


Persons Who Develop Recurrent Hepatitis C Post Liver Transplantation

Post Liver Transplantation, Genotype 1–6

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


Treatment-Naive and Treatment-Experienced Persons With Genotype 1–6 Infection in the Allograft Without Cirrhosis

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^a	12 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, B

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

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


Treatment-Naive and Treatment-Experienced Persons With Genotype 1–6 Infection in the Allograft With Compensated Cirrhosis

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^a	12 weeks	I, C
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 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 listed by pangenotypic, evidence level, and alphabetically for:

Treatment-Naive and Treatment-Experienced Persons With Genotype 1–6 Infection in the Allograft and Decompensated Cirrhosis^a

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with ribavirin starting at 600 mg/d and increased as tolerated ^b	12 weeks to 24 weeks ^c	I, B
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dosage of ribavirin (600 mg/d and increased as tolerated) ^b	12 weeks to 24 weeks ^c	I, B


^a Includes persons with CTP class B and class C cirrhosis.

^b The starting dosage of ribavirin should be 600 mg/d and increased or decreased as tolerated. If renal dysfunction is present, a lower starting dosage is recommended. Maximum ribavirin dosage is 1000 mg/d if <75 kg and 1200 mg/d if ≥75 kg body weight.

^c 24-week treatment duration is recommended for those with treatment experience.

Recommended regimen for:

Persons With Direct-Acting Antiviral Experience and Genotype 1–6 Infection in the Allograft, With or Without Compensated Cirrhosis^a

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) ^b	12 weeks	I, C

^a Excludes persons with CTP class B and class C cirrhosis.

^b For persons with cirrhosis and multiple negative baseline characteristics, consideration should be given to adding ribavirin. The starting dosage of ribavirin should be 600 mg/d and increased or decreased as tolerated. If renal dysfunction is present, a lower starting dosage is recommended. Maximum ribavirin dosage is 1000 mg/d if <75 kg body weight and 1200 mg/d if ≥75 kg body weight.

Glecaprevir/Pibrentasvir

The MAGELLAN-2 trial was an open-label, multicenter, single-arm, phase 3 study that evaluated a 12-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in 80 liver transplant recipients and 20 kidney transplant recipients without cirrhosis. All genotypes were represented except genotype 5; 57% of participants had genotype 1 infection and 24% had genotype 3. Except for those with genotype 3 infection (all of whom were treatment

naive), treatment-experienced participants were included (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). Eighty percent of participants had Metavir stage F0 or F1 fibrosis, 6% had F2, and 14% had F3. People with cirrhosis were excluded. Any stable immunosuppressive regimen was allowed, except cyclosporine >100 mg/d and prednisone >10 mg/d. SVR was attained in 98% (98/100) of participants with no on-treatment virologic breakthroughs and 1 posttreatment relapse. There were no treatment discontinuations due to drug-associated adverse effects. One episode of mild rejection occurred that was assessed to be unrelated to drug-drug interactions ([Reau, 2018](#)).

A multicenter study from Japan treated 24 liver transplant recipients with recurrent HCV with 8 weeks or 12 weeks of glecaprevir (300 mg)/pibrentasvir (120 mg), including 21% with F3/F4; 96% (23/24) achieved SVR12. All 13 participants (genotype 1 or 2, without cirrhosis) treated for 8 weeks achieved SVR ([Ueda, 2019](#)).

As data on the efficacy of glecaprevir/pibrentasvir in transplant recipients with cirrhosis and use of shorter treatment course (8 weeks versus 12 weeks) in those without cirrhosis are very limited, pending additional real-world data, a 12-week course is recommended regardless of cirrhosis stage. Additionally, for people with cirrhosis plus other negative baseline factors, adding low-dosage ribavirin (600 mg/d) may be a consideration.

Sofosbuvir/Velpatasvir

The safety and efficacy of the fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was evaluated in 79 (5 with cirrhosis, 4 direct-acting antiviral [DAA] experienced) liver transplant recipients with genotype 1, 2, 3, or 4 infection. Treatment was well tolerated with 99% of participants completing treatment. Overall SVR12 rates by genotype were 93% genotype 1a (n=15); 96% genotype 1b (n=22); 100% genotype 2 (n=3); 97% genotype 3 (n=35); and 100% genotype 4 (n=4). Twenty-three percent (18/79) of participants required a change in their immunosuppression regimen during DAA treatment, but none were for rejection or drug-drug-interactions. Most participants were on calcineurin inhibitor-based immunosuppression (71% on tacrolimus, 14% on cyclosporine) ([Agarwal, 2018](#)).

