Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

INITIAL TREATMENT OF HCV INFECTION

Initial Treatment of HCV Infection includes patients with chronic hepatitis C who have not been previously treated with IFN, PEG-IFN, RBV, or any HCV direct-acting antiviral (DAA) agent, whether experimental, investigational, or US Food and Drug Administration (FDA) approved.

Expansions and notes for abbreviations used in this section can be found in Methods Table 3. [1]

A summary of recommendations for initial treatment is found in the BOX[2].

The level of evidence available to inform the best treatment decision for each patient varies, as does the strength of the recommendation, and is rated accordingly (see **Methods Table 2** [3]). In addition, when treatment differs for a particular group, such as those infected with, specific HCV genotype or subtype, specific recommendations are given. A regimen is classified as "Recommended" when it is favored for most patients and "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." Unless otherwise indicated, such regimens should not be administered to patients with HCV infection. Specific considerations of persons with HIV/HCV coinfection [4], decompensated cirrhosis [5] (moderate or severe hepatic impairment; Child Turcotte Pugh [CTP] class B or C [6]), HCV infection post–liver transplant [7], and those with severe renal impairment [8] or end-stage renal disease (ESRD) are addressed in other sections of the Guidance.

When several regimens are offered at the same recommendation level they are listed in alphabetic order. In this case consideration of choice of regimen should be determined based on patient-specific data, including drug interactions. As always, patients receiving antiviral therapy require careful pretreatment assessment for comorbidities that may influence treatment response. All patients should have careful monitoring during treatment, particularly for anemia if RBV is included in the regimen. (See **Monitoring Section** [9])

I. Genotype 1

Three highly potent DAA oral combination regimens are recommended for HCV genotype 1–infected patients, although there are differences in the recommended regimens based on the HCV subtype. Patients with HCV genotype 1a tend to have higher relapse rates than patients with HCV genotype 1b with certain regimens. Genotype 1 HCV infection that cannot be subtyped should be treated as genotype 1a infection.

The introduction of DAAs into HCV treatment regimens increased the risk of drug interactions with other concomitant medications used by patients, and now with combinations of DAAs, attention to drug interactions is all the more important (see **Drug Interactions Table**). The product prescribing information and other resources (eg, **http://www.hep-druginteractions.org/** [10]) should be referenced regularly to ensure safety when prescribing DAA regimens. In particular, the daily fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) has a potential interaction with acid-suppressing medications, for example proton pump inhibitors, which may result in decreased absorption of ledipasvir and lower exposures. Because of over-the-counter access to acid-suppressing medications, a comprehensive assessment of all prescribed and over-the-counter medications is recommended prior to initiating treatment. If possible, acid-suppressing medications should be held prior to and during the HCV treatment period to optimize ledipasvir exposure. For patients in whom interruption of acid suppression is not possible, dosing of acid suppressants is recommended per the prescribing information.

Similarly, the daily fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (hereafter paritaprevir/ritonavir/ombitasvir plus dasabuvir or PrOD) has a substantial interaction with the long-acting inhaled beta-adrenoceptor agonist salmeterol, and concurrent administration is not recommended owing to an increased risk of cardiovascular adverse events including QT segment prolongation.

A. Genotype 1a

Several options with similar efficacy in general are recommended for treatment-naive patients with HCV genotype 1a infection (listed in alphabetic order; see text).

Daily daclatasvir (60 mg*) and sofosbuvir (400 mg) for 12 weeks (no cirrhosis) or 24 weeks with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1a infection.

Rating: Class I, Level B (no cirrhosis); Class IIa, Level B (cirrhosis)

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 1a infection.

Rating: Class I, Level A

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1a infection.

Rating: Class I, Level A

Dailysimeprevir (150 mg) and sofosbuvir (400 mg) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis without the Q80K polymorphism) with or without weight-based RBV is recommended for treatment-naive patients with HCV genotype 1a infection.

Rating: Class I, Level A

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on **HIV/HCV coinfection** [11] for patients on antiretoviral therapy.

For HCV genotype 1a–infected, treatment-naive patients, there are several regimens of comparable efficacy, as outlined above.

Daclatasvir in combination with sofosbuvir for the treatment of HCV genotype 1 infection can be recommended based on data from the phase III ALLY-2 trial, which assessed the efficacy and safety of daclatasivr and sofosbuvir for 12 weeks in patients coinfected with HIV and HCV (genotypes 1-4). (Wyles, 2015[12]) One hundred twenty-three (83%) patients receiving 12 weeks of therapy in the trial were infected with HCV genotype 1. Eighty-three (54%) of these patients were treatment naive. The sustained virologic response (SVR) rate was 96% in treatment-naive patients with HCV genotype 1a infection (n=71) receiving 12 weeks of therapy. However, only 9 treatment-naive patients had cirrhosis. Similarly, in the phase IIb study of daclatasvir and sofosbuvir (A1444040) in 88 treatment-naive patients with HCV genotype 1a infection, 21 were treated for 24 weeks (11 with RBV) and 67 were treated for 12 weeks (33 with RBV), and there were no virologic relapses. However, there were only 14 patients with cirrhosis in the 12-week

