


Patients Who Develop Recurrent HCV Infection Post Liver Transplantation

Post Liver Transplantation: Genotype 1, 4, 5, or 6 Infection

Recommended regimens listed by evidence level and alphabetically for:


Treatment-Naive and -Experienced Patients With Genotype 1, 4, 5, or 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, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin	12 weeks	I, A

^a This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended regimen for:

Treatment-Naive and -Experienced Patients With Genotype 1, 4, 5, or 6 Infection in the Allograft With Compensated Cirrhosis

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks	12 weeks	I, A

Alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 1, 4, 5, or 6 Infection in the Allograft, With or Without Compensated Cirrhosis ^a **i**

ALTERNATIVE	DURATION	RATING i
Daily daclatasvir (60 mg) ^a plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, B
Genotype 1 or 4 infection only: Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	12 weeks	Ila, C

^a The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on [HIV/HCV coinfection](#) for patients on antiretroviral therapy.

^b This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended regimen for:

Treatment-Naive and -Experienced Patients With Genotype 1, 4, 5, or 6 Infection in the Allograft and Decompensated Cirrhosis^a **i**

RECOMMENDED	DURATION	RATING i
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, B

^a Includes CTP class B and class C patients.

Post Liver Transplantation: Genotype 2 or 3 Infection

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 2 or 3 Infection in the Allograft Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^a	12 weeks	I, A
Daily daclatasvir (60 mg) ^b plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	II, A

^a This is a 3-tablet coformulation. Please refer to the prescribing information.

^b The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on [HIV/HCV coinfection](#) for patients on antiretroviral therapy.

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

Treatment-Naive and -Experienced Patients With Genotype 2 or 3 Infection in the Allograft With Compensated Cirrhosis


RECOMMENDED	DURATION	RATING
Daily daclatasvir (60 mg) ^a plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	II, A
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	12 weeks	II, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin	12 weeks	II, C

^a The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on [HIV/HCV coinfection](#) for patients on antiretroviral therapy.

^b This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 2 or 3 Infection in the Allograft and Decompensated Cirrhosis^a

RECOMMENDED	DURATION	RATING 
Daily daclatasvir (60 mg) ^b plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	II, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin	12 weeks	II, C

^a Includes CTP class B and class C patients.

^b The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on [HIV/HCV coinfection](#) for patients on antiretroviral therapy.

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 genotype 3-infected patients (all of whom were treatment naive), treatment-experienced patients were included (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). Eighty percent of patients had Metavir stage F0 or F1 fibrosis, 6% had F2, and 14% had F3. Any stable immunosuppressive regimen was allowed, except cyclosporine >100 mg/d and prednisone >10 mg/d. SVR was achieved in 98% (98/100) of patients with no virologic breakthroughs on treatment and 1 post-treatment relapse ([Reau, 2017](#)). 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 interactions. This regimen offers a ribavirin-free option for noncirrhotic liver or kidney transplant recipients. Although glecaprevir/pibrentasvir has not been studied in transplant recipients with compensated cirrhosis, this regimen may be considered in patients who are ribavirin ineligible.

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 patients 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 dose was weight based for patients without cirrhosis or with compensated cirrhosis (1000 mg [<75 kg] to 1200 mg [≥ 75 kg]). For patients 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 achieved in 96% (53/55) and 98% (55/56) of liver transplant patients without cirrhosis in the 12- and 24-week treatment arms, respectively. Among those with compensated cirrhosis, SVR was 96% in both the 12- and 24-week treatment arms. Efficacy was lower in patients 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- and 24-week treatment

arms, respectively. Among patients with CTP class C cirrhosis, SVR rates were 60% and 75% in the 12- and 24-week treatment arms, respectively. Mortality rate during the study was 10% among patients with CTP class B or class C cirrhosis ([Charlton, 2015b](#)).

