Drug Interactions Between Directly Acting Antivirals (DAAs) and Transplant Medications

	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	**Simeprevir (GALEXOS®, SMV, TMC435) Janssen**	**Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals**
Kinetic Characteristics	BOC undergoes biotransformation by CYP3A4, CYP3A5 and aldoketoreductases.[1] BOC appears to be a strong, reversible inhibitor of CYP3A4 and p-glycoprotein.[2] In a healthy volunteer study, BOC does not appear to exert significant P-gp inhibition at clinically relevant concentrations.[3]	Substrate of CYP3A4. Mild inhibitor of intestinal (but not hepatic) CYP3A4, and 1A2.[4] Simeprevir has no clinically relevant effects on CYP2C9, 2C19 and 2D6.[5] Simeprevir inhibits OATP1B1/3 and P-gp transporters.[6]	Substrate and strong inhibitor of CYP3A4 and p-glycoprotein.[7]
1) Cyclosporine			
Pharmacokinetic Studies	In healthy volunteers, the kinetics of single-dose cyclosporine 100 mg was assessed alone and in the presence of single dose BOC 800 mg and steady-state BOC 800 mg TID. In the presence of BOC, cyclosporine AUC ↑ 2.7-fold and Cmax ↑ 2-fold; BOC pharmacokinetics were not affected by cyclosporine. Co-administration of cyclosporine with BOC may require dose adjustment of CsA and close monitoring of cyclosporine blood levels as well as frequent assessments of renal function and CsA-related side effects.[8]	In the presence of steady-state simeprevir 150 mg daily, administration of single-dose cyclosporine 100 mg resulted in 16% ↑ Cmax and 19% ↑ AUC, compared to cyclosporine administered alone. Simeprevir pharmacokinetics were similar to historical controls.[9] However, interim data from a phase 2 study in HCV-infected post-liver transplant patients on individualized cyclosporine plus simeprevir 150 mg daily for 14 days resulted in 3.74-fold increase Cmax and 4.81-fold increase AUC of simeprevir, compared to historical controls. The significant increase in simeprevir plasma concentrations is presumed to be due to inhibition of OATP1B1, P-gp and CYP3A by cyclosporine. **It is not recommended to co-administer simeprevir with cyclosporine**.[6]	In healthy subjects, the pharmacokinetics of single dose cyclosporine was assessed alone at 100 mg and in the presence of steady-state TVR 750 mg q8h at a dose of 10 mg on day 1 and day 8. When coadministered with TVR, cyclosporine exposure ↑ 4.6-fold and the elimination t1/2 increased from 12 to 42 hours; the effect of first dose of TVR on cyclosporine kinetics was similar to the effect of steady-state TVR. TVR kinetics were similar to historical data, suggesting no major effect of cyclosporine on TVR.[10]
Case reports/case	In five genotype 1 liver		In a case series, patients

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series	transplant patients with HCV recurrence, BOC 800 mg three times a day was initiated after a 4-week lead-in phase. Concomitant immunosuppressant therapy (IT) included cyclosporine (3), tacrolimus (2) and everolimus (1). The mean follow-up period since HCV therapy was 14.8±3.1 weeks. Estimated oral clearances of IT decreased on average by 50%, requiring reduced dosing regimens. Anaemia occurred in all patients, with a mean fall in haemoglobin levels between baseline and week 12 of 3.12±2.27g/dL. All patients required administration of β-erythropoietin, three needed ribavirin dose reduction and one a blood transfusion. A virological response was observed in all patients (mean HCV vira load decrease at week 12: 6.64±0.35 log(10)IU/mL).[11]		with recurrent HCV post-liver transplant with null response (<2 log ↓) to pegylated-interferon/ribavirin (PR) for ≥12 weeks received a 4 week lead-in with PEG-IFN α2b with ribavirin 600-1000 mg/d followed by addition of TVR 750 mg q8h. Patients on tacrolimus were converted to cyclosporine prior to starting TVR. On the first day of TVR therapy, the cyclosporine dose was decreased from an average of 200 mg to 25 mg per day, with a target CsA trough of 100 ng/mL. To date, 4 subjects have completed 12 weeks of TVR therapy. The average CsA dose at week 16 was 68 mg. All patients required ↓ in ribavirin dose; no episodes of renal toxicity secondary to ↑ CsA levels or rejection following the end of TVR therapy were observed.[12] In a series of 9 liver transplant HCV patients treated with TVR, pegylated interferon, and ribavirin in parallel with tacrolimus (n=4), cyclosporine (n=4), or sirolimus (n=1), immunosuppressant dose-reductions were required in all patients (cyclosporine 2.5-fold, sirolimus 7-fold, tacrolimus 22-fold, respectively) during the course of the 12 week triple therapy. Tacrolimus and sirolimus were administered once weekly while the average cyclosporine dose was

