




## Sofosbuvir-Based and Elbasvir/Grazoprevir Treatment Failures

In general, persons who have experienced treatment failure with a sofosbuvir-based regimen should be retreated with 12 weeks of sofosbuvir/velpatasvir/voxilaprevir. The main exception is persons with genotype 3 and cirrhosis, in whom addition of ribavirin to sofosbuvir/velpatasvir/voxilaprevir for 12 weeks is recommended. Sixteen weeks of glecaprevir/pibrentasvir is an alternative regimen.

Elbasvir/grazoprevir treatment failure patients should also be retreated with 12 weeks of sofosbuvir/velpatasvir/voxilaprevir. However, glecaprevir/pibrentasvir for 16 weeks is not recommended as an alternative for this group of patients.

Recommended and alternative regimens listed by evidence level and alphabetically for:		
Sofosbuvir-Based Treatment Failures, With or Without Compensated Cirrhosis <sup>a</sup> 		
RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) <sup>b</sup>	12 weeks	I, A
ALTERNATIVE	DURATION	RATING 
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) except for NS3/4 protease inhibitor inclusive combination DAA regimen failures <sup>c</sup> <ul style="list-style-type: none"> <li>• <b>Not</b> recommended for genotype 3 infection with sofosbuvir/NS5A inhibitor experience.</li> </ul>	16 weeks	I, A
<sup>a</sup> For <a href="#">decompensated cirrhosis</a> , please refer to the appropriate section. <sup>b</sup> Genotype 3: Add weight-based ribavirin if cirrhosis is present and there are no contraindications. <sup>c</sup> This regimen is not recommended for patients with prior exposure to an NS5A inhibitor plus NS3/4 PI regimens (e.g., elbasvir/grazoprevir).		

### Recommended Regimen

#### Sofosbuvir/Velpatasvir/Voxilaprevir

The placebo-controlled, phase 3 POLARIS-1 trial evaluated a 12-week course of the daily fixed-dose combination of

sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) in 263 persons with a prior NS5A inhibitor-containing DAA regimen failure. The majority (55%) had experienced a sofosbuvir/ledipasvir failure ([Bourliere, 2017](#)). Virologic failure was rare (2%; 3/145) among those retreated with sofosbuvir/velpatasvir/voxilaprevir. All 3 individuals whose retreatment failed had cirrhosis; 2 persons had genotype 1a and 1 had genotype 4d. The treatment-failure patients with genotype 1a also had baseline RASs at Q80K, Z30T, and Y93H.

In the same study, a small number of persons who had a prior treatment failure with sofosbuvir/velpatasvir were retreated with sofosbuvir/velpatasvir/voxilaprevir. Two patients experienced virologic failure. Both had cirrhosis, genotype 3, and the Y93H RAS in the NS5A region at baseline. Because of the higher failure rates in the subgroup of genotype 3 patients with cirrhosis, the regimen of sofosbuvir/velpatasvir/voxilaprevir plus ribavirin for 12 weeks is recommended. If ribavirin cannot be used, extension to 24 weeks can be considered. Several real-world cohort reports also identified lower response rates after sofosbuvir/velpatasvir/voxilaprevir retreatment for 12 weeks in persons with genotype 3 and cirrhosis, lending further support to the need for regimen modification ([Papaluca, 2021](#)); ([Llaneras, 2019](#)). Serious adverse events were similar in the placebo and treatment arms; a single patient discontinued therapy due to an adverse event. Headache, diarrhea, and nausea were more common in those participants receiving sofosbuvir/velpatasvir/voxilaprevir compared to placebo.

Results from deferred treatment of the placebo arm in POLARIS-1 further support the high efficacy of 12 weeks of sofosbuvir/velpatasvir/voxilaprevir for retreatment of persons with a prior sofosbuvir/NS5A inhibitor treatment failure ([Bourliere, 2018](#)). Overall SVR in the deferred treatment group was 97% (n=147), including 96% SVR (n=76) in those with prior sofosbuvir/NS5A inhibitor experience (n=76).

The phase 3, open-label, randomized clinical trial POLARIS-4 compared a 12-week course of the daily fixed-dose combination of sofosbuvir/velpatasvir/voxilaprevir to 12 weeks of sofosbuvir/velpatasvir in NS5A inhibitor-naive, DAA-experienced patients ([Bourliere, 2017](#)). Eleven percent had prior exposure to simeprevir/sofosbuvir. Cirrhosis was common, 46% in both arms. SVR12 rates were higher for sofosbuvir/velpatasvir/voxilaprevir (98%; 178/182) compared to sofosbuvir/velpatasvir (90%; 136/151). This study supports sofosbuvir/velpatasvir/voxilaprevir as a recommended regimen for patients with a prior treatment failure with a sofosbuvir-containing regimen, regardless of the presence of compensated cirrhosis.

