvir 400 mg plus velpatasvir 100 mg resulted in SVR rates of 98% for HCV1a and 99% for HCV1b, with no significant differences in adverse effects between the placebo and treatment groups.[9] A total of 121 (19%) patients across all genotypes had compensated cirrhosis, and the SVR rates of these patients (100% and 95.8% for HCV1a and HCV1b, respectively) were similar to those without cirrhosis.

Hence, daily sofosbuvir plus velpatasvir given for 12 weeks is recommended as a treatment for treatment-naïve HCV1 patients with or without compensated cirrhosis.

Genotype 1a and 1b, treatment-experienced without liver cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) for 12 weeks in patients who previously failed on Peg-IFN ± ribavirin treatment
- Sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) for 12 weeks in patients who previously failed on Peg-IFN ± ribavirin treatment
- Sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) for 12 weeks in patients who previously failed on Peg-IFN ± ribavirin treatment

Genotype 1a and 1b, treatment-experienced with compensated liver cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) for 24 weeks in patients who previously failed on PEG-IFN ± ribavirin treatment
- Sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) for 12 weeks in patients who previously failed on PEG-IFN ± ribavirin treatment

Alternative regimens:

- Sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) with or without weight-based ribavirin (1,000 mg OD for <75 kg; 1,200 mg OD for >75 kg) for 24 weeks in patients who previously failed on PEG-IFN ± ribavirin treatment
- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) with weight-based ribavirin (1,000 mg OD for <75 kg; 1,200 mg OD for >75 kg) for 12 weeks in patients who previously failed on PEG-IFN ± ribavirin treatment

Summary of evidence

Sofosbuvir plus ledipasvir

A phase III RCT compared the efficacy of four DAA regimens in treatment-experienced HCV1 patients: (1) sofosbuvir plus ledipasvir for 12 weeks or (2) for 24 weeks; or (3) sofosbuvir plus ledipasvir plus weight-based ribavirin for 12 weeks and (4) also for 24 weeks.[10] The SVR rates in patients treated for 12 weeks were similar regardless of the addition of ribavirin (96% with ribavirin vs 94% without ribavirin). Patients treated for 24 weeks had similar SVR rates regardless of the addition of ribavirin (99%).

Therefore, the current recommendation for treatment-experienced patients without cirrhosis is sofosbuvir and ledipasvir given for 12 weeks.

In the same study, the SVR rate of treatment-experienced patients with compensated cirrhosis was lower if sofosbuvir and ledipasvir without ribavirin were given for 12 weeks (86.4%) vs 24 weeks (100%).[10] The addition of ribavirin to the 12-week regimen did not lead to a higher SVR rate (81.8%) but only 22 patients were included in this group. A post-hoc analysis of seven clinical trials that included 352 treatment-experienced patients with compensated cirrhosis showed that the addition of weight-based ribavirin to a 12-week sofosbuvir-ledipasvir regimen results in an SVR rate of 96%.[11] In contrast, the SVR rate of sofosbuvir plus ledipasvir for 24 weeks was 98%. The addition of ribavirin to the 24-week regimen did not significantly increase the SVR rate (100%). Given these findings and the potential side effects of ribavirin in patients, sofosbuvir and ledipasvir given without ribavirin for 24 weeks is recommended for treatment-experienced patients with compensated cirrhosis. Giving sofosbuvir and ledipasvir with ribavirin for 12 weeks is an alternative regimen for this group of patients.

Sofosbuvir plus daclatasvir

The combination of sofosbuvir 400 mg and daclatasvir 60 mg in treatment-experienced patients was studied in a real-world cohort study in France.[7] SVR rates were no different whether treatment duration was 12 weeks (95%) or 24 weeks (96%). Adding ribavirin did not appreciably increase SVR rates. Treatment of patients with compensated cirrhosis showed a significantly lower SVR rate with sofosbuvir plus daclatasvir for 12 weeks (87%) compared to 24 weeks (94%). Adding ribavirin to the 24-week regimen further increases the SVR rate to 98% in cirrhotic patients. Therefore, sofosbuvir plus daclatasvir for 12 weeks is recommended in treatment-experienced non-cirrhotic HCV1 patients while ribavirin should be added to the regimen and the duration extended to 24 weeks as an alternative regimen for treatment-experienced cirrhotic patients.

Sofosbuvir plus velpatasvir

A phase III trial evaluated the efficacy of the combination of sofosbuvir and velpatasvir given for 12 weeks, in which 201 patients (32%) had failed on previous HCV treatment, majority (89%) having had received IFN-based treatment.[9] The SVR rate in HCV1 patients who previously failed on other treatments was 99.1%, which was similar to those of treatment-naïve patients (98.2%). Although there was no further sub-analysis in treatment-experienced patients with compensated liver cirrhosis, no significant differences in SVR rates were seen across all other subgroups. Additionally, the SVR rate in this population was 100% in a phase II study.[12] These findings support the recommendation of daily sofosbuvir and velpatasvir for 12 weeks in treatment-experienced patients with or without compensated cirrhosis.

Genotype 1a and 1b, with decompensated (Child-Pugh B or C) liver cirrhosis

All HCV patients with decompensated liver cirrhosis should be referred to a liver transplant center for evaluation. The assessment of any antiviral treatment for this patient population should not only take SVR rates into account, but also improvement in liver function and safety.

Recommended regimens:

- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) with escalating ribavirin dose (initial dose of 600 mg in divided doses, and escalated as tolerated to weight-based dose) for 12 weeks
- Sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) with escalating ribavirin dose (initial dose of 600 mg in divided doses, and escalated as tolerated to weight-based dose) for 12 weeks
- Sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) with escalating ribavirin dose (initial dose of 600 mg in divided doses, and escalated as tolerated to weight-based dose) for 12 to 24 weeks

Alternative regimens:

- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) for 24 weeks
- Sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) for 24 weeks

Summary of evidence

Sofosbuvir plus ledipasvir

In an open-label phase II study, sofosbuvir and ledipasvir in combination with ribavirin started at a low initial dose of 600 mg a day for 12 weeks was compared with a 24-week regimen.[13] There was no difference in SVR rates between the two groups in both patients with Child-Pugh B (87% for 12 weeks vs 87% for 24 weeks) or Child-Pugh C (86% for 12 weeks vs 87% for 24 weeks) cirrhosis. Majority of patients had improvements in their liver function tests by the fourth week of treatment.

Furthermore, a multicenter RCT also compared sofosbuvir plus ledipasvir and ribavirin given for 12 vs 24 weeks in decompensated cirrhosis.[14] SVR rates were 87% and 96% in Child-Pugh B patients treated for 12 and 24 weeks,

respectively, while the SVR rates in Child-Pugh C patients were 85% and 78%, respectively. Grades 3 and 4 adverse events were significantly higher in the groups treated for 24 weeks, and the adverse events were mainly attributed to ribavirin therapy. Given the almost similar SVR rates with 12- or 24-week treatment of sofosbuvir-ledipasvir-ribavirin combination and the increased adverse events with 24-week treatment, sofosbuvir-ledipasvir-ribavirin combination treatment is recommended for 12 weeks in patients with decompensated cirrhosis. Patients who cannot tolerate ribavirin may omit this drug from the regimen but treatment duration with sofosbuvir plus ledipasvir should be extended to 24 weeks.

