Treatment-Naive Genotype 3 Without Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Persons With Genotype 3 Infection 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

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Recommended Regimens

Glecaprevir/Pibrentasvir

ENDURANCE-3 was a randomized (2:1) trial comparing 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, with 12 weeks of sofosbuvir (400 mg) and daclatasvir (60 mg) among 348 treatment-naive participants with genotype 3 infection without cirrhosis. The trial was later amended to include an open-label arm that evaluated glecaprevir/pibrentasvir for an 8-week duration among 157 treatment-naive participants with genotype 3 infection without cirrhosis. Participants receiving glecaprevir/pibrentasvir for 8 weeks or 12 weeks achieved an SVR12 rate of 95% in an intention-to-treat analysis (95% [222/233] participants receiving the 12-week regimen; 95% [149/157] participants receiving the 8-week regimen) (Foster, 2017). Virologic failure was observed in 6 participants receiving the 8-week regimen (1 virologic breakthrough; 5 relapses) and in 4 participants in the 12-week arm (1 virologic breakthrough; 3 relapses). Both the 8-week and 12-week glecaprevir/pibrentasvir regimens met noninferiority criteria for SVR12 compared with the standard-of-care arm of sofosbuvir/daclatasvir, which reported an SVR12 rate of 97%. The baseline presence of the Y93H substitution did not affect SVR rates; 100% (10/10) with the Y93H RAS achieved SVR with an 8-week treatment course compared with 96.5% (165/171) without Y93H. However, the presence of the A30K substitution was associated with a lower SVR rate; 78% (14/18) with the A30K RAS achieved SVR with an 8-week treatment course compared with 99% (161/163) without the A30K RAS (Krishnan, 2018). Of the 14 treatment-naive participants with genotype 3 infection without cirrhosis with baseline A30K RAS who received a 12-week course of glecaprevir/pibrentasvir, 93% (13/14) achieved SVR. Given the small numbers, there is insufficient evidence at this time to recommend testing for RASs or extension of therapy in the setting of an A30K substitution.

In addition, data from real-world cohorts support the effectiveness of an 8-week regimen of glecaprevir/pibrentasvir therapy for treatment-naive persons with genotype 3 infection without cirrhosis (Drysdale, 2020); (Sterling, 2019). Among treatment-naive persons with genotype 3 infection, 99% (162/164) of persons in a German cohort (Berg, 2019) and 96% (46/48) of those in an Italian cohort (D'Ambrosio, 2019) treated with 8 weeks of glecaprevir/pibrentasvir achieved SVR12. A meta-analysis of real-world cohorts

that examined glecaprevir/pibrentasvir treatment response among adults demonstrated an SVR12 rate of 99.2% (n=320) among persons with genotype 3 infection without cirrhosis who received 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 3 infection in persons without cirrhosis or with compensated cirrhosis. ASTRAL-3 demonstrated superiority of 12 weeks of sofosbuvir/velpatasvir compared with 24 weeks of sofosbuvir plus ribavirin among 552 treatment-naive and treatment-experienced participants without cirrhosis or with compensated cirrhosis (Foster, 2015a). Among the treatment-naive participants without cirrhosis, SVR12 rates were 98% (160/163) for sofosbuvir/velpatasvir compared with 90% (141/156) for sofosbuvir plus ribavirin.

The phase 3 POLARIS-2 study evaluated 12 weeks of sofosbuvir/velpatasvir in persons with genotype 3 infection without cirrhosis who were either treatment naive or interferon experienced. Eighty-nine participants with genotype 3 infection received the sofosbuvir/velpatasvir regimen; 97% (86/89) achieved SVR12 (Jacobson, 2017). There were no virologic failures.

A subsequent open-label study conducted in Russia and Sweden demonstrated similar response rates in persons with genotype 3 infection without cirrhosis (Isakov, 2019). Additionally, an observational cohort study from Germany supports the effectiveness of 12 weeks of sofosbuvir/velpatasvir among treatment-naive persons with genotype 3 infection (von Felden, 2018). Among treatment-naive persons with genotype 3 infection (25% cirrhosis in the overall cohort), 97% (162/167) were cured; there were no virologic failures. Other real-world data from cohorts across North America, Canada, and the United Kingdom also demonstrate high SVR rates with 12 weeks of sofosbuvir/velpatasvir among treatment-naive persons with genotype 3 infection without cirrhosis (Drysdale, 2020); (Mangia, 2019).