In the nontransplant setting (discussed in detail in the [Initial](#) and [Retreatment](#) sections), the phase 3, double-blind, placebo-controlled ASTRAL-1 study reported on 742 treatment-naive or treatment-experienced adults with genotype 1, 2, 4, 5, or 6 infection who were randomly assigned in a 5:1 ratio to sofosbuvir (400 mg)/velpatasvir (100 mg) or placebo for 12 weeks. All persons with genotype 5 infection (n=35) received active treatment. Thirty-two percent (201/624) of enrollees randomized to active therapy were treatment experienced and 19% (121/624) had compensated cirrhosis (CTP class A). The genotype distribution in the active treatment arm was 34% (n=210) genotype 1a; 19% (n=118) genotype 1b; 17% (n=104) genotype 2; 19% (n=116) genotype 4; 6% (n=35) genotype 5; and 7% (n=41) genotype 6. The overall SVR rate was 99% (618/624). The side effect/adverse event profile of sofosbuvir/velpatasvir was similar to placebo ([Feld, 2015](#)).

In the phase 3, open-label ASTRAL-3 study, 552 treatment-naive or treatment-experienced adults with genotype 3 infection (with or without compensated cirrhosis) were randomized in a 1:1 ratio to 12 weeks of sofosbuvir/velpatasvir or 24 weeks of sofosbuvir plus weight-based ribavirin. SVR12 rate was 95% (263/277) for the sofosbuvir/velpatasvir treatment arm, which was superior to the SVR12 rate of 80% (220/275) for participants receiving sofosbuvir plus ribavirin for 24 weeks ([Foster, 2015a](#)).

The phase 3, open-label ASTRAL-4 study enrolled 267 treatment-naive or treatment-experienced (55%) adults with genotype 1, 2, 3, 4, or 6 infection and decompensated cirrhosis (CTP class B at the time of screening). Participants were randomized in a 1:1:1 ratio to 12 weeks of sofosbuvir/velpatasvir, 12 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin, or 24 weeks of sofosbuvir/velpatasvir. SVR12 rates were 83% (75/90) for the 12-week sofosbuvir/velpatasvir regimen, 94% (82/87) for the 12-week sofosbuvir/velpatasvir plus ribavirin regimen, and 86% (77/90) for the 24-week sofosbuvir/velpatasvir regimen ([Curry, 2015b](#)). Among participants with genotype 1 infection, SVR12 rates were 88% and 96% with 12 weeks of sofosbuvir/velpatasvir without and with ribavirin respectively, and 92% with sofosbuvir/velpatasvir

for 24 weeks. Virologic relapse occurred in 12% and 9% of participants in the 12-week and 24-week sofosbuvir/velpatasvir arms, respectively, compared with 2% in the 12-week sofosbuvir/velpatasvir plus ribavirin study arm ([Curry, 2015b](#)). Although the ASTRAL-4 study was not powered to generate statistical significance, these results suggest that sofosbuvir/velpatasvir with ribavirin for 12 weeks is the optimal choice for persons with genotype 1 or 3 infection who have decompensated cirrhosis. The participant numbers were too small for genotypes 2, 4, and 6 to differentiate the comparative efficacy of the treatment arms. Reflecting the approach in nontransplant people with decompensated cirrhosis, liver transplant recipients with hepatic decompensation are recommended to receive sofosbuvir/velpatasvir plus ribavirin for 12 weeks to 24 weeks, depending on the presence of other negative prognostic features at baseline (ie, treatment experienced, genotype 3 infection, presence of hepatocellular carcinoma).

Velpatasvir is a substrate for cytochrome P450 3A4, 2C8, and 2B6, a weak inhibitor of P-glycoprotein and organic anion transporting polypeptides, and a moderate inhibitor of the breast cancer resistance protein membrane transporter. As such, velpatasvir is moderately affected by potent inhibitors and, to a greater extent, potent inducers of enzyme/drug transporter systems ([Mogalian, 2016](#)). Based on this profile, which is similar to ledipasvir, clinically significant drug-drug interactions would not be expected for coadministration of sofosbuvir/velpatasvir with common immunosuppressive agents (eg, tacrolimus, cyclosporine, corticosteroids, mycophenolate mofetil, or everolimus).