Sofosbuvir plus daclatasvir

The combination of sofosbuvir and daclatasvir with ribavirin for 12 weeks was studied in an open-label trial in HCV patients with advanced liver disease.[15] In this study, the SVR rate in decompensated patients was 81%. However, further analysis showed that patients with Child-Pugh B cirrhosis had significantly better SVR (92%) than patients with Child-Pugh C cirrhosis (50%). Furthermore, real-world data on the efficacy of a one-week regimen of sofosbuvir-daclatasvir-ribavirin reported an SVR rate of 88%.[16]

A multicenter cohort study suggests that a longer treatment duration of 24 weeks may be preferred in decompensated patients because of higher SVR rates of 95% and 100% in Child-Pugh B and C patients, respectively.[8]

Therefore, it is recommended that if tolerated, sofosbuvir-daclatasvir-ribavirin combination should be given for 24 weeks in patients with decompensated cirrhosis. Treatment may be shortened to 12 weeks if adverse events are intolerable.

Sofosbuvir plus velpatasvir

A multicenter RCT in HCV patients with Child-Pugh B cirrhosis, 78% of whom had HCV1 infection, compared the efficacy of three regimens with sofosbuvir plus velpatasvir: (1) for 12 weeks without ribavirin; (2) for 12 weeks with ribavirin; and (3) for 24 weeks without ribavirin. The SVR rates were 88%, 96% and 92%, respectively.[17] During the study, 47% of patients experienced improvement in their Child-Pugh scores while only 11% experienced worsening of scores. With these rates, the recommendation is to give sofosbuvir plus velpatasvir with ribavirin for 12 weeks for the treatment of HCV1 in patients with decompensated cirrhosis. In patients who are intolerant of or have contraindications for ribavirin, sofosbuvir and velpatasvir for 24 weeks is an alternative regimen.

Treatment of HCV genotype 2 (HCV2) infection

With the Philippines having less heterogeneity in hepatitis C genotypes compared with the rest of Southeast Asia, the prevalence of HCV2 in the Philippines is estimated at 26.4%, second to HCV1.[18] During the era of Peg-IFN and ribavirin therapy, SVR rates for genotype 2 in Asia were better than those achieved in Western countries.[19] With the availability of DAAs in the Philippines, these agents are the preferred treatment for HCV2 infection.

Genotype 2, treatment-naïve without cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg PO OD) plus Velpatasvir (100 mg PO OD) for 12 weeks
- Sofosbuvir (400 mg PO OD) plus Daclatasvir (60 mg PO OD) for 12 weeks

Genotype 2, treatment-naïve with compensated cirrhosis

Recommended regimen:

- Sofosbuvir (400 mg PO OD) plus Velpatasvir (100 mg PO OD) for 12 weeks

Alternative regimen:

- Sofosbuvir (400 mg PO OD) plus Daclatasvir (60 mg PO OD) for 16-24 weeks

Summary of evidence

Sofosbuvir plus velpatasvir

In the phase III ASTRAL-1 study, the combination of sofosbuvir 400 mg plus velpatasvir 100 mg was given for 12 weeks to 104 treatment-naïve patients with HCV2 infection without cirrhosis or with compensated cirrhosis, whereas 21 patients received placebo.[9] The SVR rate of the active treatment was 100% vs 0% in the placebo group. These findings support the recommendation for sofosbuvir plus velpatasvir given for 12 weeks to treatment-naïve HCV2-infected patients without cirrhosis or with compensated cirrhosis.

Sofosbuvir plus daclatasvir

An RCT demonstrated that sofosbuvir 400 mg plus daclatasvir 60 mg given for 12 or 24 weeks achieves a high SVR rate for patients infected with HCV2.5 Of the 26 treatment-naïve HCV2 patients included in the study, the SVR rate of the 12-week regimen was 92%. Thus, the combination of sofosbuvir plus daclatasvir given for 12 weeks to treatment-naïve HCV2 patients without cirrhosis is recommended, while treatment should be extended to 16 to 24 weeks for those with compensated cirrhosis. This recommendation is aligned with other international guidelines.

Genotype 2, treatment-experienced with Peg-IFN, without cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg PO OD) plus velpatasvir (100 mg PO OD) for 12 weeks
- Sofosbuvir (400 mg PO OD) plus daclatasvir (60 mg PO OD) for 12 weeks

Genotype 2, treatment-experienced with Peg-IFN, with compensated cirrhosis

Recommended regimen:

- · Sofosbuvir (400 mg PO OD) plus velpatasvir (100 mg PO OD) for 12 weeks

Alternative regimen:

- Sofosbuvir (400 mg PO OD) plus daclatasvir (60 mg PO OD) for 16 to 24 weeks

Summary of evidence

Sofosbuvir plus velpatasvir

In the phase III ASTRAL-2 study, the combination of sofosbuvir 400 mg plus velpatasvir 100 mg were given for 12 weeks to 134 HCV2 patients without cirrhosis or with compensated cirrhosis, whereas 132 similar patients received sofosbuvir 400 mg plus weight-based ribavirin for 12 weeks.[20] Fourteen of the 134 patients in the sofosbuvir/velpatasvir group and 15 of the 132 patients in the sofosbuvir/ribavirin group had previously been treated with an interferon-containing regimen.

SVR rate was 99% in the sofosbuvir-velpatasvir group compared with 94% in the sofosbuvir-ribavirin group, thus supporting the recommendation for sofosbuvir plus velpatasvir for 12 weeks to treatment-experienced HCV2 patients without cirrhosis or with compensated cirrhosis.

Sofosbuvir plus daclatasvir

Limited data are available. However, sofosbuvir plus daclatasvir has been given to patients previously treated with PEG-ribavirin, and can thus be considered as alternative treatment.[6]

Genotype 2, treatment-experienced with sofosbuvir and ribavirin, without cirrhosis or with compensated cirrhosis

Recommended regimen:

- Sofosbuvir (400 mg PO OD) plus velpatasvir (100 mg PO OD) with or without weight-based ribavirin for 12 weeks

Alternative regimen:

- Sofosbuvir (400 mg PO OD) plus daclatasvir (60 mg PO OD) with or without weight-based ribavirin for 12 weeks

Summary of evidence

The evidence regarding the treatment of HCV2 patients previously treated with sofosbuvir and ribavirin is limited. The recommendations to treat with sofosbuvir plus daclatsvir or velpatasvir with or without ribavirin is based on the best-available evidence on HCV1 patients.[12]

Genotype 2, with decompensated cirrhosis

This group includes those with moderate or severe hepatic impairment (Child-Pugh B or C), and who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.