and 24-week study arms. (Sulkowski, 2014[13]) Because patients with cirrhosis were not adequately represented in these studies, the optimal duration of treatment for patients with cirrhosis remains unclear. Cohort studies of a compassionate use program in Europe suggest that patients with cirrhosis may benefit from extension of therapy with daclatasvir and sofosbuvir to 24 weeks, with or without RBV. (Welzel, 2015[14]); (de Ledinghen, 2015[15]) The phase III ALLY-1 trial investigated daclatasvir and sofosbuvir with RBV (initial dose of 600 mg, then titrated) in 60 patients with advanced cirrhosis. (Poordad, 2015[16]) Only 76% of patients with HCV genotype 1A (n=34) and 100% of patients with HCV genotype 1B (n=11) achieved an SVR at 12 weeks (SVR12). It is unclear how many treatment failures were among treatment-naive patients or those with CTP class A cirrhosis. More data are needed; however, owing to the risk of the emergence of resistance to nonstructural protein 5A (NS5A) inhibitor treatment at the time of failure, extending treatment to 24 weeks for all patients with HCV genotype 1a infection and cirrhosis is recommended, and the addition of RBV may be considered. In patients with favorable characteristics, a 12-week treatment course that includes weight-based RBV(1000 mg [<75 kg] to 1200 mg [≥75 kg]) may be considered but is supported by limited data.

Ledipasvir/sofosbuvir was approved by the FDA for the treatment of HCV genotype 1 infection in treatment-naive patients based on 2 registration trials: ION-1(865 treatment-naive patients; those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for RBV. (Afdhal, 2014a [17]) SVR rate at 12 weeks (SVR12) was 97% to 99% across all arms, with no difference in SVR based on length of treatment, use of RBV, or HCV genotype 1 subtype. Sixteen percent of subjects enrolled were classified as having cirrhosis. There was no difference in SVR12 rate in those with cirrhosis (97%) versus those without cirrhosis (98%). ION-3 excluded patients with cirrhosis and investigated shortening therapy from 12 weeks to 8 weeks (with or without RBV). (Kowdley, 2014 [18]) SVR12 rate was 93% to 95% across all arms, with no difference in SVR in the intention-to-treat analysis. However, relapse rates were higher in the 8-week arms (20 of 431) regardless of RBV use compared with the 12-week arm (3 of 216). Post hoc analyses of the 2 RBV-free arms assessed baseline predictors of relapse and identified lower relapse rates in patients receiving 8 weeks of ledipasvir/sofosbuvir who had baseline HCV RNA levels below 6 million IU/mL (2%; 2 of 123), and was the same for patients with similar baseline HCV RNA levels who received 12 weeks (2%; 2 of 131). This analysis was not controlled and thus substantially limits the generalizability of this approach to clinical practice. Shortening treatment to less than 12 weeks for patients without cirrhosis should be done with caution and performed at the discretion of the practitioner.

PrOD plus weight-based RBV was approved by the FDA for the treatment of HCV genotype 1a infection in treatment-naive patients based on 3 registration trials: SAPPHIRE-I (322 treatment-naive patients with genotype 1a HCV infection without cirrhosis), PEARL-IV (305 treatment-naive patients with genotype 1a without cirrhosis), and TURQOUISE-II (261 treatment-naive and -experienced patients with HCV genotype 1a and cirrhosis). The SAPPHIRE-I trial reported a high SVR12 rate (95.3%) with 12 weeks of PrOD and RBV. (Feld, 2014 [19]) Overall, virologic failure was higher for patients with HCV genotype 1a (7 of 8 failures had genotype 1a) than patients with HCV genotype 1b (1 virologic failure). PEARL-IV was specifically designed to determine the role of PrOD with or without weight-based RBV for treatment-naive, HCV genotype 1a–infected patients without cirrhosis. (Ferenci, 2014 [20]) SVR12 was lower in the RBV-free arm than in the RBV-containing arm (90% vs 97%, respectively) owing to higher rates of virologic failure (7.8%

vs 2%, respectively), confirming the need for weight-based RBV for patients with HCV genotype 1a. TURQUOISE-II enrolled treatment-naive and -experienced patients (261 patients with HCV genotype 1a) with CTP class A cirrhosis to receive either 12 weeks or 24 weeks of treatment with PrOD and RBV. Overall, SVR12 rates were 89% in the 12-week arm and 95% in the 24-week arm. (paritaprevir [21]/ [21]ritonavir/ [21]ombitasvir [21] prescribing information [21]); (Poordad, 2014 [22]) This difference in SVR12 rate between arms was primarily driven by patients with null response to PEG-IFN and RBV; there was less difference in SVR rates in the patients with cirrhosis who were naive to therapy (92% and 95%, respectively). (paritaprevir/ritonavir/ [21]ombitasvir [21]prescribing information [21]); (Poordad, 2014 [22])

The OPTIMIST-1 and -2 trials investigated the safety and efficacy of simeprevir (150 mg) and sofosbuvir (400 mg) in chronically infected patients with HCV genotype 1 without and with cirrhosis, respectively. In the OPTIMIST-1 study, 310 treatment-naive and -experienced patients without cirrhosis were randomly assigned to 12 versus 8 weeks of the simeprevir plus sofosbuvir regimen. (Kwo, 2015 [23]) The overall SVR12 rate was 97% (150/155) versus 83% (128/155), respectively, with a statistically significantly greater relapse rate in the 8-week arm. In the 12-week arm there was no difference in SVR12; treatment-naive and -experienced patients achieved SVR12 rates of 97% and 95%, respectively. There was also no difference in SVR12 based on genotype 1 subtype or presence of the baseline Q80K resistance mutation. A post hoc analysis suggested that patients with a baseline HCV RNA level below 4 million IU/mL achieved the same SVR12 rate (96%) regardless of the length of treatment. This defined baseline HCV RNA level is different than the 6 million IU/mL defined in the ION-3 trial, suggesting these posthoc analysis cut-offs are arbitrary and unlikely to translate to clinical practice. At this time an 8-week regimen of simeprevir and sofosbuvir cannot be recommended.