Similar 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 post-transplantation patients, 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 post-transplantation, noncirrhotic patients were 94% (49/52) and 100% (49/49) for 12 weeks and 24 weeks of treatment, respectively. Among patients with compensated cirrhosis after transplantation, SVR was 97% (33/34; 32/33) in both the 12- and 24-week treatment arms. For patients 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 pre- and post-transplantation patients 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.

As the relative importance of ribavirin cannot be ascertained from the SOLAR studies (all patients received ribavirin), the safest presumption is that ribavirin may contribute to the high SVR rates observed.

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

An observational HCV-TARGET cohort study provides real-world data based on experience with 347 liver, 60 kidney, and 36 dual liver kidney transplant recipients. Among the enrolled patients, 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 those also taking ribavirin and 95% (116/122) for patients not taking ribavirin. Patients 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 patients. 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 direct-acting antiviral (DAA) therapy.

Another multicenter cohort of 162 patients (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 provider determined. Overall SVR12 rates were 94% and 98% in those treated with ledipasvir/sofosbuvir without or with ribavirin, respectively ([Kwok, 2016](#)). SVR12 rates in patients 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.

Collectively, these real-world experiences indicate high SVR rates can be attained without inclusion of ribavirin in liver transplant patients. However, since all factors leading clinicians to include or exclude ribavirin cannot be discerned from these observational studies, inclusion of ribavirin is recommended for patients with unfavorable baseline characteristics (eg, cirrhosis, prior treatment experience) and ribavirin-free therapy is recommended for patients with a favorable baseline profile.

Daclatasvir + Sofosbuvir

The phase 3, open-label ALLY-1 trial evaluated the efficacy and safety of a 12-week course of daily daclatasvir (60 mg) and sofosbuvir (400 mg) plus ribavirin (600 mg with possible escalation to 1000 mg as tolerated) among 60 patients with cirrhosis (CTP class A, B, or C) and 53 patients with HCV recurrence after liver transplantation. Treatment-naïve and -experienced patients were enrolled. Seventy-six percent (86/113) of participants had genotype 1 infection, including 77% (41/53) in the post-transplantation group. Eleven patients with genotype 3 infection and 1 patient with genotype 6 infection were also included in the post-transplantation group. The SVR12 rate was 94% (50/53) among those with recurrent HCV infection post transplantation. Among patients with genotype 3 infection, SVR12 rates were 83% (5/6) and 91% (10/11), respectively, in those with advanced cirrhosis and recurrent HCV infection post transplantation ([Poordad, 2016](#)).

Fontana and colleagues reported on the use of daclatasvir-containing regimens with sofosbuvir (n=77), simeprevir (n=18), or both (n=2) for 24 weeks in 97 liver transplant recipients with severe recurrent HCV infection ([Fontana, 2016](#)). Thirty-five percent of the cohort received ribavirin. Ninety-three percent of patients had genotype 1 infection, 31% had biopsy-proven cirrhosis, and 37% had severe cholestatic HCV. The proportion of patients with CTP class A, B, or C cirrhosis was 51%, 31%, and 12%, respectively. The mean MELD score was 13.0 ± 6.0 . The overall SVR12 rate was 87% (84/97). SVR12 rates were 91% (70/77) in the daclatasvir/sofosbuvir \pm ribavirin group and 72% (13/18) in the daclatasvir/simeprevir \pm ribavirin group. Although 8 patients died during or after therapy from graft dysfunction, CTP and MELD scores were stable or improved in 87% and 83% of patients, respectively. Three virologic breakthroughs and 2 relapses occurred in patients treated with daclatasvir/simeprevir. These data are consistent with findings from Herzer and colleagues who described 6 liver transplant recipients with recurrent genotype 1 infection, 4 (67%) of whom achieved SVR with a regimen of daclatasvir/simeprevir plus ribavirin ([Herzer, 2015](#)).