Recommended regimen:

- Sofosbuvir (400 mg PO OD) plus velpatasvir (100 mg PO OD) with weight-based ribavirin for 12 weeks

Alternative regimen:

- Sofosbuvir (400 mg PO OD) plus daclatasvir (60 mg PO OD) with ribavirin (600 mg PO OD initially and increased as tolerated to weight-based dose) for 12 weeks

Summary of evidence

Sofosbuvir plus velpatasvir

A phase III, open-label study involving both previously treated and previously untreated patients infected with HCV genotypes 1 through 6 who had decompensated cirrhosis (Child–Pugh B). In this study, SVR rates of patients with HCV genotype 2 treated for 12 weeks with and without ribavirin were similar, as well as for treatment without ribavirin for 24 weeks (all 100%).[17] Since only 4% of patients in this study had HCV2 infection (hence, genotype 2-specific ribavirin-free data is lacking) and overall response rates were higher in ribavirin-treated patients, the addition of ribavirin to sofosbuvir plus velpatasvir is recommended, in line with international guidelines.

Sofosbuvir plus daclatasvir

The ALLY-1 study assessed the safety and efficacy of a 60-mg once-daily dosage of daclatasvir plus sofosbuvir at 400 mg once daily, given with ribavirin at 600 mg/day for 12 weeks in patients with cirrhosis, including Child-Pugh B and C patients. The SVR rate for patients with genotype 2 was 80%.[15]

Treatment of HCV genotype 3 infection

HCV genotype 3 (HCV3) is not a common genotype in the Philippines but may be associated with significant morbidity and mortality. In addition, the all-oral DAAs have lower efficacy in genotype 3 patients, especially among treatment-experienced and cirrhotic patients.

Before the advent of DAAs, the treatment of HCV3 infection included the combination of Peg-IFN and ribavirin given for 16 to 72 weeks but was associated with low SVR rates. It was later replaced by the combination of sofosbuvir and ribavirin or sofosbuvir plus peg-IFN plus ribavirin. However, both of these regimens are less favored at present with the availability of the all-oral DAA regimens, which provide higher SVR rates as well as more convenient, all-oral dosing with better safety and tolerability profiles.

Genotype 3, treatment-naïve without cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) for 12 weeks
- Sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) for 12 weeks

Summary of evidence

Sofosbuvir plus daclatasvir

Among treatment-naïve genotype 3 patients without cirrhosis, the phase 3 trial ALLY-3 showed that daclatasvir and sofosbuvir combination given for 12 weeks was associated with a 97% SVR rate.[21]

Sofosbuvir plus velpastavir

The ASTRAL-3 study showed that the fixed-dose combination of sofosbuvir and velpatasvir given for 12 weeks was associated with an SVR rate of 98%.[20]

Genotype 3, treatment-naïve with compensated cirrhosis

Recommended regimen:

- Sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) for 12 weeks

Alternative regimen:

- Sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) for 24 weeks with weight-based ribavirin (1,000 or 1,200 mg a day in patients weighing <75 and ≥75 kg, respectively).
- If intolerant of ribavirin, treatment with daily sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) can be given for 24 weeks.

Summary of evidence

Sofosbuvir plus velpatasvir

In the ASTRAL-3 trial, the SVR rate was 93% for the fixed-dose combination of sofosbuvir and velpatasvir given for 12 weeks among treatment-naïve genotype 3 patients with compensated cirrhosis.[20]

Sofosbuvir plus daclatasvir

In the ALLY-3 trial, the presence of cirrhosis was associated with lower SVR rates from the daclatasvir plus sofosbuvir combination. In the ALLY-3+ trial, daclatasvir and sofosbuvir given with ribavirin for 12 or 16 weeks was associated with SVR rates of 83% and 89%.22 In real world data from France, daclatasvir and sofosbuvir given for 24 weeks was associated with an SVR rate of 86%.[23] Thus, this combination is recommended only as an alternative regimen.

Genotype 3, treatment-experienced without cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) for 12 weeks
- Sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) for 12 weeks

Summary of evidence

Sofosbuvir plus velpatasvir

Among non-cirrhotic genotype 3 patients previously treated with pegylated interferon and ribavirin, ASTRAL-3 showed SVR rates of 91% with 12 weeks of the fixed-dose combination of sofosbuvir and velpatasvir.[20]

Sofosbuvir plus daclatasvir

In ALLY-3, daclatasvir and sofosbuvir for 12 weeks among these patients was associated with an SVR rate of 93%.[21]

Genotype 3, treatment-experienced, with compensated cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) for 12 weeks with weight-based ribavirin
- If intolerant of ribavirin, treatment with daily sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) can be given for 24 weeks.

Alternative regimens:

- Sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) for 24 weeks with weight-based ribavirin
- If intolerant of ribavirin, treatment with daily sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) can be given for 24 weeks.

Summary of evidence

SVR rates are generally lower for cirrhotic genotype 3 patients who have been previously treated with Peg-IFN and ribavirin.

Sofosbuvir plus velpatasvir

In the ASTRAL-3 trial, the fixed-dose combination of sofosbuvir plus velpatasvir given for 12 weeks was associated with an SVR rate of 89%.[21] In some studies, the addition of ribavirin to 12 weeks' treatment with sofosbuvir and velpatasvir was associated with higher SVR rates. Hence, this combination with the addition of ribavirin, if tolerated, is recommended for 12 weeks.

Sofosbuvir plus daclatasvir

In the ALLY-3+ trial, daclatasvir plus sofosbuvir given with ribavirin for 12 or 16 weeks was associated with SVR rates of 88% and 89%, respectively.[22] Furthermore, real-world studies from France showed that daclatasvir plus sofosbuvir given for 24 weeks was associated with an SVR rate of 87%.[23] Given the longer duration of treatment required for daclatasvir-containing regimens, these are recommended as alternatives.

Genotype 3, with decompensated cirrhosis

This group includes those with moderate or severe hepatic impairment (Child-Pugh B or C), and who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.

Recommended regimens:

- Sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) for 12 weeks with weight-based ribavirin
- Sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) for 12 weeks with weight-based ribavirin
- If intolerant of ribavirin, treatment with daily sofosbuvir (400 mg OD) plus either daclatasvir (60 mg OD) or

velpatasvir (100 mg) can be given for 24 weeks, but SVR rates are lower

Summary of evidence

The aims of treatment of HCV infection in patients with decompensated cirrhosis include the improvement of liver function in those awaiting liver transplantation and the prevention of infection of the liver allograft after transplantation. Treatment should be undertaken in conjunction with a liver transplant center as treatment can lead to further decompensation.