The OPTIMIST-2 study was a single arm, open-label trial investigating 12 weeks of simeprevir plus sofosbuvir in 103 treatment-naive and -experienced patients with cirrhosis. (Lawitz, 2015 [24]) The overall SVR12 rate was 83% (86/103), with 88% (44/50) of treatment-naive and 79% (42/53) of treatment-experienced patients achieving SVR12. In addition, patients infected with HCV genotype 1a and 1b without the Q80K mutation had similar SVR12 rates (84% [26/31] and 92% [35/38], respectively). However, patients with HCV genotype 1a infection and the Q80K mutation had lower SVR12 rates (74% [25/34]). Thus, extending treatment to 24 weeks, with or without RBV, is recommended for patients with cirrhosis receiving simeprevir plus sofosbuvir to decrease the risk of relapse. At this time it is unclear whether extending treatment, with or without the addition of RBV, will increase efficacy in genotype 1a–infected patients with the Q80K mutation. Given the lower response rate in patients with cirrhosis, it is reasonable to avoid this regimen in patients with this baseline mutation.

The safety profiles of all the recommended regimens above are excellent. Across numerous phase III programs, less than 1% of patients without cirrhosis discontinued treatment early and adverse events were mild. Most adverse events occurred in RBV-containing arms. Discontinuation rates were higher for patients with cirrhosis (approximately 2% for some trials) but still very low.

B. Genotype 1b

Several options with similar efficacy in general are recommended for treatment-naive patients with HCV genotype 1b infection (listed in alphabetic order; see text).

Daily daclatasvir (60 mg*) and sofosbuvir (400 mg) for 12 weeks (no cirrhosis) or 24 weeks with or without weight-based RBV (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1b infection.

Rating: Class I, Level B (no cirrhosis); Class IIa, Level B (cirrhosis)

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 1b infection.

Rating: Class I, Level A

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 1b infection.

Rating: Class I, Level A

Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks (no cirrhosis) or 24 weeks with or without weight-based RBV (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1b infection.

Rating: Class I, Level A

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on **HIV/HCV coinfection** [11] for patients on antiretroviral therapy.

For HCV genotype 1b–infected, treatment-naive patients, there are 4 regimens of comparable efficacy, as outlined above.

There is no measurable difference demonstrated to date in treatment response to daclatasvir and sofosbuvir or ledipasvir/sofosbuvir for HCV genotype 1 subtypes, thus the supporting evidence

remains the same as for HCV genotype 1a–infected patients (see **Genotype 1**). In the ALLY-2 arm of daclatasvir and sofosbuvir for 12 weeks in treatment-naive patients, only 12 were genotype 1b and all achieved SVR12. (Wyles, 2015[12]) Furthermore, in the ALLY-1 study all 11 genotype 1b infected patients with advanced cirrhosis achieved SVR12. Due to the limited numbers of genotype 1b patients represented in the phase 3 trials of this regimen, there is not enough evidence to support a different approach by subtype at this time.

PrOD (plus RBV for those with cirrhosis) was approved by the FDA for the treatment of HCV genotype 1b infection in treatment-naive patients based on 3 registration trials: SAPPHIRE-I (151 treatment-naive patients with HCV genotype 1b and without cirrhosis), PEARL-III (419 treatment-naive patients, all with genotype 1b and without cirrhosis), and TURQOUISE-II (119 treatment-naive and -experienced patients with genotype 1b with cirrhosis). SAPPHIRE-I reported a high SVR12 rate (98%) with 12 weeks of PrOD and RBV in patients with HCV genotype 1b. (Feld, 2014 [19]) Given the high SVR12 rates seen in SAPPHIRE-I, PEARL-III was specifically designed to determine the role of weight-based RBV with PrOD in treatment-naive patients with HCV genotype 1b without cirrhosis. (Ferenci, 2014 [20]) SVR12 rate was 99% in both arms, confirming that there is no added benefit from the use of weight-based RBV for patients without cirrhosis who have HCV genotype 1b infection. TURQUOISE-II enrolled treatment-naive and -experienced patients with CTP class A cirrhosis to receive either 12 weeks or 24 weeks of treatment with PrOD and RBV. Overall, SVR12 rates were 98.5% in the 12-week arm and 100% in the 24-week arm. (Poordad, 2014 [22]) To address the need for RBV with this regimen in patients with HCV genotype 1b and cirrhosis, the TURQUOISE-III study evaluated the safety and efficacy of PrOD without RBV for 12 weeks in patients with HCV genotype 1b infection and compensated cirrhosis. Sixty patients (62% men, 55% treatment experienced, 83% with the IL28B non-CC genotype, 22% with platelet counts <90 x 10^9/L, and 17% with albumin levels <3.5 g/dL) were enrolled. All patients completed treatment, and all patients achieved an SVR12. On the basis of this study, treating patients with HCV genotype 1b with PrOD but without RBV is recommended, regardless of prior treatment experience or presence of cirrhosis. (Feld, 2015[25])

To date, there is no measurable difference demonstrated in treatment response to simeprevir plus sofosbuvir for HCV genotype 1 subtypes (with the exception of patients with genotype 1a with cirrhosis who also have the baseline Q80K mutation), thus the supporting evidence remains the same as for HCV genotype 1a–infected patients (see **Genotype 1** [26]).