Ledipasvir/Sofosbuvir

The SOLAR-1 study was a large, US-based, multicenter, open-label, phase 2 trial that included 223 liver transplant recipients with genotype 1 or 4 infection whose baseline characteristics encompassed a broad spectrum of histologic and clinical severity of HCV recurrence. One hundred and eleven participants were Metavir stage F0 to F3, 51 had compensated CTP class A cirrhosis, and 61 had decompensated CTP class B or class C cirrhosis. Study participants were randomly assigned to 12 weeks or 24 weeks of a fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin. The ribavirin dosage was weight based for participants without cirrhosis or with compensated cirrhosis (1000 mg/d [<75 kg] to 1200 mg/d [≥ 75 kg]). For those with CTP class B or class C cirrhosis, ribavirin was initiated at 600 mg/d followed by dose escalation as tolerated. Only 4% of enrolled participants discontinued treatment prematurely because of adverse events related to the study drugs ([Charlton, 2015b](#)). On an intention-to-treat basis, SVR was attained in 96% (53/55) and 98% (55/56) of liver transplant recipients without cirrhosis in the 12-week and 24-week treatment arms, respectively. Among those with compensated cirrhosis, SVR rate was 96% in both the 12-week and 24-week treatment arms. Efficacy was lower in persons with CTP class B or class C cirrhosis post liver transplantation. Among those with CTP class B cirrhosis, SVR rates were 86% and 88% in the 12-week and 24-week treatment arms, respectively. Among persons with CTP class C cirrhosis, SVR rates were 60% and 75% in the 12-week and 24-week treatment arms, respectively. Mortality rate during the study was 10% among participants with CTP class B or class C cirrhosis ([Charlton, 2015b](#)).

Comparable results were achieved using an identical study design in the SOLAR-2 study, which was conducted in Europe, Australia, Canada, and New Zealand. The study included 168 liver transplant recipients with genotype 1 or 4 infection. Among the posttransplantation participants, 101 had no cirrhosis (Metavir stage F0 to F3), 67 had CTP class A compensated cirrhosis, 45 had CTP class B cirrhosis, and 8 had CTP class C decompensation. SVR rates in posttransplant recipients without cirrhosis were 94% (49/52) and 100% (49/49) for 12 weeks and 24 weeks of treatment, respectively. Among those with compensated cirrhosis after transplantation, SVR rate was 97% (33/34; 32/33) in both the 12-week and 24-week treatment arms. For participants with CTP class B cirrhosis, comparable SVR rates were 95% (21/22) and 100% (23/23), respectively. Among those with CTP class C cirrhosis, SVR rates were 33% (1/3) and 80% (4/5), respectively. Considering both pretransplant and posttransplant enrollees with CTP class B or class C cirrhosis, SVR rates were 85% (61/72) and 90% (70/78) for 12 weeks and 24 weeks of treatment, respectively.

An observational HCV-TARGET cohort study provides real-world data based on experience with 347 liver, 60 kidney, and 36 dual liver and kidney transplant recipients. Among the enrollees, 86% had genotype 1 infection, 44% had cirrhosis, 26% had a history of liver decompensation, and 54% had a prior treatment failure with a non-NS5A inhibitor regimen ([Saxena, 2017](#)). Among the 279 participants treated with ledipasvir/sofosbuvir for 12 weeks or 24 weeks, the SVR rates were 97% (152/157) for participants taking ribavirin and 95% (116/122) for those not taking ribavirin. Participants who received ribavirin were more frequently genotype 1a (versus genotype 1b), treatment experienced, and without renal dysfunction. The rate of therapy discontinuation due to an adverse event was 1.3%, highlighting the safety of the drug combination. Acute graft rejection occurred during or after cessation of therapy in 1.4% (6/415) of transplant recipients. These episodes were not judged to be a direct consequence of the antiviral regimen but serve to remind clinicians of the need to monitor immunosuppressive agent levels during DAA therapy.

Another multicenter cohort of 162 adults (98% genotype 1) assessed treatment with ledipasvir/sofosbuvir (with or without ribavirin) for 8 weeks, 12 weeks, or 24 weeks. Duration of treatment and ribavirin use were clinician determined. Overall SVR12 rates were 94% and 98% in those treated with ledipasvir/sofosbuvir without or with ribavirin, respectively ([Kwok, 2016](#)). SVR12 rates in persons treated for 8 weeks, 12 weeks, or 24 weeks with the ribavirin-free regimen were 86% (6/7), 94% (65/69), and 95% (39/41), respectively. SVR12 rates in the ribavirin-inclusive groups were 97% (38/39) and 100% (6/6) for 12 weeks and 24 weeks of treatment, respectively.

