

## Perspective

# Hepatitis C Virus Direct-Acting Antiviral Drug Interactions and Use in Renal and Hepatic Impairment

*Direct-acting antiviral (DAA) drugs exhibit considerable variability in mechanisms of metabolism and the extent to which they are substrates, inhibitors, or inducers of cytochrome P450 enzymes or P-glycoprotein and other drug transporters. Thus, potential drug-drug interactions with other commonly used therapies also vary, as do the effects of renal and hepatic impairment on DAA drug exposure. Drug-drug interaction profiles and use in cases of renal or hepatic impairment are reviewed for the DAAs simeprevir; sofosbuvir; ledipasvir; the fixed-dose combination regimen of paritaprevir, ritonavir, and ombitasvir plus dasabuvir; and the investigational drugs daclatasvir and asunaprevir. This article summarizes a presentation by Lucas Hill, PharmD, at the IAS–USA continuing education program held in Chicago, Illinois, in October 2014.*

**Keywords:** HCV, hepatitis C virus, direct-acting antiviral drugs, DAAs, drug-drug interactions, renal impairment, hepatic impairment, drug exposure

There are numerous potential drug-drug interactions that must be considered when using direct-acting antiviral (DAA) drugs for treatment of hepatitis C virus (HCV) infection. The following summarizes characteristics of interactions between newer DAAs and cytochrome P450 (CYP450) enzymes and drug transporters that affect the exposure to these and other commonly used drugs, as well as the effects of renal or hepatic impairment on DAA drug exposure.

### Simeprevir

Exposure to the HCV protease inhibitor simeprevir is increased by approximately 60% when the drug is taken with food. Simeprevir is a substrate of the intestinal uptake transporter P-glycoprotein (P-gp). It is distributed to the liver by organic anion-transporting polypeptide (OATP), is metabolized primarily by hepatic CYP450 3A (CYP3A), and is an inhibitor of both OATP and P-gp as well as a mild inhibitor of intestinal (nonhepatic) CYP3A and CYP1A2.

Drugs that are CYP3A or P-gp substrates, particularly those with a narrow therapeutic index, are of special con-

cern when coadministered with simeprevir. Table 1 shows the known drugs that can decrease simeprevir concentrations through induction of CYP3A4 and P-gp (eg, anticonvulsants, antimycobacterials, and HIV nonnucleoside reverse transcriptase inhibitors), and drugs that increase simeprevir concentrations through inhibition of CYP3A4 (eg, macrolides, antifungals, boosted HIV protease inhibitors, and cobicistat). Diltiazem and verapamil, also potent CYP3A4 inhibitors, are not mentioned in the simeprevir prescribing information, and caution should be used when these drugs are coadministered with simeprevir.

Also shown in Table 1 are drugs that exhibit increased concentrations when coadministered with simeprevir (eg, antiarrhythmics, calcium channel blockers, and statins). Phosphodiesterase type 5 inhibitors can be used without dose adjustment for erectile dysfunction but should be started at the lowest dose possible when used for pulmonary hypertension. For calcium channel blockers, monitoring blood pressure before making dose changes is generally sufficient. Statins are CYP3A4 substrates, and dosing recommendations with concomitant simeprevir are a maximum of 10 mg daily of rosuvastatin (an OATP substrate)

and 40 mg daily of atorvastatin (a P-gp and OATP substrate). For other statins, the dose can be halved during simeprevir administration. Levels of digoxin (a P-gp substrate) should be monitored when coadministered with simeprevir.

Potential interactions between simeprevir and immunosuppressants are an important consideration for post-liver transplant patients. Cyclosporine is a potent CYP3A4 and P-gp inhibitor, and coadministration results in an approximately 6-fold increase in simeprevir exposure; therefore, coadministration of cyclosporine and simeprevir is not recommended. Coadministration of simeprevir and tacrolimus results in a small increase in simeprevir exposure and a small decrease in tacrolimus exposure. It is recommended that tacrolimus levels be monitored, with dose adjustment as needed. The pharmacokinetics of concomitant simeprevir and sirolimus have not been formally studied, and patients taking concomitant simeprevir and sirolimus should be monitored to determine if a dose adjustment is necessary.