The safety profiles to date of all recommended regimens above are excellent. Across numerous phase III programs, less than 1% of patients without cirrhosis discontinued treatment early and adverse events were mild. Most adverse events occurred in RBV-containing arms. Discontinuation rates were higher for patients with cirrhosis (approximately 2% for some trials) but still very low.

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 1.*

- **Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks.**

  Rating: Class IIb, Level A

- **PEG-IFN and RBV with or without sofosbuvir, simeprevir, telaprevir, or boceprevir for 12 weeks to 48 weeks.**

  Rating: Class IIb, Level A

- **Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral.**

  Rating: Class III, Level A

*See sections on HIV/HCV coinfection [4], decompensated cirrhosis [5], liver transplantation [7], and renal impairment [8].

Although regimens of sofosbuvir and RBV or PEG-IFN and RBV plus sofosbuvir, simeprevir, telaprevir, or boceprevir for 12 weeks to 48 weeks (some using response-guided therapy) are also FDA approved, they are inferior to the current recommended regimens. Most of the IFN-containing regimens are associated with higher rates of serious adverse events (eg, anemia and rash), longer treatment duration, high pill burden, numerous drug-drug interactions, more frequent dosing, higher intensity of monitoring for continuation and stopping of therapy, and the requirement to be taken with food or with high-fat meals. Although the phase III NEUTRINO trial reported the highest SVR rate (89%) for an IFN-containing regimen (sofosbuvir [400 mg daily]) in combination with PEG-IFN 2a (180 ?g by subcutaneous injection weekly) and weight-based RBV in HCV genotype 1 infection and limited exposure to IFN to just 12 weeks, the safety and tolerability profile limits its usefulness in the setting of FDA-approved, highly efficacious oral DAA combinations. (Lawitz, 2013a [27])

PEG-IFN and RBV for 48 weeks for treatment-naive patients infected with HCV genotype 1 has been superseded by treatments incorporating DAAs and should not be used.

II. Genotype 2

Recommended regimen for treatment-naive patients with HCV genotype 2 infection.

Daily daclatasvir (60 mg*) and sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 2 infection who cannot tolerate RBV.

Rating: Class IIa, Level B

Daily sofosbuvir (400 mg) and weight-based RBV for 12 weeks is recommended for treatment-naive patients with HCV genotype 2 infection.

Rating: Class I, Level A

Extending treatment to 16 weeks is recommended in patients with cirrhosis.

Rating: Class IIb, Level C

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on **HIV/HCV coinfection** [11] for patients on antiretoviral therapy.

Daclatasvir with sofosbuvir for 12 weeks was approved by the FDA for the treatment of HCV genotype 3 infection in patients without and with cirrhosis. Although daclatasvir with sofosbuvir was not approved for the treatment of HCV genotype 2 infection, daclatasvir maintains adequate activity against HCV genotype 2 despite a 50% effective concentration (EC_{50}) that increases by several logs in the presence of the prevalent M31 polymorphism. (Wang, 2014 [28]) In fact, daclatasvir with sofosbuvir was associated with high rates of SVR in treatment-naive patients with HCV genotype 2 infection with both 12 weeks and 24 weeks of therapy. (Wyles, 2015 [12]); (Sulkowski, 2014 [13]) It is unclear if there is a subgroup of HCV genotype 2–infected patients who would benefit from extending treatment to 24 weeks. For patients who require treatment but cannot tolerate RBV, an alternative regimen of daclatasvir with sofosbuvir for 12 weeks is recommended and consideration of extending treatment to 24 weeks for patients with poor baseline characteristics (cirrhosis) is reasonable.

Sofosbuvir (400 mg daily) was combined with weight-based RBV for treatment-naive patients with HCV genotype 2 infection in 3 clinical trials, each of which enrolled patients with HCV genotype 2 or 3: FISSION, POSITRON, and VALENCE. (Lawitz, 2013a [27]); (Jacobson, 2013c [29]); (Zeuzem, 2013c [30]) The FISSION study randomized patients to receive daily PEG-IFN and RBV (800 mg) for 24 weeks or sofosbuvir plus daily weight-based RBV for 12 weeks. (Lawitz, 2013a [27]) The SVR rate was higher (94%) in patients who received sofosbuvir plus RBV than in

those who received PEG-IFN and RBV (78%; 52/67). Across all 3 trials, 201 of the 214 (94%) patients with HCV genotype 2 achieved SVR with sofosbuvir plus RBV. Among patients who did not achieve SVR, sofosbuvir resistance–associated variants (RAVs) were not detected. (US FDA, 2013a [31]) Based on real-world data from Trio Health, lower response rates were seen in treatment-naive patients with cirrhosis than in those without cirrhosis. (Dieterich, 2014a [32]) Although data to support extension of therapy are not yet available for treatment-naive patients with HCV genotype 2 infection, longer treatment duration improves SVR in treatment-experienced patients with cirrhosis. (Jacobson, 2013c [29]); (Foster, 2015 [33]) Owing to the small numbers of patients with HCV genotype 2 infection and cirrhosis enrolled in the registration trials, several phase IIIb studies are ongoing to specifically determine the appropriate length of treatment for this subgroup of patients (NCT01962441, NCT 02128542). Until these data are available, extending treatment from 12 weeks to 16 weeks in HCV genotype 2–infected patients with cirrhosis is recommended**.**

Alternative regimens for treatment-naive patients with HCV genotype 2 infection.