The multicenter ANRS CO23 CUPILT study investigators reported their experience with sofosbuvir plus an NS5A inhibitor (daclatasvir or ledipasvir ± ribavirin) among 512 liver transplant recipients with recurrent HCV who met inclusion criteria for analysis ([Houssel-Debry, 2018](#)). The genotype distribution of the participants was 70% (n=359) genotype 1, 1% (n=7) genotype 2, 18% (n=93) genotype 3, 10% (n=50) genotype 4, and <1% (n=3) genotype 5. Twenty-one percent had cirrhosis and 34% had prior treatment experience. The regimens and treatment durations were sofosbuvir plus an NS5A inhibitor without ribavirin for 12 weeks (n=156) or 24 weeks (n=239), and sofosbuvir plus an NS5A inhibitor and ribavirin for 12 weeks (n=47) or 24 weeks (n=70). SVR12 rates were 94%, 99%, 96%, and 93%, respectively. Twenty participants experienced treatment failure. In a multivariate analysis, fibrosis stage, prior treatment, genotype, and baseline HCV viral load did not adversely impact SVR12 rates in the 4 treatment groups. The investigators concluded that 12 weeks of sofosbuvir plus an NS5A inhibitor without ribavirin was an effective regimen regardless of fibrosis stage, genotype, and prior treatment experience.

Collectively, these real-world experiences indicate high SVR rates can be attained without inclusion of ribavirin in liver transplant recipients. However, all factors leading clinicians to include or exclude ribavirin cannot be discerned from these observational studies. The safest presumption is that ribavirin may contribute to the high SVR rates and be relevant for people with unfavorable baseline characteristics (eg, cirrhosis, prior treatment experience). Thus, ribavirin-free therapy is recommended for people with a favorable baseline profile; ribavirin-inclusive therapy is recommended for those with an unfavorable baseline profile.

Most clinical trials to date have focused on persons who were at least 6 months post transplantation, but there is no a priori reason not to consider earlier treatment if the person is on stable immunosuppression and has recovered from postoperative complications. Treatment during the first 6 months to 12 months post transplantation certainly seems reasonable to reduce the likelihood of treating people with more advanced liver disease. A phase 2 study of prophylactic ledipasvir/sofosbuvir enrolled 16 liver transplant recipients (most with hepatocellular carcinoma as the indication) with genotype 1 infection. Treatment was initiated immediately preoperatively and continued for 4 weeks post transplantation ([Levitsky, 2016](#)). SVR12 post transplantation was attained in 88% (15/16) of recipients. While these results are too preliminary to be the basis for recommendations, the findings provide additional data on the safety of ledipasvir/sofosbuvir early in the post-transplantation period.

Sofosbuvir/Velpatasvir/Voxilaprevir

There is limited experience with sofosbuvir/velpatasvir/voxilaprevir in liver transplant recipients. In a single case report of a prior DAA regimen failure, successful treatment of recurrent HCV after liver transplant with sofosbuvir/velpatasvir/voxilaprevir was achieved ([Cardona-Gonzalez, 2018](#)). The individual had genotype 3 infection and acute hepatitis post liver transplant. He was treated with sofosbuvir/velpatasvir/voxilaprevir for 16 weeks with ribavirin added during the last 8 weeks of therapy. In a subsequent case series, 6 liver transplant recipients with HCV genotype 1 ± genotype 4 infection who had a previous DAA treatment failure were treated with sofosbuvir/velpatasvir/voxilaprevir. Participants received a 12-week course of therapy and all achieved SVR. Minor reductions in calcineurin inhibitor dosages were required; no adverse events or rejection episodes were reported ([Higley, 2020](#)).

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with DAAs are sparse but utilization of a pangenotypic regimen should be considered. When the optimal antiviral regimen or treatment duration is unclear, expert consultation should be sought.

Drug-Drug Interactions Between DAAs and Calcineurin Inhibitors

The interactions of DAA agents and calcineurin inhibitors are complex and unpredictable without formal studies of drug-drug interactions. A summary of drug-drug interactions between calcineurin inhibitors and DAAs with recommended dosages is provided in the table below. Based on the metabolism of grazoprevir and elbasvir, a 15-fold increase in grazoprevir AUC and a 2-fold increase in elbasvir AUC can be expected with cyclosporine coadministration. Therefore, this combination should be avoided. Since a 40% to 50% increase in tacrolimus level is predicted during coadministration with grazoprevir, no dosing adjustments are anticipated but tacrolimus levels should be monitored.