Sofosbuvir plus velpatasvir

In the ASTRAL-4 study, the SVR rates with sofosbuvir plus velpatasvir for 12 weeks without or with ribavirin among 39 patients with Child-Pugh B cirrhosis were 50% and 85%, respectively, and 50% with sofosbuvir plus velpatasvir without ribavirin for 24 weeks.[17]

Sofosbuvir plus daclatasvir

The data supporting the use of sofosbuvir plus daclatasvir in patients with HCV3 infection and decompensated cirrhosis is limited. Foster et al showed that the SVR rates with the use of 12 weeks of daclatasvir plus sofosbuvir with or without ribavirin in such patients were 60% and 71%, respectively.[16] Furthermore, Welzel et al reported that the use of daclatasvir and sofosbuvir with and without ribavirin for 24 weeks was associated with SVR rates of 80% and 87%, respectively, among Child B patients and 78% and 100%, respectively among Child C patients.[8] However, the number of patients in each group ranged only from two to 15 patients.

Treatment of HCV genotype 4 infection

HCV genotype 4 (HCV4) represents 12% to 15% of the total global HCV infections. It is most prevalent in Northern and Equatorial Africa and the Middle East, and is rare in the United States, Canada, South America and Asia.[24] It is likely that the clinical course of genotype 4 infection is similar to that of other genotypes, although only a few studies have investigated the outcome of acute HCV4 infection. Prospective studies have shown that acute HCV4 spontaneous resolve in 20% to 50% of cases, although these rates are reduced in patients with HIV or Schistosoma mansoni coinfection.[25]

In the era prior to DAAs, treatment-naïve genotype 4 patients treated with a 48-week course of Peg-IFN plus ribavirin had SVR rates that ranged from 43% to 70%, with even lower SVR rates in those with cirrhosis (25% to 30%).[26-28] The response of HCV4 to Peg-IFN plus ribavirin is better than HCV1 but worse than HCV2 and HCV3. Studies on predictive factors for treatment response among HCV4 patients, though limited, report that negative predictive factors at baseline include high viral load, presence of cirrhosis and steatosis, insulin resistance, IL-28B polymorphism TT, and HIV coinfection.

Recently, DAAs with pangenotypic activity such as simeprevir, sofosbuvir and daclatasvir have been recommended in triple regimens with Peg-IFN or ribavirin for the treatment of HCV4 infection. Available data with newer all-oral regimens in the treatment of genotype 4 infection suggest that SVR12 rates in treatment-naive patients are greater than 95%, similar to the SVR rates seen with genotype 1 infection.[24]

Genotype 4, treatment-naïve without cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) for 12 weeks
- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) for 12 weeks
- Sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) for 12 weeks
- Sofosbuvir (400 mg OD) plus simeprevir (150 mg OD) for 12 weeks

Summary of evidence

Sofosbuvir plus velpatasvir

In a phase III, double-blind, placebo-controlled study that included 624 HCV patients, of which 19% had HCV4 infection, patients received either sofosbuvir plus velpatasvir in a once-daily, fixed-dose combination tablet or matching placebo for 12 weeks. The rate of SVR among patients receiving sofosbuvir-velpatasvir was 99%, and 100% of HCV4 patients achieved SVR12.[9]

Sofosbuvir plus ledipasvir

After 12 weeks of therapy, 95% of patients achieved SVR in the SYNERGY trial, which assessed the efficacy and safety of the combination of sofosbuvir plus ledipasvir without ribavirin in patients with genotype 4 infection.29 Because of the lack of data with genotype 4, it is not clear whether treatment duration can be shortened to eight weeks (as in certain patients infected with genotype 1 based on the ION-3 study results).

Sofosbuvir plus daclatasvir

There is no data available with this combination in patients infected with HCV4. Nevertheless, given the antiviral effectiveness of both sofosbuvir and daclatasvir against this genotype in vitro, it is likely that the response would be similar to those of patients infected with genotype 1.

Sofosbuvir plus simeprevir

There is no data with this combination in patients infected with HCV genotype 4. Nevertheless, given the antiviral effectiveness of both sofosbuvir and simeprevir against this genotype, it is likely that the results of the COSMOS trial in patients infected with genotype 1 may be extrapolated.[30]

Genotype 4, treatment-naïve with compensated cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) for 12 weeks
- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) with weight-based ribavirin for (1,000 or 1,200 mg in patients weighing <75 or ≥75 kg, respectively) for 12 weeks.
- For those intolerant to ribavirin, sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) without ribavirin may be given for 24 weeks

Summary of evidence

Sofosbuvir plus velpatasvir

The ASTRAL-1 study included 64 genotype 4 treatment-naïve patients with or without cirrhosis, all of whom achieved SVR12 (100%).[9] Fixed-dose combination of sofosbuvir 400 mg plus velpatasvir 100 mg OD for 12 weeks was approved by the Food and Drug Administration for the treatment of HCV genotype 4 infection in patients with and without cirrhosis, and is recommended in these guidelines.

Sofosbuvir plus ledipasvir

The SYNERGY trial was an open-label study that evaluated ledipasvir plus sofosbuvir for 12 weeks in 21 HCV4-infected patients, of whom 60% were treatment-naïve and 43% had advanced fibrosis (Metavir stage F3 or F4).[31] One patient took the first dose and then withdrew consent. All the rest of the 20 patients who completed treatment achieved SVR12 (SVR12 rate was 95% in the intention-to-treat population and 100% in the per-protocol population). Furthermore, an open-label single-arm study that included 22 HCV4-infected, treatment-naïve patients (although only one with cirrhosis) achieved an SVR12 rate of 95% (21/22).[32] These two pilot studies support the use of this regimen in treatment-naïve patients with HCV4 infection and compensated cirrhosis. However, the recommendation to add weight-based ribavirin is extrapolated from data on HCV1 patients.

Genotype 4, Peg-IFN and ribavirin treatment-experienced without cirrhosis

Recommended regimen:

- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) for 12 weeks

Genotype 4, Peg-IFN and ribavirin treatment-experienced with compensated Cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) with weight-based ribavirin for 12 weeks. Treatment of sofosbuvir plus ledipasvir with ribavirin can be prolonged to 24 weeks in treatment-experienced patients with compensated cirrhosis and negative predictors of response, such as a platelet count <75 x 103/μl
- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) for 24 weeks

Alternative regimen:

- Sofosbuvir (400 mg OD) with weight-based ribavirin for 24 weeks for treatment-experienced patients in whom Peg-IFN is contraindicated

Summary of evidence

Sofosbuvir plus ledipasvir

In the open-label SYNERGY trial, 20 patients with HCV genotype 4 infection were treated with ledipasvir/sofosbuvir for 12 weeks.[31] Of these patients, 40% were treatment-experienced and 40% had advanced fibrosis. Preliminary data demonstrate efficacy, with 95% achieving SVR12 based on an intention-to-treat analysis. An open-label single-arm study by Abergel et al which included 22 HCV genotype 4-infected, treatment-naïve patients (only 1 with cirrhosis) reported an SVR12 rate of 95% (21/22).32 These two studies support the use of this regimen in patients with HCV genotype 4 infection.

Genotype 4 with decompensated cirrhosis

This group includes those with moderate or severe hepatic impairment (Child-Pugh B or C), and who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.

