Multiple DAA Treatment Failures (All Genotypes), Including Sofosbuvir/Velpatasvir/Voxilaprevir or Sofosbuvir Plus Glecaprevir/Pibrentasvir

Recommended regimens listed by evidence level and alphabetically for:

Sofosbuvir/Velpatasvir/Voxilaprevir Treatment Failures, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) plus daily sofosbuvir (400 mg) and weight-based ribavirin	16 weeks[b]	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) plus weight-based ribavirin	24 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Extension of treatment to 24 weeks should be considered in extremely difficult cases (e.g., genotype 3 with cirrhosis) or failure following sofosbuvir plus glecaprevir/pibrentasvir.

Recommended Regimens

Glecaprevir/Pibrentasvir Plus Sofosbuvir and Ribavirin

There are limited data, mostly retrospective case series, on the re-treatment of DAA non-responders. Pibrentasvir has improved in vitro activity compared to other NS5A inhibitors against most NS5A RASs (Ng, 2017b). A small study demonstrated the efficacy (22/23 patients) of glecaprevir/pibrentasvir plus sofosbuvir and ribavirin for heavily DAA-experienced patients (including those with genotype 3 and/or cirrhosis), although no sofosbuvir/velpatasvir/voxilaprevir failures were included (Wyles, 2019).

Failure to respond to sofosbuvir/velpatasvir/voxilaprevir is especially problematic. Dietz et al. described 40 such patients, 70% of whom had cirrhosis, and most not associated with specific RAS patterns following their sofosbuvir/velpatasvir/voxilaprevir treatment. The investigators attempted re-treatment with a host of different rescue treatments, varying from 12-24 weeks, and reported an overall 81% SVR rate. Therefore, such innovative rescue treatments with “multiple targeted therapies” may be effective in most patients, but there remain individuals in need of newer options (Dietz, 2021b).

There is 1 case report examining retreatment of patients in whom therapy with sofosbuvir/velpatasvir/voxilaprevir failed. In this study, a quad regimen of sofosbuvir, glecaprevir/pibrentasvir, and ribavirin for 24 weeks was successful (Bernhard,

2020). Another case report describes an individual (genotype 1a, cirrhosis) who failed multiple regimens (including 24 weeks of sofosbuvir/velpatasvir/voxilaprevir and 24 weeks of glecaprevir/pibrentasvir plus sofosbuvir and ribavirin) who was then treated variously with multiple DAA regimens for 52 weeks, who finally achieved an SVR (Trudeau, 2022). This case suggests that on-treatment protracted HCV RNA-negativity beyond 24 weeks might be necessary to allow for immune reconstitution and viral clearance for these most difficult-to-treat patients.

Sixteen weeks of glecaprevir/pibrentasvir plus sofosbuvir and ribavirin is recommended based on the improved resistance profile of pibrentasvir and high response rate seen with this duration of therapy among genotype 3 patients in the MAGELLAN-3 trial (Wyles, 2019). Extension to 24 weeks or longer with this regimen could be considered; while there are case report data using this duration (Bernhard, 2020); (Fierer, 2020), no clinical trial data are available to support such an approach.

Sofosbuvir/Velpatasvir/Voxilaprevir Plus Ribavirin

Although there are no published studies examining retreatment of patients in whom therapy with sofosbuvir/velpatasvir/voxilaprevir failed, in the POLARIS-1 study—which studied sofosbuvir/velpatasvir/voxilaprevir treatment among patients who had a prior DAA therapy failure—treatment failure with this triple antiviral regimen was seen more commonly in persons with cirrhosis (7% cirrhosis vs 1% without cirrhosis), and those with genotype 3 or 4 (5% genotype 3, 9% genotype 4 vs 0% genotype 1) (Bourliere, 2017). Baseline RASs did not affect SVR nor did failure select for additional RAS variants. The recommendation to treat with longer therapy in conjunction with ribavirin when retreating with the same DAA regimen (sofosbuvir/velpatasvir/voxilaprevir) is based on extrapolation from prior studies showing benefit with this strategy in different populations (Gane, 2017).

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Bernhard B, Stickel F. Successful fourth line treatment of a relapse patient with chronic hepatitis C virus infection genotype 3a using sofosbuvir, glecaprevir/pibrentasvir, and ribavirin: a case report. *Z Gastroenterol*. 2020;58(5):451-455.

Bourliere M, Gordon SC, Flamm SL, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. *N Engl J Med*. 2017;376(22):2134-2146.

J D, VC DMaio, De Salazar A, et al. Failure on voxilaprevir, velpatasvir, sofosbuvir and efficacy of rescue therapy. *J Hepatol*. 2021;74(4):801-810. doi:10.1016/j.jhep.2020.11.017.

Fierer DS, Wyles DL. Re-treatment of hepatitis C infection after multiple failures of direct-acting antiviral therapy. *Open Forum Infect Dis*. 2020;7(4):ofaa095.

Gane EJ, Shiffman ML, Etzkorn K, et al, et al. Sofosbuvir-velpatasvir with ribavirin for 24 weeks in hepatitis C virus patients previously treated with a direct-acting antiviral regimen. *Hepatology*. 2017;66(4):1083-1089.

Ng TI, Krishnan P, Pilot-Matias T, et al. In vitro antiviral activity and resistance profile of the next-generation hepatitis C virus NS5A inhibitor pibrentasvir. *Antimicrob Agents Chemother*. 2017;61(5):pii: e02558-16. doi:10.1128/AAC.02558-16. Print 2017 May.

Trudeau S, Mendiratta V, Dababneh Y, Hollingsworth J, Gordon SC. Letter to the Editor: Successful treatment of multidrug resistant hepatitis C after >12 months of continuous therapy with direct-acting antivirals. *Hepatology*. 2022. doi:10.1002/hep.32688.

Wyles D, Weiland O, Yao B, et al. Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C virus infection. *J Hepatol*. 2019;70(5):1019-1023. doi:10.1016/j.jhep.2019.01.031.