

Treatment-Naive Genotype 1a Without Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for:

Treatment-Naive Genotype 1a 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)	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	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (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

The daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) is administered as three 100 mg/40 mg fixed-dose combination pills. Based on favorable data for 8 weeks of treatment among 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 or 12 weeks of glecaprevir/pibrentasvir ([Zeuzem, 2018](#)). 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 study 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. The single relapse occurred in a genotype 1a patient; SVR for genotype 1a was 98% (47/48) ([Forns, 2017](#)).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected adults 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 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.

In an integrated analysis of 602 DAA-naive, noncirrhotic patients with genotype 1 infection treated with 8 weeks of glecaprevir/pibrentasvir in 6 phase 2 or 3 clinical trials, SVR12 was 99.2% (597/602) ([Naganuma, 2019](#)). Real-world cohorts from Germany (63% genotype 1a) and Italy (32% genotype 1a) show similarly high efficacy in treatment-naive, noncirrhotic patients with genotype 1 infection 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 was 100% in both the German (228/228) ([Berg, 2019](#)) and the Italian (307/307) ([D'Ambrosio, 2019](#)) cohorts.

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-naive 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 who were treatment naive (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 SVR with no difference observed by subtype (98% 1a; 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (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 SVR12 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-naive patients with genotype 1, 2, 3, 4, 5, or 6 infection—with or without compensated cirrhosis—to receive 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 for 12 weeks, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR12 with a single relapse observed with each subtype.

In a single-arm, phase 3 study from Asia that included 375 treatment-naive and -experienced patients with genotype 1, 2, 3, 4, 5, or 6 infection (18% with cirrhosis) treated with 12 weeks of sofosbuvir/velpatasvir, SVR was achieved in 95% (362/375) ([Wei, 2019](#)). Of the 129 participants with genotype 1 infection (17% genotype 1a), 100% achieved SVR. A real-world, pooled analysis of 12 cohorts that evaluated adults treated with 12 weeks of sofosbuvir/velpatasvir demonstrated an SVR of 99.1% (1599/1613) among participants with genotype 1, with or without compensated cirrhosis ([Mangia, 2020](#)).

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 two 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 was 97% to 99% across all study arms with no difference in SVR12 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 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 who received 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.

Published, real-world cohort data generally show comparable effectiveness of 8-week and 12-week courses of ledipasvir/sofosbuvir in treatment-naive patients without cirrhosis ([Backus, 2016](#)); ([Ingiliz, 2016](#)); ([Ioannou, 2016](#)); ([Kowdley, 2016](#)); ([Terrault, 2016](#)). However, only about half of patients eligible for 8 weeks of treatment received it, assignment of duration was not randomized, and baseline characteristics may have varied between 8- and 12-week groups.

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, 2017](#)); ([Ioannou, 2016](#)); ([Wilder, 2016](#)); ([O'Brien, 2014](#)). 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 similar 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). For others with potential negative prognostic factors, shortening treatment duration should be done at the discretion of the practitioner.

Alternative Regimen

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 sustained virologic response rates at 12 weeks (SVR12) were 92% (144/157) in treatment-naive patients with genotype 1a infection and 99% (129/131) in genotype 1b patients. 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, noncirrhotic patients, respectively, who received 12 weeks of elbasvir/grazoprevir without ribavirin ([Sulkowski, 2015b](#)). The C-WORTHY trial enrolled both HCV-monoinfected and HIV/HCV-coinfected patients.

The presence of certain baseline NS5A RASs significantly reduces SVR12 rates with a 12-week course of elbasvir/grazoprevir in genotype 1a-infected patients ([Zeuzem, 2017](#)). Baseline NS5A RASs were identified in 12% (19/154) of genotype 1a-infected patients enrolled in the C-EDGE study, of which 58% (11/19) achieved SVR12 compared to an SVR12 rate of 99% (133/135) in patients without these RASs receiving 12 weeks of elbasvir/grazoprevir ([Zeuzem, 2017](#)). Among treatment-naive patients, the presence of baseline NS5A RASs with >5-fold reduced sensitivity to elbasvir was associated with the most significant reduction in SVR12 with only 22% (2/9) of genotype 1a patients with these RASs achieving SVR12.

In the phase 3 open-label C-EDGE TE trial of elbasvir/grazoprevir that enrolled treatment-experienced patients, 58 genotype 1a-infected patients received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, and there were no virologic failures ([Kwo, 2017](#)). Subsequent integrated analysis of the elbasvir/grazoprevir phase 2 and 3 trials demonstrated an SVR12 rate of 100% (6/6) in genotype 1 patients with pretreatment NS5A RASs treated with elbasvir/grazoprevir plus ribavirin for 16 or 18 weeks ([Jacobson, 2015b](#)); ([Thompson, 2015](#)).

Based on known inferior response in patients with baseline NS5A RASs, NS5A resistance testing is recommended in

genotype 1a patients who are being considered for elbasvir/grazoprevir therapy. If baseline RASs are present (ie, substitutions at amino acid positions 28, 30, 31, or 93), another recommended regimen should be used (additional information is available in the [RAS](#) section).

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