These data along with those from other studies suggest that daclatasvir should preferentially be combined with sofosbuvir rather than simeprevir in liver transplant recipients, particularly among patients with advanced liver disease ([EASL, 2015a](#)). Daclatasvir-containing regimens appear to be well tolerated overall, with anemia noted when ribavirin is used. Cyclosporine and tacrolimus increase daclatasvir area under the curve (AUC) by 40% and 5%, respectively; these changes are not clinically significant. Daclatasvir does not cause clinically meaningful changes in calcineurin inhibitor, mammalian target of rapamycin (mTOR) inhibitor, steroid, or mycophenolate levels.

Simeprevir + Sofosbuvir

The prospective, randomized, phase 2 GALAXY study assessed the use of simeprevir (150 mg) plus sofosbuvir (400 mg), with or without weight-based ribavirin, for 12 weeks or 24 weeks in 46 liver transplant recipients (44 noncirrhotic) with recurrent genotype 1 infection ([O'Leary, 2017](#)). Among the randomized participants, the SVR12 rates were 100% with simeprevir plus sofosbuvir for 12 weeks, 82% with simeprevir plus sofosbuvir and ribavirin for 12 weeks, and 94% with simeprevir plus sofosbuvir for 24 weeks.

A retrospective multicenter analysis evaluated the efficacy and safety of simeprevir plus sofosbuvir, with or without ribavirin, among 123 liver transplant recipients with recurrent genotype 1 infection. Twenty percent of patients received ribavirin (at the discretion of the treating physician). Excluding 2 patients with nonvirologic failure, the SVR4 and SVR12 rates by modified intention-to-treat analysis were 92% and 91%, respectively ([Pungpapong, 2015](#)).

Another retrospective study from 21 HCV-TARGET centers reported on the efficacy of simeprevir plus sofosbuvir (79%; n=119) or simeprevir plus sofosbuvir and ribavirin (21%; n=32) among 151 liver transplant recipients with recurrent genotype 1 infection ([Brown, 2016](#)). Duration of therapy was 12 weeks for most patients; 10% (15/151) of participants received 24 weeks of treatment. Allograft cirrhosis had developed in 64% (97/151) of patients and 40% (60/151) had decompensated hepatic function. Overall SVR12 was 88% (133/151); 7% of patients experienced virologic relapse. Serious adverse events were reported in 12% of patients, and 3 deaths occurred that were unrelated to therapy.

In healthy volunteers, coadministration of a single dose of cyclosporine with simeprevir resulted in a 19% increase in cyclosporine concentration and simeprevir concentration similar to historical data ([Simeprevir prescribing information](#)).

[2013](#)). However, the phase 2 SATURN study reported that HCV-infected liver transplant recipients with genotype 1b infection taking simeprevir plus daclatasvir and ribavirin concomitantly with cyclosporine experienced a 5-fold increase in plasma simeprevir exposure compared with phase 3 trials of simeprevir in the absence of cyclosporine ([Forns, 2017b](#)). This interaction may be caused by cyclosporine's inhibition of organic anion transporting polypeptide 1B1 (OATP1B1), P-glycoprotein (P-gp), and cytochrome P450 3A (CYP3A). Given these findings, simeprevir should not be coadministered with cyclosporine.

Coadministration of a single dose of tacrolimus with simeprevir in healthy volunteers did not result in a notable change in tacrolimus concentration ([Simeprevir prescribing information, 2103](#)). An interim analysis of the SATURN study data noted an 85% increase in plasma simeprevir exposure when used concomitantly with tacrolimus compared with historical data ([Forns, 2017b](#)); ([Ouwkerk-Mahadevan, 2016b](#)). Based on phase 1 studies, a 2-fold increase in simeprevir concentration is unlikely to be clinically significant. Clinicians may consider use of sofosbuvir plus simeprevir in patients receiving tacrolimus with therapeutic drug monitoring, particularly in those expected to have difficulty tolerating ribavirin (eg, patients with impaired renal function or anemia) or in patients who are unable to forgo proton pump inhibitor therapy (these agents attenuate ledipasvir absorption).

