


Treatment-Naive Genotype 1b Without Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Patients Genotype 1b Without Cirrhosis

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks ^a	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are HIV-uninfected and whose HCV RNA level is <6 million IU/mL	8 weeks ^c	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

^a An 8-week regimen can be considered in those with genotype 1b infection and mild fibrosis (see text for details).

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

^c For HIV/HCV coinfecting patients, a treatment duration of 12 weeks is recommended.

Recommended Regimens

Elbasvir/Grazoprevir

The fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) is recommended based on data from the phase 3 C-EDGE trial, which assessed the efficacy and safety of this regimen for 12 weeks in treatment-naive adults (genotypes 1, 4, and 6) ([Zeuzem, 2015f](#)). Patients were enrolled from 60 centers in 9 countries on 4 continents. Three hundred eighty-two patients (91% of the study cohort) were infected with genotype 1 (50% genotype 1a, 41% genotype 1b). The SVR12 was 92% (144/157) in treatment-naive patients with genotype 1a and 99% (129/131) in those with genotype 1b. Findings from this phase 3 study support earlier phase 2 findings from the C-WORTHY trial in which SVR12 rates of 92% (48/52) and 95% (21/22) were demonstrated among genotype 1a and genotype 1b treatment-naive non-cirrhotic patients, respectively, who received 12 weeks of elbasvir/grazoprevir without ribavirin ([Sulkowski, 2015b](#)). The C-WORTHY trial enrolled both HCV-monoinfected and HIV/HCV-coinfecting patients.

A phase 3, global STREAGER trial of 89 treatment-naive patients with genotype 1b infection and low fibrosis stage (defined as a transient elastography score <9.5 or a Fibrotest® score <0.59 [F0 to F2]) evaluated the efficacy of 8 weeks of elbasvir/grazoprevir and found an SVR rate of 98% (87/89), supporting the option of using a shorter treatment duration for genotype 1b patients with low scores using these fibrosis staging modalities ([Abergel, 2018](#)).

In contrast to genotype 1a, the presence of baseline substitutions associated with NS5A resistance did not appear to affect genotype 1b response to elbasvir/grazoprevir. Thus, current data do not support extending the treatment duration or adding ribavirin in genotype 1b patients with NS5A RASs.

Glecaprevir/Pibrentasvir

Based on favorable data for 8 weeks of treatment for noncirrhotic patients in the phase 2 SURVEYOR-1 study (33/34 patients with SVR and no virologic failures) ([Kwo, 2017b](#)), ENDURANCE-1 enrolled 703 noncirrhotic, genotype 1 patients who were DAA-naive or in whom a previous interferon-based regimen failed. Participants were randomized to receive 8 weeks or 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 ([Zeuzem, 2016](#)). Of those enrolled, 43% had genotype 1a, 85% had fibrosis stage 0 or 1, and 62% were treatment naive. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority to the 12-week arm. A single patient experienced on-treatment virologic failure in this study (genotype 1a, day 29). Notably, there were no documented relapses in either arm.

EXPEDITION-1 investigated the use of glecaprevir/pibrentasvir in DAA-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, 145 (99%) achieved SVR12. All genotype 1b patients achieved SVR ([Forns, 2017](#)).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected persons with genotype 1, 2, 3, 4, 5, or 6, utilized 8 weeks of treatment for noncirrhotic patients and 12 weeks for cirrhotic patients (the recommended durations approved by the FDA). The overall SVR12 rate was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection ([Rockstroh, 2017](#)). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a vs 1b) nor the presence of baseline RASs impacted SVR12 results in DAA-naive genotype 1 patients.