Recommended regimens:

- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) with ribavirin (initial dose of 600 mg in divided doses, and escalated as tolerated to weight-based dose) for 12 weeks
- Sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) with ribavirin (initial dose of 600 mg in divided doses, and escalated as tolerated to weight-based dose) for 12 weeks. The dose of daclatasvir may need to be increased or decreased with the concomitant use of cytochrome P450 3A/4 inducers or inhibitors, respectively.

Summary of evidence

In the SOLAR-1 study, patients infected with either HCV1 or HCV4 with decompensated cirrhosis were randomly assigned to receive daily fixed-dose combination of ledipasvir (90 mg) plus sofosbuvir (400 mg), with ribavirin (initial dose of 600 mg, increased as tolerated) for 12 or 24 weeks.[13] The SVR rates in Child-Pugh B patients who received treatment for 12 weeks was 87% and 89% for 24 weeks. SVR rates for Child-Pugh C patients were 86% and 87%, respectively. In majority of patients, the MELD and Child-Pugh scores decreased from baseline by Week 4. During the study, only one patient (with Child-Pugh C cirrhosis) died. As expected, the frequency of serious adverse events increased with treatment duration in both patients with Child-Pugh B (10% vs 34% by week 12 vs 24) and C (26% vs 42%, respectively). Most serious adverse events were related to ribavirin. The mean daily dose of ribavirin was 600 mg/day and therapy was discontinued in 7% and 8% of class B and C patients, respectively, in those treated for 24 weeks.

Genotype 4, ribavirin-ineligible with decompensated cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) for 24 weeks
- Sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) for 24 weeks. The dose of daclatasvir may need to be increased or decreased with the concomitant use of cytochrome P450 3A/4 inducers or inhibitors, respectively.

Genotype 4, failed with prior sofosbuvir-based therapy, with decompensated cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) with ribavirin (initial dose of 600 mg in divided doses, and escalated as tolerated to weight-based dose) for 24 weeks

Genotype 4, failed with simeprevir-Peg-IFN-ribavirin, with decompensated cirrhosis

Recommended regimens:

- Patients infected with HCV genotype 1 or 4 who failed on a regimen combining PegIFN-α, ribavirin and simeprevir should be retreated with a combination of sofosbuvir with daclatasvir or ledipasvir

Genotype 4, failed with daclatasvir-Peg-IFN-ribavirin, with decompensated cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus simeprevir (150 mg PD) for 24 weeks

Genotype 4, failed with regimens containing sofosbuvir and simeprevir, with decompensated cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) for 24 weeks
- Sofosbuvir (400 mg OD) plus daclatasvir (60 mg OD) for 24 weeks. The dose of daclatasvir may need to be increased or decreased with the concomitant use of cytochrome P450 3A/4 inducers or inhibitors, respectively.

Genotype 4, failed with regimens containing daclatasvir or ledipasvir, with decompensated cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus simeprevir (150 mg PD) for 24 weeks

Treatment of HCV genotype 5 and 6 infection

Genotypes 5 and 6 (HCV5 and HCV6) are studied less extensively and are less prevalent compared to the other genotypes. However, HCV5 is endemic in the northern part of South Africa, where it accounts for 40% of HCV infection.33 The reported prevalence of HCV5 in other parts of the world ranges from 1% to 14%. On the other hand, most reports of HCV6 infections are from Asian countries, including China, Hong Kong, Thailand, Indonesia, China, Vietnam, Myanmar and Korea, with prevalence rates ranging from 1.4% to 49%. There are scant reports of HCV6 infections in Canada, Australia and the United States, and in these countries, most of these patients were immigrants from endemic areas. Due to globalization, the epidemiology these two uncommon genotypes are expected to change.

There are limited data about the clinical, biological and pathological features of these two genotypes. Moreover, there are relatively few studies on the optimal treatment regimen for patients with genotype 5 or 6 chronic HCV infection, particularly for DAAs. Most of the available data regarding treatment are from a few small non-randomized trials. Response of HCV5 and HCV6 to 48 weeks of treatment with Peg-IFN plus ribavirin is better than that for genotypes 1 and 4: SVR rates that may reach 70% for HCV5 and 85% for HCV6.[33]

Genotype 5 and 6, treatment-naïve with or without liver cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) for 12 weeks
- Sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) for 12 weeks

Summary of evidence

Sofosbuvir plus ledipasvir

In an open-label, multicenter, single-arm, phase 2 trial conducted in France, investigators enrolled 21 treatment-naïve patients with HCV5 infection to receive a 12-week course of sofosbuvir plus ledipasvir.[32] Twenty patients (95%) achieved SVR12, regardless of cirrhosis status.

Additionally, in an open-label, phase 2 study conducted at two centers in New Zealand on HCV3- and HCV6-infected patients, 25 treatment-naïve and treatment-experienced patients with HCV6 infection were treated with a 12-week course of sofosbuvir plus ledipasvir.[34] Twenty-four patients (96%) achieved SVR12 and the single lone patient who did not achieve SVR12 dropped out of the study at week eight and did not complete the full 12 weeks of therapy.

Sofosbuvir plus velpatasvir

In the phase III ASTRAL-1 trial, treatment-naïve and treatment-experienced patients with chronic HCV genotypes 1, 2, 4, 5, or 6 infection were randomized in a 5:1 ratio to receive a 12-week course of either the combination of sofosbuvir plus velpatasvir or placebo.[9] The study included 24 treatment-naive patients with HCV5 and 36 patients with HCV6 who were with or without cirrhosis. Of the 24 HCV5 patients, 23 patients (96%) achieved SVR12 while all (100%) HCV6 patients achieved SVR12.

Genotype 5 and 6, treatment-experienced with or without liver cirrhosis

Recommended regimens:

- Sofosbuvir (400 mg OD) plus ledipasvir (90 mg OD) for 12 weeks in patients who previously failed on Peg-IFN/ribavirin treatment
- Sofosbuvir (400 mg OD) plus velpatasvir (100 mg OD) for 12 weeks in patients who previously failed on Peg-IFN/ribavirin treatment

Summary of evidence

Similar to treatment-naïve patients, there are limited data available on the retreatment of patients with genotype 5 or 6 hepatitis C infection who have failed prior therapy.

