Treatment-Naive Genotype 4 Without Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 4 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)[b]	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, B

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[b] An 8-week regimen can be considered in patients with favorable baseline characteristics (ie, no cirrhosis, HCV RNA <6 million IU/mL, and absence of genotype 4r).

Recommended Regimens

Glecaprevir/Pibrentasvir

Based on favorable data for 12 weeks of treatment for noncirrhotic patients in part 4 of the phase 2 SURVEYOR-2 study (100% SVR12 in 34 patients with genotype 4, 5, or 6) (Kwo, 2017b), ENDURANCE-4 enrolled 121 DAA-naive or -experienced (sofosbuvir plus ribavirin ± peginterferon) genotype 4, 5, or 6 patients without cirrhosis to receive 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills (Asselah, 2018b). Of those enrolled, 86% had fibrosis stage F0 to F1 and 68% were treatment naive. The genotype distribution was 63% genotype 4, 21% genotype 5, and 16% genotype 6. The overall SVR12 rate for the intention-to-treat population was 99% (120/121), including 99% (75/76) for genotype 4, 100% for genotype 5 (26/26), and 100% (19/19) for genotype 6.

Genotype 4, 5, and 6 patients were not included in the randomized study to compare an 8-week versus 12-week course of glecaprevir/pibrentasvir for DAA-naive, noncirrhotic patients. However, part 4 of the SURVEYOR-2 study investigated an 8-week course of glecaprevir/pibrentasvir in DAA-naive patients without cirrhosis (Asselah, 2018b). In the intention-to-treat analysis, 43/46 patients with genotype 4, 2/2 with genotype 5, and 9/10 with genotype 6 achieved SVR12; there were no known virologic failures.

EXPEDITION-1 investigated use of glecaprevir/pibrentasvir in treatment-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 99% (145/146) achieved SVR12, including 16/16(100%) with genotype 4, 2/2 (100%) with genotype 5, and 7/7 (100%) with genotype 6 (Forns, 2017). Based on these studies, glecaprevir/pibrentasvir was approved for treatment of genotype 4-infected, DAA-naive, noncirrhotic patients for a duration of 8 weeks.

Ledipasvir/Sofosbuvir

In the HEPNED-001 study from the Netherlands, 40 treatment-naive, noncirrhotic patients with (n=30) and without (n=10) HIV coinfection were treated with ledipasvir/sofosbuvir for 8 weeks; 93% (28/30) of HIV/HCV-coinfected patients and 100% (10/10) of HCV-monoinfected patients achieved SVR12 (Boerekamps, 2019). Patients were predominantly infected with genotypes 4a and 4d; 2.5% each were infected with 4c and 4t. In another study that evaluated 8 weeks of ledipasvir/sofosbuvir among treatment-naive, noncirrhotic patients from Saudi Arabia with genotype 4 infection, SVR12 was 98% (Babatin, 2019). Notably, 91% of patients had a baseline HCV RNA level <6 million IU/mL. These pilot studies support the use of ledipasvir/sofosbuvir in patients with genotype 4 infection, with 8-weeks therapy a consideration for those with favorable characteristics (ie, no cirrhosis, HCV RNA <6 million IU/mL, and absence of genotype 4r).

In a study of from Rwanda, 300 treatment-naive patients with genotype 4 infection were treated with ledipasvir/sofosbuvir for 12 weeks. The major subtypes among participants were 4k (n=134), 4r (n=48), 4q (n=42), and 4v (n=24). Overall SVR was 87% with subtype differences evident; SVR for 4r infection was 56% compared to 93% for other subtypes (Gupta, 2019). The influence of subtype on SVR warrants consideration of the use of ledipasvir, although 4r is rare in non-African populations.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 4 infection in patients with or without cirrhosis. ASTRAL-1 included 64 genotype 4-infected, treatment-naive patients without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (100%) (Feld, 2015).

The POLARIS-2 phase 3 study randomized DAA-naive patients to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) versus 12 weeks of sofosbuvir/velpatasvir. Of 57 patients with genotype 4 in the sofosbuvir/velpatasvir arm, 98% achieved SVR and 1 patient experienced relapse (Jacobson, 2017).

Elbasvir/Grazoprevir

The phase 3 C-EDGE treatment-naive trial of elbasvir/grazoprevir included 18 patients with genotype 4 infection. With 12 weeks of therapy, SVR was 100% (18/18) (Zeuzem, 2015). A similar SVR12 of 96% (54/56) was seen in treatment-naive patients with genotype 4 infection from the combined phase 2/3 elbasvir/grazoprevir database of HIV/HCV coinfected patients treated for 12 weeks (Rockstroh, 2015).

An integrated analysis of a phase 2/3 trial evaluated elbasvir/grazoprevir with or without ribavirin among 111 treatment-naive patients with genotype 4 infection (predominantly subtype 4a and 4d); 26% of participants had HIV/HCV coinfection and 13% had cirrhosis. Elbasvir/grazoprevir without ribavirin for 12 weeks resulted in an SVR12 of 96% (97/101) (Asselah, 2018c). Baseline RASs and subtype did not appear to impact SVR12 rates.

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Related References

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