CERTAIN-1 evaluated 8 weeks of glecaprevir/pibrentasvir among 129 Japanese DAA-naive noncirrhotic patients (97% genotype 1b); SVR12 was of 99% (128/129) ([Chayama, 2018](#)). Real-world cohorts from Germany (34% genotype 1a) and Italy (67% genotype 1a) demonstrate similarly high efficacy among treatment-naive, noncirrhotic genotype 1 patients treated with 8 weeks of glecaprevir/pibrentasvir using a modified intention-to-treat analysis (excluding those not completing treatment or lost to follow-up). SVR rates were 100% in both the German (228/228) ([Berg, 2019](#)) and the Italian (307/307) ([D'Ambrosio, 2019](#)) cohorts.

Ledipasvir/Sofosbuvir

The fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on a pair of 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 ribavirin ([Afdhal, 2014a](#)). SVR12 rates were 97% to 99% across all study arms with no difference in SVR based on length of treatment, use of ribavirin, or genotype 1 subtype. Sixteen percent of participants 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 ledipasvir/sofosbuvir therapy from 12 weeks to 8 weeks (with or without ribavirin) ([Kowdley, 2014](#)). SVR12 rates were 93% to 95% across all study arms, with no difference in SVR in the intention-to-treat analysis. However, relapse rates were higher in the 8-week arms (20/431)—regardless of ribavirin use—compared with the 12-week arm (3/216). Post hoc analyses of the ribavirin-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 <6 million IU/mL (2%; 2/123). The same held true for patients with similar baseline HCV RNA levels who received 12 weeks of treatment (2%; 2/131). This analysis was not controlled, which limits the generalizability of this approach to clinical practice.

Real-world cohort studies of ledipasvir/sofosbuvir for treatment-naive, noncirrhotic black patients reported lower SVR12 rates with shorter duration therapy compared to white patients, although the absolute difference in SVR12 rates was <5% ([Su, 2016](#)); ([Wilder, 2016](#)); ([O'Brien, 2014](#)); ([Ioannou, 2016](#)). A subsequent real-world study among a Northern California Kaiser Permanente cohort of 436 black patients—most of whom were treated with an 8-week regimen—found comparable SVR12 rates with 8 and 12 weeks of therapy (95.6% and 95.8%, respectively) ([Marcus, 2018](#)). Similarly, a Maryland

Veterans Health Administration real-world cohort of black patients with predominantly genotype 1 infection found SVR12 rates of 93.7% (131/140) and 91.4% (332/363) with 8- and 12-week regimens, respectively ([Tang, 2018](#)). These data coupled with the availability of excellent rescue therapies for patients in whom initial DAA therapy fails support the use of 8 weeks of ledipasvir/sofosbuvir for black patients without cirrhosis and HCV RNA <6 million IU/mL.

Based on available data, shortening treatment to less than 12 weeks is not recommended for HIV/HCV-coinfected patients (see [HIV/HCV Coinfection](#) section).

Sofosbuvir/Velpatasvir

The fixed-dose combination of 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naïve patients based on ASTRAL-1. This placebo-controlled trial involved a 12-week course of sofosbuvir/velpatasvir administered to 624 participants with genotype 1, 2, 4, 5, or 6 infection who were treatment naïve (n=423) or previously treated with interferon-based therapy, with or without ribavirin or a protease inhibitor (n=201); ([Feld, 2015](#)). Of the 328 genotype 1 patients included, 323 achieved SVR12 with no difference observed by subtype (98% 1a, 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR12 (99%). The presence of baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR rate for genotype 1 ([Hézode, 2018](#)). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir vs placebo groups.

The phase 3 POLARIS-2 study randomized 941 DAA-naïve patients with genotype 1, 2, 3, 4, 5, or 6—with or without compensated cirrhosis—to receive either 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) or 12 weeks of sofosbuvir/velpatasvir ([Jacobson, 2017](#)). Of participants treated with sofosbuvir/velpatasvir, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR with a single relapse observed in each subtype.

Last update: November 6, 2019

Related References

Abergel A, Hezode C, Asselah T, et al. [A phase 3, global, multicenter, open-label study to investigate the efficacy of elbasvir/grazoprevir fixed-dose combination for 8 weeks in treatment-naïve, HCV GT1b-infected patients, with non-severe fibrosis: STREAGER](#). *The International Liver Congress*. 2018.