Sofosbuvir plus ledipasvir

Abergel et al conducted an open-label, multicenter, single-arm, phase 2 trial involving 20 treatment-experienced patients with HCV5 infection. Nineteen patients (95%) achieved SVR12 regardless of cirrhosis status.[32]

Additionally, Gane et al conducted an open-label, phase 2 trial involving 126 HCV patients, of which 25 patients had genotype 6 infection. Among the 25 patients, two (8%) were treatment-experienced and two (8%) had cirrhosis at baseline. Twenty-four (96%) of the 25 patients achieved SVR12.[34]

Sofosbuvir plus velpatasvir

The ASTRAL-1 trial included 34 patients (6%) with genotype 5 and 41 patients (7%) with genotype 6. Among the treatment-experienced patients, 11 of 11 (100%) with genotype 5 infection and three of three (100%) with genotype 6 infection achieved SVR12.[9]

Additional principles of HCV treatment using all-oral direct-acting antivirals

Assessment prior to treatment initiation

All patients with HCV infection should be assessed for antiviral treatment. At baseline and before treatment with combination therapy, the following should be performed:35

1. Medical history, clinical examination
2. Standard laboratory tests: complete blood count (CBC), international normalized ratio (INR), renal function and liver function tests: ALT, AST, bilirubin, albumin and alkaline phosphatase.
3. HCV RNA (quantitative viral load) preferably within the past six months
4. HCV genotype testing
5. Pregnancy test - if clinically indicated
6. Screen for HBV, HIV status and, if HIV seropositive, current antiretroviral regimen and degree of viral suppression
7. Evaluation for liver fibrosis and cirrhosis. In the assessment of the degree of liver fibrosis and cirrhosis, use of aminotransferase/platelet ratio index (APRI) for the assessment of hepatic fibrosis is recommended. Other non-invasive tests that require more resources such as transient elastography or FibroTest can be used when available and if resources are available.
8. Others: Calculated glomerular filtration rate (GFR), Cardiac and pulmonary evaluation.

Table I. Contraindications or warning to direct-acting antivirals

Drug	Contraindication or warning
Sofosbuvir/Ledipasvir	– Amiodarone co-administration – P-glycoprotein (gp) inducers – Renal failure (eGFR <30 mL/min/1.73 m^2)
Sofosbuvir	– Amiodarone co-administration (caution also with beta-blockers) – Renal failure (eGFR <30 mL/min/1.73 m^2)
Daclatasvir	Drugs inducing or inhibiting CYP3A
Sofosbuvir/Velpatasvir	Amiodarone co-administration

Table II. Contraindications to ribavirin

Absolute contraindications
• Pregnancy or unwillingness to use contraception • Breastfeeding women • Severe concurrent medical disease, including severe infections • Poorly controlled cardiac failure • Chronic obstructive pulmonary disease • Previous ribavirin hypersensitivity • Co-administration of didanosine
Relative contraindications
• Abnormal haematological indices: - Hb <10 g/dL - Neutrophil count <1.5x10^9/L - Platelet count <90x10^9/L • Serum creatinine >1.5 mg/dL • Haemoglobinopathies (sickle cell disease or thalassaemia) • Significant coronary artery disease

Contraindications to treatment

Monitoring during treatment

During DAA treatment, the following parameters should be monitored:

- HCV RNA quantification at four weeks, 12 weeks or end of treatment and 24 weeks or longer after completion of therapy
- Consider discontinuation of therapy if ALT increases by 10-fold or if the patient has jaundice, weakness, nausea, vomiting or derangement in hepatic function panel. Asymptomtic patients with increase ALT should be monitored closely.

Monitoring after treatment

Post-treatment testing and surveillance for complications should include HCV RNA at 12 weeks after treatment. In cirrhotic patients, liver ultrasound and alfa-fetoprotein (AFP) every six months should be done to screen for hepatocellular carcinoma. Endoscopy every one to two years may be done to exclude esophageal varices.

Treatment of patients with HBV-HCV coinfection

It is important to check for the presence of HBV infection before starting HCV treatment. HBV and HCV coinfection

Table III. Monitoring during treatment

Time	DAA alone			DAA with Ribavirin		
	CBC, liver and renal function test	Adherence and side effects	HCV RNA	CBC, liver and renal function test	Adherence and side effects	HCV RNA
Baseline	X		X	X		X
Week 1				X	X	
Week 2				X	X	
Week 4	X	X		X	X	
Week 8				X	X	
Week 12				X	X	
Week 12 after end of treatment			X	X		X

may result in an accelerated disease course, with HCV considered to be the main driver of disease. Testing for HBV coinfection would include testing for HBsAg, anti-HBc and anti-HBs.[36]

Persons coinfected with HBV and HCV can be treated with antiviral therapy for HCV. SVR rates are likely to be similar to those in HCV-monoinfected persons. During treatment and after HCV clearance, there is a risk of reactivation of HBV, and this may require treatment with concurrent anti-HBV antiviral therapy. Drug-drug interactions must be checked before initiating treatment. For example, telbivudine may be associated with a higher risk of neuropathy if given with interferon-containing regimens.

HBsAg-positive patients who are not on HBV antiviral whose HBV DNA levels meet treatment cut-offs (i.e., HBV DNA ≥20,000 IU/mL for HBeAg-positive patients and ≥2,000 IU/mL for HBeAg-negative patients) should be started on HBV antiviral therapy.[37] Those whose baseline HBV DNA not meet treatment criteria may be given prophylactic antiviral until 12 more weeks after completion of DAA therapy. If no prophylaxis would be given, monitor HBV DNA levels during and immediately after DAA therapy. Antivirals should be initiated if there is a 10-fold increase in baseline or if >1,000 IU/mL are measured for those with undetectable HBV DNA at baseline.

Treatment of HIV-HCV coinfected patients

The treatment of HIV-HCV coinfected patients follows the same recommendations as HIV-negative individuals, except for caution with the use of some DAAs. Treatment should only be recommended after consultation with an infectious disease specialist or HIV-care provider. Delay of initiation of HIV antiretroviral (ARV) treatment until completion of hepatitis C treatment can be considered. Sofosbuvir plus velpatasvir can be used with most ARVs, except for efavirenz.

Velpatasvir increases tenofovir disoproxil fumarate levels; this combination should be avoided if estimated glomerular filtration rate (eGFR) is less than 60 mL/min.

Dose adjustment is required for daclatasvir when it is used with efavirenz.

Ribavirin should not be used with a zidovudine-containing ARV regimen because this combination results in increased rates of anemia.

Treatment of patients with renal impairment

For patients with eGFR 30-80 mL/min, no dose adjustment is required when using sofosbuvir plus velpatasvir or daclatasvir.

For patients with eGFR <30mL/min or end-stage renal disease, Peg-IFN plus ribavirin 200 mg PO OD are recommended.

References

1. **Lok AS, Gardiner DF, Lawitz E, et al.** Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med. Jan 19 2012;366(3):216-224.
2. **Burgess SV, Hussaini T, Yoshida EM.** Concordance of sustained virologic response at weeks 4, 12 and 24 post-treatment of hepatitis c in the era of new oral direct-acting antivirals: A concise review. Ann Hepatol. Mar-Apr 2016;15(2):154-159.
3. **Afdhal N, Zeuzem S, Kwo P, et al.** Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. May 15 2014;370(20):1889-1898.
4. **Kowdley KV, Gordon SC, Reddy KR, et al.** Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. May 15 2014;370(20):1879-1888.
5. **Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al.** Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. Jan 16 2014;370(3):211-221.
6. **Wyles DL, Ruane PJ, Sulkowski MS, et al.** Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1. N Engl J Med. Aug 20 2015;373(8):714-725.
7. **Pol S, Bourliere M, Lucier S, et al.** Safety and efficacy of daclatasvir-sofosbuvir in HCV genotype 1-mono-infected patients. J Hepatol. Jan 2017;66(1):39-47.
8. **Welzel TM, Petersen J, Herzer K, et al.** Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological

response rates in patients with HCV infection and advanced liver disease in a real-world cohort. Gut. Nov 2016;65(11):1861-1870.