None.

Several other available DAAs have activity in vivo against HCV genotype 2. Simeprevir has moderate potency against HCV genotype 2 but has not formally been tested in combination with sofosbuvir in HCV genotype 2 infection. (Moreno, 2012 [34])

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 2.

- **PEG-IFN and RBV for 24 weeks**

  Rating: Class IIb, Level A

- **Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral**

  Rating: Class III, Level A

- **Telaprevir-, boceprevir-, or ledipasvir-containing regimens**

  Rating: Class III, Level A

PEG-IFN 2a (180 µg weekly) or PEG-IFN 2b (1.5 µg/kg weekly) plus RBV (800 mg daily) for 24 weeks was compared with sofosbuvir (400 mg daily) plus weight-based RBV in the FISSION trial. (Lawitz, 2013a [27]) The SVR12 rate achieved with PEG-IFN and RBV was lower than that achieved with sofosbuvir and RBV overall (78% and 95%, respectively) and in the subgroups of patients with or without cirrhosis. Safety and tolerability of PEG-IFN and RBV was inferior to that observed with sofosbuvir and RBV, with greater frequency of reported adverse events and laboratory abnormalities and a higher rate of treatment discontinuation owing to adverse events. Further, therapy with PEG-IFN and RBV is 12 weeks longer than with sofosbuvir plus RBV.

Because of its poor activity in vitro and in vivo, boceprevir should not be used as therapy for patients with HCV genotype 2 infection. Although telaprevir plus PEG-IFN and RBV has antiviral activity against HCV genotype 2, (Foster, 2011 [35]) the additional adverse effects and longer duration of therapy required do not support the use of this regimen. Similarly, although ledipasvir has adequate activity against HCV genotype 2, this is lost in the presence of the highly prevalent L31M polymorphism and thus is not recommended for treatment of HCV genotype 2 infection. (Nakamoto, 2014 [36])

III. Genotype 3

Recommended regimens for treatment-naive patients with HCV genotype 3 infection.

Daily daclatasvir (60 mg*) and sofosbuvir (400 mg) for 12 weeks (no cirrhosis) or 24 weeks with or without weight-based RBV (cirrhosis) is recommended for treatment-naive patients with HCV genotype 3 infection.

Rating: Class I, Level A (no cirrhosis); Class IIa, Level C (cirrhosis)

Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is recommended for IFN-eligible, treatment-naive patients with HCV genotype 3 infection.

Rating: Class I, Level A

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on **HIV/HCV coinfection**[11] for patients on antiretoviral therapy.

Daclatasvir with sofosbuvir for 12 weeks was approved by the FDA for treatment of HCV genotype 3 infection. The recommendation is based on ALLY-3, a phase III study of the once-daily NS5A inhibitor daclatasvir plus sofosbuvir for 12 weeks; the study included 101 treatment-

naive patients and demonstrated an SVR12 rate of 90%. In treatment-naive patients without cirrhosis (Metavir F0-F3), 97% achieved SVR12, and in treatment-naive patients with cirrhosis (Metavir F4), 58% achieved SVR12. (Nelson, 2014 [37]). This suggests that patients with genotype 3-infection and cirrhosis are likely to benefit from an extension of therapy to 24 weeks. This has been confirmed in cohort studies, including the European compassionate use program, which reported SVR12 rates of 76% versus 88% when daclatasvir and sofosbuvir was used for 12 weeks and 24 weeks in HCV genotype 3–infected patients with cirrhosis, respectively. (Hezode, 2015[38])

The triple-arm, controlled BOSON study (Foster, 2015 [33]) randomly assigned treatment-naive and -experienced patients with HCV genotype 3 infection to either sofosbuvir and RBV for 16 weeks (n=196) or 24 weeks (n=199) or sofosbuvir plus PEG-IFN and RBV for 12 weeks (n=197). The SVR12 rate among treatment-naive patients was 77% (70/91), 88% (83/94), and 95% (89/94) for each arm, respectively. The greater SVR12 in the IFN-containing arm was noted regardless of evidence of cirrhosis with SVR12 rates of 83% (58/70) versus 57% (12/21), 90% (65/72) versus 82% (18/22), and 96% (68/71) versus 91% (21/23), for those in each arm without versus with cirrhosis, respectively. Although the regimen of sofosbuvir plus PEG-IFN and RBV has greater adverse event rates and requires an increase in monitoring, the shortened 12 weeks of treatment coupled with superior results makes this the recommended regimen for IFN-eligible patients, until superior IFN-free options are defined.

Alternative regimen for treatment-naive patients with HCV genotype 3 infection.

Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks is an alternative regimen for treatment-naive patients with HCV genotype 3 infection who are IFN-ineligible.