Afdhal NH, Zeuzem S, Kwo PY, et al. [Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection](#). *N Engl J Med*. 2014;370(20):1889-1898.

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.

Chayama K, Suzuki F, Karino Y, et al. [Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 1 hepatitis C virus infection with and without cirrhosis](#). *J Gastroenterol*. 2018;53(4):557-565. doi:10.1007/s00535-017-1391-5.

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.

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.

Hezode C, Reau N, Svarovskaia ES, et al. [Resistance analysis in patients with genotype 1-6 HCV infection treated with sofosbuvir/velpatasvir in the phase III studies.](#) *J Hepatol.* 2018;68(5):895-903.

Ioannou GN, Beste LA, Chang MF, et al. [Effectiveness of sofosbuvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir and dasabuvir regimens for treatment of patients with hepatitis C in the Veterans Affairs national health care system.](#) *Gastroenterology.* 2016;151(3):457-471.e5.

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.

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.* 2014;370(20):1879-1888.

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.

Marcus JL, Hurley LB, Chamberland S. [No difference in effectiveness of 8 vs 12 weeks of ledipasvir and sofosbuvir for treatment of hepatitis C in black patients.](#) *Clin Gastroenterol Hepatol.* 2018;16(6):927-935. doi:10.1016/j.cgh.2018.03.003.

O'Brien TR, Lang Kuhs KA, Pfeiffer RM. [Subgroup differences in response to 8 weeks of ledipasvir/sofosbuvir for chronic hepatitis C.](#) *Open Forum Infect Dis.* 2014;1(3):ofu110.

Rockstroh J, Lacombe K, Viani RM, et al. [Efficacy and safety of Glecaprevir/Pibrentasvir in patients co-infected with hepatitis C virus and human immunodeficiency virus-1: the EXPEDITION-2 Study \[Abstract LBP-522\].](#) In: *The International Liver Congress. EASL. The International Liver Congress. EASL.*; 2017. Available at: [http://dx.doi.org/10.1016/S0168-8278\(17\)30467-1](http://dx.doi.org/10.1016/S0168-8278(17)30467-1).

Su F, Green PK, Berry K, Ioannou GN. [The association between race/ethnicity and the effectiveness of direct antiviral agents for hepatitis C virus infection.](#) *Hepatology.* 2016;65(2):426-438.

Sulkowski MS, Hézode C, Gerstoft J, et al. [Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir \(MK-5172\) and elbasvir \(MK-8742\) with or without ribavirin in patients with HCV GT1 mono-infection and HIV/HCV coinfection \(C-WORTHY\): a randomised, open-label phase 2 trial.](#) Vierling JM, Mallolas J, Pol S, et al., eds. *Lancet.* 2015;285(9973):1087-1097. doi:10.1016/S0140-6736(14)61793-1.

Tang L, Parker A, Flores Y, et al. [Treatment of hepatitis C with 8 weeks of ledipasvir/sofosbuvir: highly effective in a predominantly black male patient population.](#) *J Viral Hepat.* 2018;25(2):205-208. doi:10.1111/jvh.12796.

Wilder JM, Jeffers LJ, Ravendhran N, et al. [Safety and efficacy of ledipasvir-sofosbuvir in black patients with hepatitis C virus infection: a retrospective analysis of phase 3 data.](#) *Hepatology.* 2016;63(2):437-444.

Zeuzem S, Ghalib R, Reddy KR, 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.

Zeuzem S, Feld J, Wang S. [ENDURANCE-1: efficacy and safety of 8- versus 12-week treatment with ABT-493/ABT-530 in patients with chronic HCV genotype 1 infection \[abstract 253\].](#) In: *The Liver Meeting 2016. The Liver Meeting 2016.* Boston, MA; 2016.