9. **Feld JJ, Jacobson IM, Hezode C, et al.** Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N Engl J Med. Dec 31 2015;373(27):2599-2607.
10. **Afdhal N, Reddy KR, Nelson DR, et al.** Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. Apr 17 2014;370(16):1483-1493.
11. **Reddy KR, Bourliere M, Sulkowski M, et al.** Ledipasvir and sofosbuvir in patients with genotype 1 hepatitis C virus infection and compensated cirrhosis: An integrated safety and efficacy analysis. Hepatology. Jul 2015;62(1):79-86.
12. **Pianko S, Flamm SL, Shiffman ML, et al.** Sofosbuvir Plus Velpatasvir Combination Therapy for Treatment-Experienced Patients With Genotype 1 or 3 Hepatitis C Virus Infection: A Randomized Trial. Ann Intern Med. Dec 1 2015;163(11):809-817.
13. **Charlton M, Everson GT, Flamm SL, et al.** Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. Gastroenterology. Sep 2015;149(3):649-659.
14. **Manns M, Samuel D, Gane EJ, et al.** Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis. Jun 2016;16(6):685-697.
15. **Poordad F, Schiff ER, Vierling JM, et al.** Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatology. May 2016;63(5):1493-1505.
16. **Foster GR, Irving WL, Cheung MC, et al.** Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol. Jun 2016;64(6):1224-1231.
17. **Curry MP, O'Leary JG, Bzowej N, et al.** Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. N Engl J Med. Dec 31 2015;373(27):2618-2628.
18. **Petruzziello A, Marigliano S, Loquercio G, et al.** Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol. 2016 Sep 14;22(34):7824-40.
19. **Nguyen LH, Nguyen MH.** Systematic review: Asian patients with chronic hepatitis C infection. Aliment Pharmacol Ther. 2013 May;37(10):921-36.
20. **Foster GR, Afdhal N, Roberts SK, et al.** ASTRAL-2 Investigators; ASTRAL-3 Investigators. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. N Engl J Med. 2015 Dec 31;373(27) 2608-17
21. **Nelson DR, Cooper JN, Lalezari JP, et al.** All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology 2015; 61:1127-1135.
22. **Leroy V, Angus P, Bronowicki JP, et al.** Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). Hepatology 2016; 63: 1430-41.
23. **Hézode C, Lebray P, De Ledinghen V, et al.** Daclatasvir plus sofosbuvir, with or without ribavirin, for hepatitis C virus genotype 3 in a French early access programme. Liver Int 2017;37(9):1314-1324.
24. **Abdel-Ghaffar TY, Sira MM, El Naghi S.** Hepatitis C genotype 4: The past, present, and future. World J Hepatol. 2015 Dec 8;7(28):2792-810.
25. **Micallef JM, Kaldor JM, Dore GJ.** Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat 2006;13:34–41.
26. **Khattab MA, Ferenci P, Hadziyannis SJ, et al.** Management of hepatitis C virus genotype 4: Recommendations of An International Expert Panel. J Hepatol 2011;54: 1250–1262.
27. **Kamal S, Nasser I.** Hepatitis C genotype 4: what we know and what we don't yet know. Hepatology 2008;47:1371–1383.
28. **Antaki N, Craxì A, Kamal SM, Moucari M, Van der Merwe S, Haffar S, et al.** The neglected hepatitis C virus genotype 4, 5 and 6: an international consensus report. Liver Int 2010;30:342–355.
29. **Kapoor R, Kohli A, Sidharthan S, Sims Z, Petersen TL, Osinusi A, et al.** All-oral treatment for genotype 4 chronic hepatitis C infection with sofosbuvir and ledipasvir: interim results from the NIAID SYNERGY trial. Hepatology 2014;60:321A.
30. **Corregidor A, et al.** Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet 2014;384:1756–1765.
31. **Kohli A, Kapoor R, Sims Z et al.** Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study. Lancet Infect Dis. 2015;15(9):1049-54.
32. **Abergel A, Asselah T, Metivier S, Loustaud-Ratti V et al.** Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: an open-label, multicentre, single-arm, phase 2 study. Lancet Infect Dis. 2016;16(4):459-64.
33. **Al Naamani K, Al Sinani S, Deschenes M.** Epidemiology and treatment of hepatitis C genotypes 5 and 6. Can J Gastroenterol [Internet] 2013 Jan;27(1):e8–e12.
34. **Gane EJ, Hyland RH, Svarovskaia E, et al.** Efficacy of Ledipasvir and Sofosbuvir, With or Without Ribavirin for 12 weeks in Patients with HCV Genotype 3 or 6 Infection. Gastroenterology 2015;149:1454-1461.
35. **Guidelines for the prevention, care and treatment of persons with hepatitis C infection.** Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/handle/10665/205035/9789241549615_eng.pdf;jsessionid=463135AF574D2CF70D495345F9E0796B?sequence=1, accessed 09 June 2018).
36. **Guidelines for the prevention, care and treatment of persons with hepatitis B infection.** Geneva: World Health Organization; 2015 (http:// apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1&ua=1, accessed 09 June 2018).

Recommendations for treatment-naive chronic hepatitis C patients

Genotype	Treatment line	Without cirrhosis	With compensated cirrhosis (Child-Pugh A)	Decompensated cirrhosis (Child- Pugh B/C)
1a and 1b	First line	SOF + LDV 12 weeks SOF + DCV 12 weeks SOF + VEL 12 weeks	SOF + LDV 12 weeks SOF + VEL 12 weeks	SOF + LDV + RBV^ 12 weeks SOF + VEL + RBV^ 12 weeks SOF + DCV + RBV^ 12-24 weeks#
	Second line		SOF + DCV + RBV* 24 weeks# SOF + DCV 24 weeks#	SOF + LDV 24 weeks SOF + VEL 24 weeks
2	First line	SOF + VEL 12 weeks SOF + DCV 12 weeks	SOF + VEL 12 weeks	SOF + VEL + RBV^ 12 weeks
	Second line		SOF + DCV 16-24 weeks	SOF + DCV + RBV^ 24 weeks#
3	First line	SOF + VEL 12 weeks SOF + DCV 12 weeks	SOF + VEL 12 weeks	SOF + VEL + RBV^ 12 weeks SOF + DCV + RBV^ 12 weeks#
	Second line		SOF + DCV + RBV* 24 weeks SOF + DAC* 24 weeks	SOF + VEL 24 weeks SOF + DAC 24 weeks
4	First line	SOF + LDV 12 weeks SOF + DCV 12 weeks SOF + VEL 12 weeks SOF + SIM 12 weeks	SOF + LDV + RBV* 12 weeks SOF + VEL 12 weeks	SOF +LDV + RBV^ 12 weeks SOF + DCV + RBV^ 12-24 weeks#
	Second line		SOF + LDV 24 weeks	SOF + LDV 24 weeks
5 or 6	First line	SOF + LDV 12 weeks SOF + VEL 12 weeks	SOF + LDV 12 weeks SOF + VEL 12 weeks	SOF +LDV 12 weeks SOF + VEL 12 weeks
	Second line			