Rating: Class I, Level A

The VALENCE study, which enrolled patients with HCV genotype 2 or 3, assessed the efficacy and safety of sofosbuvir (400 mg daily) plus weight-based RBV for 24 weeks. This trial included 250 treatment-naive (42%) and -experienced (58%) subjects with HCV genotype 3 infection. The overall SVR12 rate was 84% and was higher among treatment-naive than -experienced patients (93% vs 77%, respectively). (Zeuzem, 2014 [39]) These results suggest that higher response rates can be achieved with a 24-week regimen of sofosbuvir plus RBV than those reported for HCV genotype 3–infected participants receiving 12- or 16-week regimens in the FISSION (Lawitz, 2013a [27]) (12 weeks, SVR12 rate: 63%), POSITRON, (Jacobson, 2013c [29]) (12 weeks, SVR 12 rate: 61%) and FUSION (12 weeks, SVR12 rate: 30%; 16 weeks, SVR12 rate: 62%) trials. The primary reason for the higher SVR rate with extended therapy among treatment-naive patients was due to a reduction in the relapse rate from 40% to 5%. In a subanalysis, response rates were similarly high among those with (n=45) and without (n=100) cirrhosis (92% and 93%,

respectively). These data were confirmed in the randomized controlled BOSON trial as described above. (Foster, 2015 [33]) In the BOSON trial, this 24-week regimen had lower SVR rates than the 12-week regimen of sofosbuvir plus PEG-IFN and RBV in treatment-naive patients, regardless of the presence of cirrhosis. Therefore, this is an alternative regimen for patients who cannot take IFN.

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 3 infection.

- **PEG-IFN and RBV for 24 weeks to 48 weeks**

  Rating: Class IIb, Level A

- **Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral**

  Rating: Class III, Level A

- **Telaprevir-, boceprevir-, or simeprevir-based regimens should not be used for patients with genotype 3 HCV infection.**

  Rating: Class III, Level A

Although the combination of PEG-IFN and RBV is an FDA-approved regimen for HCV genotype 3 infection, its less acceptable adverse effect profile requires more intensive monitoring and its overall lower efficacy makes it less desirable than the recommended regimen.

Because of their limited in vitro and in vivo activity against HCV genotype 3, boceprevir, telaprevir, and simeprevir should not be used as therapy for patients with HCV genotype 3 infection.

Very limited phase II data are available from a single-center study (ELECTRON-II) that examined ledipasvir/sofosbuvir with (n=26) or without (n=25) RBV for 12 weeks in treatment-naive patients with HCV genotype 3 infection, 15% of whom had cirrhosis. All 26 (100%) patients in the RBV-containing arm achieved SVR12 compared with 16 of 25 (64%) of those in the RBV-free arm. Although these data raise the possibility that the addition of ledipasvir to sofosbuvir and RBV may shorten the course of therapy for persons with HCV genotype 3 infection, the high EC_{50} of ledipasvir for HCV genotype 3 infection (Wong, 2013 [40]); (Kohler, 2014 [41]) and the homogenous patient population studied limit the generalizability of this study. Until further data are available to confirm these findings, a recommendation for use of this regimen cannot be made. (Gane, 2013b [42])

IV. Genotype 4

Three options with similar efficacy in general are recommended for treatment-naive patients with HCV genotype 4 infection (listed in alphabetic order; see text).

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 4 infection.

Rating: Class IIb, Level B

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV for 12 weeks is recommended for treatment-naive patients with HCV genotype 4 infection.

Rating: Class I, Level B

Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks is recommended for treatment-naive patients with HCV genotype 4 infection.

Rating: Class IIa, Level B

The SYNERGY trial was an open-label study evaluating 12 weeks of ledipasvir/sofosbuvir in 21 HCV genotype 4–infected patients, of whom 60% were treatment naive and 43% had advanced fibrosis (Metavir stage F3 or F4). (Kohli, 2015 [43]) One patient took the first dose and then withdrew consent. All of the 20 patients who completed treatment achieved an SVR12; thus, the SVR12 rate was 95% in the intention-to-treat analysis and 100% in the per-protocol analysis. Abergel and colleagues reported data from an open-label single-arm study including 22 HCV genotype 4–infected, treatment-naive patients (only 1 with cirrhosis) with an SVR12 rate of 95% (21/22). (Abergel, 2015 [44]) These 2 pilot studies support the use of this regimen in patients with HCV genotype 4 infection.

PEARL-I was an open-label phase IIb study that included a cohort of 86 treatment-naive patients with HCV genotype 4 infection with or without cirrhosis who received 12 weeks of the daily fixed-dose combination of paritaprevir/ritonavir/ombitasvir (PrO) with or without weight-based RBV. SVR12 rates were 100% (42/42) in the group receiving RBV and 90.9% (40/44) in the group not receiving RBV. Adverse effects were generally mild, with headache, asthenia, fatigue, and nausea most commonly reported. There were no discontinuations owing to adverse events. (Hezode, 2015

[38])

Several studies support the use of sofosbuvir and RBV in treatment-naive patients with HCV genotype 4 infection. In a small study of Egyptian patients in the United States who were treated with sofosbuvir plus weight-based RBV, SVR12 was achieved in 79% (11/14) and 100% (14/14) of these treatment-naive patients treated for 12 weeks and 24 weeks, respectively. (Ruane, 2014 [45]) In a phase II study in Egypt, patients with HCV genotype 4 infection received daily sofosbuvir plus weight-based RBV for 12 weeks or 24 weeks; among treatment-naive patients SVR12 rates were 84% (21/25) and 92% (22/24), respectively. (Doss, 2015 [46]) PHOTON-2, an open-label study of HIV/HCV-coinfected patients, included 31 treatment-naive patients with HCV genotype 4 infection who received daily sofosbuvir plus weight-based RBV for 24 weeks. In this study, 84% of patients (26/31) achieved SVR12. (Molina, 2015 [47])

Alternative regimen for treatment-naive patients with HCV genotype 4 infection.

Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is an acceptable regimen for treatment-naive patients with HCV genotype 4 infection.

Rating: Class II, Level B

In the phase III NEUTRINO trial, (Lawitz, 2013a [27]) 28 treatment-naive patients with HCV genotype 4 infection were treated with sofosbuvir (400 mg daily) plus PEG-IFN 2a (180 µg weekly) and weight-based RBV for 12 weeks. Of the 28 patients with HCV genotype 4 infection, 27 (96%) achieved SVR12. The single patient who did not achieve SVR had cirrhosis and had a relapse after therapy. The adverse event profile was similar to that associated with PEG-IFN and RBV therapy.

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 4 infection.

- **PEG-IFN and RBV with or without simeprevir for 24 weeks to 48 weeks**

  Rating: Class IIb, Level A

-

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

- **Telaprevir- or boceprevir-based regimens**

  Rating: Class III, Level A

PEG-IFN and RBV for 48 weeks was the previously recommended regimen for patients with HCV genotype 4 infection. (Ghany, 2009 [48]); (AASLD/IDSA/IAS-USA, 2014 [49]) Adding sofosbuvir (400 mg daily) to PEG-IFN and RBV increases response rates and markedly shortens therapy with no apparent additional adverse effects. The addition of simeprevir to PEG-IFN and RBV increases response rates but has inferior SVR rates to the other available regimens and requires a longer duration of PEG-IFN and RBV, which increases the risk of adverse events and thus is no longer recommended. (Moreno, 2013b [50])

Because of their limited activity against genotype 4 HCV in vitro and in vivo, boceprevir and telaprevir should not be used as therapy for patients with HCV genotype 4 infection.

V. Genotype 5 or 6

Few data are available to help guide decision making for patients infected with HCV genotype 5 or 6. Nonetheless, ledispavir/sofosbuvir is recommended. (Kapoor, 2014 [51]); (Abergel, 2015 [44]) (Gane, 2014 [52])

Recommended regimen for treatment-naive patients with HCV genotype 5 or 6 infection.

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 5 or 6 infection.

Rating: Class IIa, Level B

Although there are limited data on patients with HCV genotype 5 infection, the in vitro activity for sofobuvir and ledipasvir is quite good with EC_{50} of 15 nM and 0.081 nM, respectively. Abergel and colleagues reported data from an open-label, single arm study that included 41 HCV genotype 5–infected patients with an overall SVR12 rate of 95% (39/41). (Abergel, 2015 [44]) The SVR12 rate was also 95% specifically in treatment-naive patients (20/21), of whom only 3 had cirrhosis but who all 3 achieved SVR12.

Alternative regimen for treatment-naive patients with HCV genotype 5 or 6 infection.

Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is an alternative regimen for treatment-naive patients with HCV genotype 5 or 6 infection.

Rating: Class IIa, Level B

In the phase III NEUTRINO trial, (Lawitz, 2013a [27]) treatment-naive patients with HCV genotypes 1 (n=291), 4 (n=28), 5 (n=1), and 6 (n=6) were treated with sofosbuvir (400 mg daily) plus PEG-IFN 2a (180 µg weekly) and weight-based RBV for 12 weeks. All 6 patients with HCV genotype 6 and the 1 patient with HCV genotype 5 achieved SVR12. The adverse event profile in these patients and in the larger study population was similar to that seen with PEG-IFN and RBV therapy.

Ledipasvir has in vitro activity against most HCV genotype 6 subtypes (except for 6e). (Wong, 2013 [40]); (Kohler, 2014 [41]) A small, 2-center, open-label study (NCT01826981) investigated the safety and in vivo efficacy of ledipasvir/sofosbuvir for 12 weeks in treatment-naive and -experienced patients with HCV genotype 6 infection. Twenty-five patients (92% were treatment naive) who were primarily Asian (88%) had infection from 7 different subtypes (32%, 6a; 24%, 6e; 12%, 6l; 8%, 6m; 12%, 6p; 8%, 6q; 4%, 6r). Two patients (8%) had cirrhosis. The SVR12 rate was 96% (24/25), and the 1 patient who experienced relapse had discontinued therapy at week 8 because of drug use. No patient discontinued treatment owing to adverse events.

In the phase III NEUTRINO trial, (Lawitz, 2013a [27]) treatment-naive patients with HCV genotypes 1 (n=291), 4 (n=28), 5 (n=1), and 6 (n=6) were treated with sofosbuvir (400 mg daily) plus PEG-IFN 2a (180 µg weekly) and weight-based RBV for 12 weeks. All 6 patients with HCV genotype 6 and the 1 patient with HCV genotype 5 achieved SVR12. The adverse event profile in these patients and in the larger study population was similar to that seen with PEG-IFN and RBV therapy.

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 5 or 6 infection.

- **PEG-IFN and RBV with or without simeprevir for 24 weeks to 48 weeks**

  Rating: Class IIb, Level A

- **Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral**

  Rating: Class III, Level A

- **Telaprevir- or boceprevir-based regimens**

  Rating: Class III, Level A

PEG-IFN and RBV for 48 weeks was the previous alternative regimen for patients infected with HCV genotype 5, but the availability of recommended regimens that substantially reduce exposure to IFN and RBV make this regimen a poor option. Because of their limited activity against genotypes 5 and 6 HCV in vitro and in vivo, boceprevir and telaprevir should not be used as therapy for patients with HCV genotype 5 or 6 infection.