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			48.5 mg daily during triple therapy. Four 4 patients were HCV RNA negative by week 4 and 8 patients were HCV RNA negative by week 12.[13]
2) Sirolimus			
Pharmacokinetic Studies	In healthy volunteers, the kinetics of single-dose sirolimus 2 mg was assessed alone and in the presence of BOC 800mg TID. In the presence of BOC, sirolimus AUC ↑ 8.1-fold and Cmax ↑ 4.8-fold; BOC pharmacokinetics were not affected by sirolimus. Coadministration of BOC and sirolimus would likely require significant dose reduction of sirolimus and/or prolongation of the dosing interval, with close monitoring of sirolimus concentrations and frequent assessments of renal function and sirolimus-related side effects.[14]	Concomitant use of simeprevir and sirolimus may result in mildly increased or decreased plasma concentrations of sirolimus. Routine monitoring of blood concentrations of sirolimus is acceptable.[6]	
Cohort Studies			In a case series, 10 HCV genotype-1 infected, post-liver transplant patients received pegylated interferon 2a, ribavirin, and TVR 1125mg q12h. All subjects were on stable sirolimus dosing prior to starting antiviral therapy. Sirolimus doses were pre-emptively reduced to 0.5mg (except for one patient whose dose was reduced by 50%, ie 1mg) of pre-treatment doses. Sirolimus trough levels were then monitored daily until stable dosing regimen was achieved. In the presence of TVR, dose-normalized AUC of sirolimus ↑ 26.1-fold, and

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			Cmax ↓ 80%. By week 5 to 12, mean dose reduction of sirolimus was 89% of the original dose.[15]
3) Tacrolimus			
Pharmacokinetic Studies	In healthy volunteers, the kinetics of single-dose tacrolimus 0.5 mg was assessed alone and in the presence of single dose BOC 800 mg and steady-state BOC 800 mg TID. In the presence of BOC, tacrolimus AUC ↑ 17-fold and Cmax ↑ 9.9-fold; BOC pharmacokinetics were not affected by tacrolimus. Coadministration of BOC and tacrolimus would likely require significant dose reduction of tacrolimus and/or prolongation of the dosing interval, with close monitoring of tacrolimus concentrations and frequent assessments of renal function and tacrolimus-related side effects.[8]	In the presence of steady-state simeprevir 150 mg daily, administration of single-dose tacrolimus 2 mg resulted in 24% ↓ Cmax and 17% ↓ AUC, compared to tacrolimus administered alone. Simeprevir pharmacokinetics were similar to historical controls. These changes are not considered clinically relevant and a priori dose adjustments are not required with coadministration.[9] Routine monitoring of blood concentrations of tacrolimus is acceptable.[6]	In healthy subjects, the pharmacokinetics of single dose tacrolimus was assessed alone (2 mg) and at a dose of 0.5 mg in the presence of steady-state TVR 750 mg q8h. When coadministered with TVR, tacrolimus exposure ↑ 70-fold and the elimination t1/2 increased from 40.7 to 196 hours; TVR kinetics were similar to historical data, suggesting no major effect of tacrolimus on TVR.[10]
Cohort Studies	In five genotype 1 liver transplant patients with HCV recurrence, BOC 800 mg three times a day was initiated after a 4-week lead-in phase. Concomitant immunosuppressant therapy (IT) included cyclosporine (3), tacrolimus (2) and everolimus (1). The mean follow-up period since HCV therapy was 14.8±3.1 weeks. Estimated oral clearances of IT decreased on average by 50%, requiring reduced dosing regimens. Anaemia occurred in all patients, with a mean fall in haemoglobin levels between baseline and week 12 of 3.12±2.27g/dL. All patients	Interim data from a phase 2 study in HCV-infected post-liver transplant patients on individualized tacrolimus plus simeprevir 150 mg daily for 14 days resulted in 79% increase Cmax and 85% increase AUC of simeprevir, compared to historical controls. The increase in simeprevir plasma concentrations is presumed to be due to inhibition of OATP1B1 by cyclosporine. No dose adjustment is required for either drug when simeprevir is co-administered with tacrolimus. Routine monitoring of blood	In a case series, HCV-1a infected, post-liver transplant patients received pegylated interferon 2a/b, ribavirin, and TVR. All subjects were on stable tacrolimus dosing prior to starting antiviral therapy. Tacrolimus doses were pre-emptively reduced to 50% of pre-treatment doses and given once weekly. Trough TAC levels were checked q2d for the first 2 weeks, then weekly until TVR therapy was complete. Baseline TAC dosing was resumed after 5 days of stopping TVR. No episodes of acute rejection or TAC

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	required administration of β-erythropoietin, three needed ribavirin dose reduction and one a blood transfusion. A virological response was observed in all patients (mean HCV vira load decrease at week 12: 6.64±0.35 log(10)IU/mL).[11]	concentrations of tacrolimus is acceptable.[6]	toxicity were noted; 4 patients had early rapid virologic response, 2 patients had complete early virologic response, 1 patient was a non-responder. The main adverse effect was anemia (n=6 required transfusions); dehydration, renal insufficiency and infections also reported.[16] In a series of 9 liver transplant HCV patients treated with TVR, pegylated interferon, and ribavirin in parallel with tacrolimus (n=4), cyclosporine (n=4), or sirolimus (n=1), immunosuppressant dose-reductions were required in all patients (cyclosporine 2.5-fold, sirolimus 7-fold, tacrolimus 22-fold, respectively) during the course of the 12 week triple therapy. Tacrolimus and sirolimus were administered once weekly while the average cyclosporine dose was 48.5 mg daily during triple therapy. Four 4 patients were HCV RNA negative by week 4 and 8 patients were HCV RNA negative by week 12.[13]

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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