SOF=sofosbuvir 400 mg; LDV=ledipasvir 90 mg; DCV=daclatasvir 60 mg; VEL=velpatasvir 100 mg; RBV=ribavirin.
**Ribavirin 1,000 mg for weight <75kg; 1,200 mg for weight ≥75kg,*
^Escalating ribavirin, starting at 600 mg/day, until weight-based dose as tolerated
#It is recommended to check HCV RNA at 12 weeks. Treatment should be extended to 24 weeks if HCV RNA is still detectable at 12 weeks

Recommendations for treatment experienced (PEG/ribavirin) chronic hepatitis C patients

Genotype	Treatment line	Without cirrhosis	With compensated cirrhosis (Child-Pugh A)	Decompensated cirrhosis (Child- Pugh B/C)
1a and 1b	First line	SOF + LDV 12 weeks SOF + DCV 12 weeks SOF + VEL 12 weeks	SOF + LDV 24 weeks SOF + VEL 12 weeks SOF + DCV + RBV* 24 weeks#	SOF + LDV + RBV^ 12 weeks SOF + VEL + RBV^ 12 weeks SOF + DCV + RBV^ 12-24 weeks#
	Second line		SOF + DCV + RBV* 24 weeks# SOF + LDV +RBV*12 weeks	SOF + LDV 24 weeks SOF + VEL 24 weeks
2	First line	SOF + VEL 12 weeks SOF + DCV 12 weeks	SOF + VEL 12 weeks	SOF + VEL + RBV^ 12 weeks
	Second line		SOF + DCV 12 weeks	SOF + VEL 24 weeks SOF + DCV + RBV^ 12-24 weeks#
3	First line	SOF + VEL 12 weeks SOF + DCV 12 weeks	SOF + VEL + RBV* 12 weeks	SOF + VEL + RBV^ 12 weeks SOF + DCV + RBV^ 12weeks#
	Second line		SOF + DCV + RBV* 24 weeks SOF + VEL* 24 weeks SOF + DAC* 24 weeks	SOF + VEL 24 weeks SOF + DAC 24 weeks
4	First line	SOF + LDV 12 weeks	SOF + LDV + RBV* 12 weeks	SOF + LDV + RBV^ 12 weeks SOF + DCV + RBV^ 12 weeks#
	Second line		SOF + RBV* 24 weeks	SOF + LDV 24 weeks
5 or 6	First line	SOF + LDV 12 weeks SOF + VEL 12 weeks	SOF + LDV 12 weeks SOF + VEL 12 weeks	SOF + LDV 12 weeks SOF + VEL 12 weeks
	Second line			SOF + LDV 24 weeks SOF + VEL 24 weeks

SOF=sofosbuvir 400 mg; LDV=ledipasvir 90 mg; DCV=daclatasvir 60 mg; VEL=velpatasvir 100 mg; RBV=ribavirin.
**Ribavirin 1,000 mg for weight <75kg; 1,200 mg for weight ≥75kg,*
^Escalating ribavirin, starting at 600 mg/day, until weight-based dose as tolerated
#It is recommended to check HCV RNA at 12 weeks. Treatment should be extended to 24 weeks if HCV RNA is still detectable at 12 weeks

Treatment recommendations for chronic hepatitis C patients with no available GENOTYPE, regardless of treatment experience:

Without cirrhosis	Treatment line	With compensated cirrhosis (Child-Pugh A)	Decompensated cirrhosis (Child- Pugh B/C) refer to transplant center
SOF + DCV 12 weeks SOF + VEL 12 weeks	First line	SOF + VEL 12 weeks	SOF + VEL + RBV^ 12 weeks SOF + DCV + RBV^ 12-24 weeks#
	Second line	SOF + DCV + RBV* 24 weeks#	SOF + VEL 24 weeks

SOF=sofosbuvir 400 mg; DCV=daclatasvir 60 mg; VEL=velpatasvir 100 mg; RBV=ribavirin.
**Ribavirin 1,000 mg for weight <75kg; 1,200 mg for weight ≥75kg,*
^Escalating ribavirin, starting at 600 mg/day, until weight-based dose as tolerated
#It is recommended to check HCV RNA at 12 weeks. Treatment should be extended to 24 weeks if HCV RNA is still detectable at 12 weeks

Treatment recommendations for HIV-HCV co-infected patients with UNKNOWN GENOTYPE, regardless of treatment experience

Without cirrhosis	With compensated cirrhosis (Child-Pugh A)	Decompensated cirrhosis (Child- Pugh B/C)
SOF + DCV 12 weeks	SOF + DCV + RBV* 12-24 weeks#	Refer to transplant center

SOF=sofosbuvir 400 mg; DCV=daclatasvir 60 mg (90 mg if on Efavirenz); RBV=ribavirin.
**Ribavirin 1,000 mg for weight <75kg; 1,200 mg for weight ≥75kg,*
#It is recommended to check HCV RNA at 12 weeks. Treatment should be extended to 24 weeks if HCV RNA is still detectable at 12 weeks

Key drug-drug interactions with direct-acting agents used in HCV therapy

Concomitant medications	DCV	LDV	SMV	SOF	VEL
Acid-reducing agentsa		X			X
Amiodarone	X	X	X	X	X
Anticonvulsantsa	X	X	X	X	X
Azole antifungalsa	X[b]		X		
Calcineurin inhibitorsa			X		
Calcium channel blockersa	X		X		
Cisapride			X		
Digoxin	X	X	X		
Glucocorticoidsa	X		X		
Herbals St. John's wort Milk thistle	X	X	X X	X	X
HMG-CoA reductase inhibitors (statins)[a]	X	X	X		
Macrolide antimicrobialsa	X[b]		X		
Other antiarrythmicsa			X		
Phosphodiesterase inhibitorsa			X		
Rifamycin antimicrobialsa	X	X	X	X	X
Sedativesa			X		

[a]Some drug interactions are not class specific; see product prescribing information for specific drugs within a class.
[b]Requires a daclatasvir dose modification

Adapted from:
American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Last Updated: May 24, 2018. Available at: www.hcvguidelines.org.

Liverpool HEP iChart [mobile app]. Version 2.0.0. Liverpool, UK: Liverpool Drug Interactions Group; July 2018.