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse, and awaiting availability of a pangenotypic regimen may be considered. Until then, when treatment is necessary, the choice of antiviral combination and duration of treatment should maximize efficacy against each genotype represented in the assay. When the correct combination or duration is unclear, expert consultation should be sought.

Initial Treatment Table: Drug Interactions With Direct-Acting Antivirals and Selected Concomitant Medications

Concomitant Medications	Daclatasvir	Ledipasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir
Acid-reducing agents*		X	X		
Alfuzosin/tamsulosin			X		
Amiodarone	X	X	X	X	X
Anticonvulsants	X	X	X	X	X
Antiretrovirals*	See HIV section	See HIV section	See HIV section	See HIV section	See HIV section
Azole antifungals*	X**		X	X	
Buprenorphine/naloxone			X		
Calcineurin inhibitors*			X	X	
Calcium channel blockers*	X		X	X	
Cisapride			X	X	
Digoxin	X	X		X	
Ergot derivatives			X		
Ethinyl estradiol–containing products			X		
Furosemide			X		
Gemfibrozil			X		
Glucocorticoids*	X		X (inhaled, intranasal	X	

Herbals **St. John's wort** **Milk thistle**	**X**	**X**	**X**	**X** **X**	**X**
Macrolide antimicrobials*	**X****			**X**	
Other antiarrythmics*			**X**	**X**	
Phosphodiesterase type 5 inhibitors*			**X**	**X**	
Pimozide			**X**		
Rifamycin antimicrobials*	**X**	**X**	**X**	**X**	**X**
Salmeterol			**X**		
Sedatives*			**X**	**X**	
Simeprevir		**X**			
Statins*	**X**	**X**	**X**	**X**	

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

Changes made on August 7, 2015

Links
[1] http://www.hcvguidelines.org/node/11
[2] http://www.hcvguidelines.org/node/72
[3] http://www.hcvguidelines.org/node/29
[4] http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-hivhcv-coinfection
[5] http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-decompensated-cirrhosis
[6] http://www.hcvguidelines.org/node/11#ctpclass
[7] http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-who-develop-recurrent-hcv-infection-post–liver
[8] http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-renal-impairment
[9] http://www.hcvguidelines.org/node/92

[10] http://www.hep-druginteractions.org/
[11] http://www.hcvguidelines.org/node/71
[12] http://www.hcvguidelines.org/full-report/references#wyles2015
[13] http://www.hcvguidelines.org/full-report/references#sulkowski2014
[14] http://www.hcvguidelines.org/full-report/references#welzel2015
[15] http://www.hcvguidelines.org/full-report/references#deledinghen2015
[16] http://www.hcvguidelines.org/full-report/references#poordad2015
[17] http://www.hcvguidelines.org/full-report/references#afdhal2014a
[18] http://www.hcvguidelines.org/full-report/references#kowdley2014
[19] http://www.hcvguidelines.org/full-report/references#feld2014
[20] http://www.hcvguidelines.org/full-report/references#ferenci2014
[21] http://www.rxabbvie.com/pdf/viekirapak_pi.pdf
[22] http://www.hcvguidelines.org/full-report/references#poordad2014
[23] http://www.hcvguidelines.org/full-report/references#kwo2015
[24] http://www.hcvguidelines.org/full-report/references#lawitz2015
[25] http://www.hcvguidelines.org/full-report/references#feld2015
[26] http://hcvguidelines.org/full-report/initial-treatment-hcv-infection#genotype1
[27] http://www.hcvguidelines.org/full-report/references#lawitz2013a
[28] http://www.hcvguidelines.org/full-report/references#wang2014
[29] http://www.hcvguidelines.org/full-report/references#jacobson2013c
[30] http://www.hcvguidelines.org/full-report/references#zeuzem2013c
[31] http://www.hcvguidelines.org/full-report/references#usfda2013a
[32] http://www.hcvguidelines.org/full-report/references#dieterich2014a
[33] http://www.hcvguidelines.org/full-report/references#foster2015
[34] http://www.hcvguidelines.org/full-report/references#moreno2012
[35] http://www.hcvguidelines.org/full-report/references#foster2011
[36] http://www.hcvguidelines.org/full-report/references#nakamoto2014
[37] http://www.hcvguidelines.org/full-report/references#nelson2014
[38] http://www.hcvguidelines.org/full-report/references#hezode2015
[39] http://www.hcvguidelines.org/full-report/references#zeuzem2014
[40] http://www.hcvguidelines.org/full-report/references#wong2013
[41] http://www.hcvguidelines.org/full-report/references#kohler2014
[42] http://www.hcvguidelines.org/full-report/references#gane2013b
[43] http://www.hcvguidelines.org/full-report/references#kohli2015
[44] http://www.hcvguidelines.org/full-report/references#abergel2015
[45] http://www.hcvguidelines.org/full-report/references#ruane2014
[46] http://www.hcvguidelines.org/full-report/references#doss2015
[47] http://www.hcvguidelines.org/full-report/references#molina2015
[48] http://www.hcvguidelines.org/full-report/references#ghany2009
[49] http://www.hcvguidelines.org/full-report/references#aasld-idsa-iasusa
[50] http://www.hcvguidelines.org/full-report/references#moreno2013b
[51] http://www.hcvguidelines.org/full-report/references#kapoor2014
[52] http://www.hcvguidelines.org/full-report/references#gane2014