DAA Interactions With Calcineurin Inhibitors

	Cyclosporine (CSA)	Tacrolimus (TAC)
Sofosbuvir (SOF)	4.5-fold ↑ in SOF AUC, but GS-331007 metabolite unchanged; no a priori dose adjustment	No interaction observed; no a priori dose adjustment
Ledipasvir	No data; no a priori dose adjustment	No data; no a priori dose adjustment
Elbasvir / grazoprevir (EBR/GZR)	15-fold ↑ in GZR AUC and 2-fold ↑ in EBR AUC;	43% ↑ in TAC; no a priori dose adjustment

	Cyclosporine (CSA)	Tacrolimus (TAC)
	combination is not recommended	
Velpatasvir	No interaction observed; no a priori dose adjustment	No data; no a priori dose adjustment
Glecaprevir / pibrentasvir (GLE/PIB)	5-fold ↑ in GLE AUC with higher doses (400 mg) of CSA; not recommended in persons requiring stable CSA doses >100 mg/day	1.45-fold ↑ in TAC AUC; no a priori dose adjustment; monitor TAC levels and titrate TAC dose as needed
Sofosbuvir / velpatasvir / voxilaprevir (SOF/VEL/VOX)	9.4-fold ↑ in VOX AUC; combination is not recommended	No data; no a priori dose adjustment
AUC=area under the curve		

Related References

Agarwal K, Castells L, Mullhaupt B, et al. [Sofosbuvir/velpatasvir for 12 weeks in genotype 1-4 HCV-infected liver transplant recipients](#). *J Hepatol*. 2018;69(3):603-607. doi:10.1016/j.jhep.2018.05.039.

Cardona-Gonzalez MG, Goldman JD, Narayan L, Brainard DM, Kowdley KV. [Sofosbuvir, velpatasvir, and voxilaprevir for treatment of recurrent hepatitis C virus infection after liver transplantation](#). *Hepatol Commun*. 2018;2(12):1446-1450.

Charlton M, Everson GT, Flamm SL, et al. [Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease](#). *Gastroenterology*. 2015;149(3):649-659.

Curry MP, O'Leary JG, Bzowej N, et al. [Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis](#). *N Engl J Med*. 2015;373(27):2618-2628.

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.

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.

Higley C, Hsu CC, Smith C, Nadella S, Lalos AT. [Safety and efficacy of sofosbuvir/velpatasvir/voxilaprevir in post-liver transplant patients with previous direct-acting antiviral failure: six case reports.](#) *World J Hepatol.* 2020;12(12):1341-1348.

Houssel-Debry P, Coilly A, Fougerou-Leurent C, et al. [12 weeks of a ribavirin-free sofosbuvir and nonstructural protein 5A inhibitor regimen is enough to treat recurrence of hepatitis C after liver transplantation.](#) *Hepatology.* 2018;68(4):1277-1287.

Kwok RM, Ahn J, Schiano TD, et al. [Sofosbuvir plus ledipasvir for recurrent hepatitis C in liver transplant recipients.](#) *Liver Transpl.* 2016;22(11):1536-1543.

Levitsky J, Verna EC, O'Leary JG, et al. [Perioperative ledipasvir-sofosbuvir for HCV in liver-transplant recipients.](#) *N Engl J Med.* 2016;375(21):2106-2108.

Mogalian E, German P, Kearney BP, et al. [Use of multiple probes to assess transporter- and cytochrome P450-mediated drug-drug interaction potential of the pangenotypic HCV NS5A inhibitor velpatasvir.](#) *Clin Pharmacokinet.* 2016;55(5):605-613. doi: 10.1007/s40262-015-0334-7.

Reau N, Kwo PY, Rhee S, et al. [Glecaprevir/pibrentasvir treatment in liver or kidney transplant patients with hepatitis C virus infection.](#) *Hepatology.* 2018;68(4):1298-1307.

Saxena V, Khungar V, Verna EC, et al. [Safety and efficacy of current DAA regimens in kidney and liver transplant recipients with hepatitis C: results from the HCV-TARGET study.](#) *Hepatology.* 2017;66(4):1090-1101.

Ueda Y, Kobayashi T, Ikegami T, et al. [Efficacy and safety of glecaprevir and pibrentasvir treatment for 8 or 12 weeks in patients with recurrent hepatitis C after liver transplantation: a Japanese multicenter experience.](#) *J Gastroenterol.* 2019;54(7):660-666. doi:10.1007/s00535-019-01561-1.

Last Update: July 12, 2012

Last Review: January 15, 2025