Sofosbuvir/Velpatasvir

To date, there have been no studies evaluating the safety and efficacy of the fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) in liver transplant recipients. For this reason, very limited recommendations on its use post liver transplantation can be made. However, with no treatment options for liver transplant recipients with genotype 2 or 3 infection who have decompensated cirrhosis, expert opinion led to the recommendation to use sofosbuvir/velpatasvir with weight-based ribavirin for these patients. Similarly, recognition of the need for alternative options for patients with genotype 2 or 3 infection and cirrhosis—especially those who are treatment experienced—led to inclusion of sofosbuvir/velpatasvir as an alternative regimen for patients with compensated cirrhosis. The safety of sofosbuvir and other NS5A inhibitors has been demonstrated and discussed above.

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-naïve or -experienced patients with genotype 1, 2, 4, 5, or 6 infection who were randomly assigned in a 5:1 ratio to sofosbuvir/velpatasvir or placebo for 12 weeks ([Feld, 2015](#)). All patients with genotype 5 infection (n=35) received active treatment. Thirty-two percent (201/624) of patients 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 was 99% (95% CI, 98 to >99). The side effect/adverse event profile of sofosbuvir/velpatasvir was similar to placebo.

In the phase 3, open-label ASTRAL-3 study, 552 treatment-naïve or -experienced patients 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. The SVR₁₂ rate was 95% (95% CI, 92 to 98) for the sofosbuvir/velpatasvir treatment arm, which was superior to the SVR₁₂ rate of 80% (95% CI, 75 to 85) for patients receiving sofosbuvir plus ribavirin for 24 weeks ([Foster, 2015a](#)).

The phase 3, open-label ASTRAL-4 study enrolled 267 treatment-naïve or -experienced (55%) patients with genotype 1, 2, 3, 4, or 6 infection and decompensated cirrhosis (CTP class B at the time of screening). Patients 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 patients 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 patients in the 12-week and 24-week sofosbuvir/velpatasvir arms, respectively, compared to 2% in the 12-week sofosbuvir/velpatasvir plus ribavirin study arm. 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 patients 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 patients with decompensated cirrhosis, liver transplant recipients with hepatic decompensation are recommended to receive sofosbuvir/velpatasvir plus ribavirin for 12 weeks.

Velpatasvir is a substrate for CYP3A4, CYP2C8, and CYP2B6, a weak inhibitor of P-gp and OATP transporters, and a moderate inhibitor of the breast cancer resistance protein (BCRP) 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).

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 correct combination or duration is unclear, expert consultation should be sought.

Drug Interactions Between DAAs and Calcineurin Inhibitors

The interaction of DAA agents and calcineurin inhibitors is complex and unpredictable without formal studies of drug-drug interactions. A summary of drug interactions between calcineurin inhibitors and DAAs with recommended dosing 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.

Table. DAA Interactions With Calcineurin Inhibitors

	Cyclosporine	Tacrolimus
Sofosbuvir	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
PrOD	5.8-fold ? in CSA AUC; modeling suggest using 1/5 of CSA dose during PrOD treatment, monitor CSA levels and titrate CSA dose as needed	57-fold ? in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrOD treatment, monitor TAC levels and titrate TAC dose as needed
Elbasvir / Grazoprevir	15-fold ? in GZR AUC and 2-fold ? in EBR AUC; combination is not recommended	43% ? in TAC; no a priori dose adjustment
Velpatasvir	No interaction observed; no a priori dose adjustment	No data; no a priori dose adjustment
GP	5-fold ? in GLE AUC with higher doses (400 mg) of CSA; not recommended in patients 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
SOF/VEL/VOX	9.4-fold ? in VOX AUC; combination is not recommended	No data; no a priori dose adjustment

Abbreviations: AUC, area under the curve; CSA, cyclosporine; DAC, daclatasvir; EBR/GZR, elbasvir/grazoprevir; GLE/PIB, glecaprevir/pibrentasvir; LED, ledipasvir; SMV, simeprevir; SOF, sofosbuvir; TAC, tacrolimus; VEL, velpatasvir.

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