Treatment-Naive Genotype 4 Without Cirrhosis

Recommended and alternative regimens listed by pangenotypic, 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 sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)[b]	12 weeks	I, A

[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, 93% (43/46) of patients with genotype 4, 100% (2/2) with genotype 5, and 90% (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 100% (16/16) with genotype 4, 100% (2/2) with genotype 5, and 100% (7/7) 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. A meta-analysis of real-world cohorts that examined glecaprevir/pibrentasvir treatment response among adults demonstrated an SVR12 of 98.3% (n=55) among noncirrhotic participants with genotype 4 infection with 8 weeks of treatment (Lampertico, 2020).

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). A real-world, pooled analysis of 12 cohorts that evaluated adults treated with 12 weeks of sofosbuvir/velpatasvir demonstrated an SVR of 99.6% (238/239) among participants with genotype 4, with or without compensated cirrhosis (Mangia, 2020).

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. In a study among treatment-naive participants with genotype 4 infection that compared 8 weeks versus 12 weeks of elbasvir/grazoprevir treatment for those with F0 to F2 fibrosis (all with F3 to F4 fibrosis received 12 weeks of treatment), SVR rates were 94% (50/53) in the 8-week arm and 96% (26/27) in the 12-week arm (Asselah, 2020).

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 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.

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Related References

Asselah T, Kowdley KV, Zadeikis N, et al. Efficacy of glecaprevir/pibrentasvir for 8 or 12 weeks in patients with hepatitis C virus genotype 2, 4, 5, or 6 infection without cirrhosis. *Clin Gastroenterol Hepatol*. 2018;16(3):417-426.

Asselah T, Reesink H, Gerstoft J, et al. Efficacy of elbasvir and grazoprevir in participants with hepatitis C virus genotype 4 infection: a pooled analysis. *Liver Int*. 2018;38(9):1583-1591.

Asselah T, Pol S, Hezode C, et al. Efficacy and safety of elbasvir/grazoprevir for 8 or 12 weeks for hepatitis C virus genotype 4 infection: a randomized study. *Liver Int*. 2020;40(5):1042-1051.

Babatin MA, AlGhamdi AS, Assiri AM, et al. Treatment efficacy of ledipasvir/sofosbuvir for 8 weeks in non-cirrhotic chronic hepatitis C genotype 4 patients. *Saudi J Gastroenterol*. 2019;25(1):55-60. doi:10.4103/sjg.SJG_189_18.

Boerekamps A, Vanwolleghem T, Van Der Valk M, et al. 8 weeks of sofosbuvir/ledipasvir is effective in DAA-naive non-cirrhotic HCV genotype 4 infected patients (HEPNED-001 study). *J Hepatol*. 2019;70(3):554-557. doi:10.1016/j.jhep.2018.10.032.

Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med*. 2015;373(27):2599-2607.

Forns X, Lee SS, Valdes J, et al. Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis (EXPEDITION-1): a single-arm, open-label, multicentre phase 3 trial. *Lancet Infect Dis*. 2017;17(10):1062-1068.

Gupta N, Mbituyumuremyi A, Kabahizi J, et al. Treatment of chronic hepatitis C virus infection in Rwanda with ledipasvir-sofosbuvir (SHARED): a single-arm trial. *Lancet Gastroenterol Hepatol*. 2019;4(2):119-126. doi:10.1016/S2468-1253(18)30382-0.

Jacobson IM, Lawitz E, Gane EJ, et al. Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials. *Gastroenterology*. 2017;153(1):113-122.

Kwo PY, Poordad F, Asatryan A, et al. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. *J Hepatol*. 2017;67(2):263-271.

Lampertico P, Carrión JA, Curry M, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of patients with chronic HCV infection: a meta-analysis. *J Hepatol*. 2020;72(6):1112-1121.

Mangia A, Milligan S, Khalili M, et al. Global real-world evidence of sofosbuvir/velpatasvir as simple, effective HCV treatment: analysis of 5552 patients from 12 cohorts. *Liver Int*. 2020;40(8):1841-1852.

Rockstroh JK, Nelson M, Katlama C, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK- 8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. *Lancet HIV*. 2015;2(8):e319-327. doi:10.1016/S2352-3018(15)00114-9.

Zeuzem S, Ghalib R, K. Reddy R, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. *Ann Intern Med*. 2015;163(1):1-13.