Another study provided information about the use of sofosbuvir/velpatasvir in persons with genotype 3b infection, a subtype rarely encountered in the United States. The single-arm, open-label, phase 3 trial of adults enrolled from Asia treated with sofosbuvir/velpatasvir reported an overall SVR rate of 86% among 84 participants with genotype 3 infection, with or without cirrhosis (Wei, 2019). Among participants with genotype 3a, 95% (40/42) achieved SVR12. In the subgroup of participants with genotype 3b infection without cirrhosis, 89% (25/28) achieved SVR12 with 12 weeks of sofosbuvir/velpatasvir. All participants with genotype 3b infection enrolled in this trial had NS5A RASs at A30K or L31M, or both. Another study among 90 treatment-naive persons with genotype 3 infection without cirrhosis—most receiving opioid agonist therapy—treated with only 8 weeks of sofosbuvir/velpatasvir demonstrated an SVR rate of 96% (86/90) (Boyle, 2020). A real-world, pooled analysis of 12 cohorts that evaluated adults treated with 12 weeks of sofosbuvir/velpatasvir demonstrated an SVR rate of 98.3% (1649/1677) among participants with genotype 3 infection, with or without compensated cirrhosis (Mangia, 2020).

Related References

Berg T, Naumann U, Stoehr A, et al. **Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of chronic hepatitis C infection: data from the German hepatitis C registry**. *Aliment Pharmacol Ther*. 2019;49(8):1052-1059. Doi:10.1111/apt.15222.

Boyle A, Marra F, Peters E, et al. **Eight weeks of sofosbuvir/velpatasvir for genotype 3 hepatitis C in previously untreated patients with significant (F2/3) fibrosis**. *J Viral Hepat*. 2020;27(4):371-375.

D'Ambrosio R, Pasulo L, Puoti M, et al. **Real-world effectiveness and safety of glecaprevir/pibrentasvir in 723 patients with chronic hepatitis C**. *J Hepatol*. 2019;70(3):379-387. doi:10.1016/j.jhep.2018.11.011.

Drysdale K, Ntuli Y, Bestwick J, et al. English hepatitis C registry data show high response rates to directly acting anti-virals, even if treatment is not completed. *Aliment Pharmacol Ther*. 2020;52(1):168-181. doi: 10.1111/apt.15780.

Foster GR, Afdhal NH, Roberts SK. **Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection.** *N Engl J Med.* 2015;373(27):2608-2617.

Foster GR, Gane E, Asatryan A, et al. **ENDURANCE-3: safety and efficacy of glecaprevir/pibrentasvir compared to sofosbuvir plus daclatasvir in treatment-naive HCV genotype 3-infected patients without cirrhosis**. *J Hepatol*. 2017;66(1):S33.

Isakov V, Chulanov V, Abdurakhmanov D, et al. **Sofosbuvir/velpatasvir for the treatment of HCV: excellent results from a phase-3, open-label study in Russia and Sweden**. *Infect Dis (Lond)*. 2019;51(2):131-139. doi:10.1080/23744235.2018.1535186.

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.

Krishnan P, Pilot-Matias T, Schnell G, et al. **Pooled resistance analysis in HCV genotype 1-6 infected patients treated with glecaprevir/pibrentasvir in phase 2 and 3 clinical trials**. *Antimicrob Agents Chemother*. 2018;62(10):pii: e01249-18.

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 a simple, effective regimen for the treatment of chronic hepatitis C patients: integrated analysis of 12 clinical practice cohorts**. Presented at: The International Liver Congress; April 10-14, 2019; Vienna, Austria.

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.

Sterling RK, Zeuzem S, Welzel TM, et al. 956–Safety and efficacy of glecaprevir/pibrentasvir for the treatment of HCV genotype 1-6: Results of the HCV-TARGET study. *Gastroenterology*. 2019;156(6), S-1220.

von Felden J, Vermehren J, Ingiliz P, et al. **High efficacy of sofosbuvir/velpatasvir and impact of baseline resistance-associated substitutions in hepatitis C genotype 3 infection**. *Aliment Pharmacol Ther*. 2018;47(9):1288-1295. doi:10.1111/apt.14592.

Wei L, Lim SG, Xie Q, et al. **Sofosbuvir-velpatasvir for treatment of chronic hepatitis C virus infection in Asia: a single-arm, open-label, phase 3 trial**. *Lancet Gastroenterol Hepatol*. 2019;4(2):127-134. doi:10.1016/S2468-1253(18)30343-1.

Additional Reading

- Persons With HIV/HCV Coinfection
- Persons With Renal Impairment
- Management of Acute HCV Infection

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