Data from both clinical trials ([Bourliere, 2018](#)); ([Bourliere, 2017](#)) and real-world cohorts ([Da, 2020](#)); ([Belperio, 2019](#)); ([Degasperi, 2019](#)); ([Llaneras, 2019](#)) that evaluated the efficacy and safety of sofosbuvir/velpatasvir/voxilaprevir among DAA-experienced persons support the use of this regimen for persons with a prior DAA treatment failure. A more recent real-world evaluation of 144 patients from the UK who were retreated with sofosbuvir/velpatasvir/voxilaprevir following virologic failure with first-line DAA treatment regimens found an overall retreatment SVR12 of 90 percent ([Smith, 2021b](#)). Interestingly, pre-retreatment RASs were not associated with SVR when HCV genotype was taken into account. Patients with genotype 3, persons with cirrhosis, and those who had sofosbuvir/velpatasvir failure had significantly lower re-treatment response with sofosbuvir/velpatasvir/voxilaprevir. Possibly alternative or longer re-treatment regimens should be considered in such persons.

In resource-limited countries where sofosbuvir/velpatasvir/voxilaprevir is not available, innovative retreatment regimens using first-generation DAAs often proved successful (i.e., after a failure to NS5a/SOF in HCV genotype 1, switching to sofosbuvir when reused in combination with a new DAA class such as a protease inhibitor) ([Dietz, 2021](#)).

## Alternative Regimen

### Glecaprevir/Pibrentasvir

In parts 1 and 2 of the MAGELLAN-1 trial, 42 patients with genotype 1 who had previously been treated with either an NS5A inhibitor or an NS3/4A protease inhibitor were retreated with glecaprevir/pibrentasvir ([Poordad, 2018](#)); ([Poordad, 2017](#)). Twenty-four percent of the study participants had cirrhosis; 79% had genotype 1a. In the subgroup of persons previously treated with an NS5A inhibitor (ledipasvir or daclatasvir) and not concomitantly treated with a NS3/4A protease inhibitor, the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for 16 weeks achieved an SVR of 94% (16/17). The single patient who did not respond to therapy had an on-treatment virologic failure.

A phase 3b open-label study further supports the efficacy of 16 weeks of glecaprevir/pibrentasvir for retreatment of individuals with genotype 1 infection and a history of sofosbuvir/NS5A inhibitor treatment failure ([Lok, 2019](#)). The study randomized sofosbuvir/NS5A inhibitor-experienced, genotype 1 patients without cirrhosis to 12 weeks (n=78) or 16 weeks (n=49) of glecaprevir/pibrentasvir. Participants with cirrhosis were randomized to 12 weeks (n=21) or 16 weeks (n=29) of glecaprevir/pibrentasvir plus weight-based ribavirin. Enrollment in the 12-week plus ribavirin arm for participants with cirrhosis was halted early due to 2 viral breakthroughs on therapy and 1 case of early relapse. SVR was numerically higher in the 16-week study arms (94% and 97% without and with cirrhosis, respectively) compared to the 12-week arms (90% and 86% without and with cirrhosis, respectively). No clear impact of ribavirin was detected in the study and the majority of virologic failures were among those with genotype 1a treated for 12 weeks without ribavirin. No virologic failures were seen in genotype 1b patients. These data further support glecaprevir/pibrentasvir for 16 weeks as an efficacious retreatment approach for sofosbuvir/NS5A inhibitor experienced patients.

## Glecaprevir/Pibrentasvir for Genotype 3 Sofosbuvir/Ribavirin Treatment Failures

The SURVEYOR-II, part 3 trial evaluated the safety and efficacy of a 12-week or 16-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) among treatment-naïve or interferon-experienced (standard or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon), genotype 3 patients without cirrhosis or with compensated cirrhosis. Among the 34 treatment-experienced participants with prior exposure to sofosbuvir who were treated for 16 weeks, regardless of cirrhosis status, SVR12 was 97% (33/34). The lone virologic failure was due to relapse in a patient with cirrhosis. No NS5A RASs were present prior to treatment; however, the L31F and Y93H substitutions were present at retreatment failure ([Wyles, 2018](#)). Sixteen weeks of glecaprevir/pibrentasvir is an alternative regimen for genotype 3 patients with prior exposure to sofosbuvir plus ribavirin given the high SVR and lack of need for the addition of ribavirin. This regimen was not evaluated for genotype 3 patients who experienced a prior treatment failure with a regimen containing both sofosbuvir and an NS5A inhibitor. Given the lack of data this regimen is not recommended for genotype 3 infection with prior sofosbuvir/NS5A inhibitor experience.

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