Simeprevir is generally considered safe for patients with any degree of renal impairment. The drug is primarily hepatically metabolized and cleared, with less than 1% of it recovered in the urine. With severe renal impairment, there is a slight (62%) increase in the simeprevir area under the concentration-time curve (AUC) that is not considered clinically significant. The drug is also highly protein bound and thus unlikely to be removed by dialysis. In practice, simeprevir has been used to achieve cure in patients on dialysis.

With regard to use in cases of hepatic impairment, 2.4- and 5.2-fold increases in simeprevir AUC have been reported in patients with Child-Turcotte-Pugh (CTP) class B and C disease, respectively. Simeprevir maximum concentration ( $C_{max}$ ) is generally twice as high among HCV-infected patients as among

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**Table 1.** Drugs That Affect Simeprevir Concentrations or Whose Concentrations Are Affected by Simeprevir

Drugs That Decrease Simeprevir Concentrations	Drugs That Increase Simeprevir Concentrations	Drugs With Concentrations Increased by Simeprevir	
<ul style="list-style-type: none"> <li>• Anticonvulsants               <ul style="list-style-type: none"> <li>- Carbamazepine</li> <li>- Oxcarbazepine</li> <li>- Phenobarbital</li> <li>- Phenytoin</li> </ul> </li> <li>• Antimycobacterials               <ul style="list-style-type: none"> <li>- Rifabutin</li> <li>- Rifampin</li> <li>- Rifapentine</li> </ul> </li> <li>• Dexamethasone (systemic)</li> <li>• Nonnucleoside reverse transcriptase inhibitors               <ul style="list-style-type: none"> <li>- Efavirenz</li> <li>- Etravirine</li> <li>- Nevirapine</li> </ul> </li> <li>• St John's wort</li> <li>• Tipranavir</li> </ul>	<ul style="list-style-type: none"> <li>• Antifungals               <ul style="list-style-type: none"> <li>- Fluconazole</li> <li>- Itraconazole</li> <li>- Ketoconazole</li> <li>- Posaconazole</li> <li>- Voriconazole</li> </ul> </li> <li>• Boosted protease inhibitors</li> <li>• Calcium channel blockers               <ul style="list-style-type: none"> <li>- Diltiazem</li> <li>- Verapamil</li> </ul> </li> <li>• Cobicistat</li> <li>• Macrolides               <ul style="list-style-type: none"> <li>- Clarithromycin</li> <li>- Erythromycin</li> <li>- Telithromycin</li> </ul> </li> <li>• Milk thistle</li> </ul>	<ul style="list-style-type: none"> <li>• Antiarrhythmics               <ul style="list-style-type: none"> <li>- Amiodarone</li> <li>- Disopyramide</li> <li>- Flecainide</li> <li>- Mexiletine</li> <li>- Propafenone</li> <li>- Quinidine</li> </ul> </li> <li>• Calcium channel blockers               <ul style="list-style-type: none"> <li>- Amlodipine</li> <li>- Diltiazem</li> <li>- Felodipine</li> <li>- Nicardipine</li> <li>- Nifedipine</li> <li>- Nisoldipine</li> <li>- Verapamil</li> </ul> </li> <li>• Cisapride</li> <li>• Digoxin</li> </ul>	<ul style="list-style-type: none"> <li>• Erythromycin</li> <li>• Phosphodiesterase type 5 inhibitors               <ul style="list-style-type: none"> <li>- Sildenafil</li> <li>- Tadalafil</li> <li>- Vardenafil</li> </ul> </li> <li>• Sedative anxiolytics               <ul style="list-style-type: none"> <li>- Midazolam (oral)</li> <li>- Triazolam (oral)</li> </ul> </li> <li>• Statins               <ul style="list-style-type: none"> <li>- Atorvastatin (40 mg)</li> <li>- Lovastatin</li> <li>- Pitavastatin</li> <li>- Pravastatin</li> <li>- Rosuvastatin (10 mg)</li> <li>- Simvastatin</li> </ul> </li> </ul>

uninfected controls. Moderate and severe hepatic impairment increased AUCs among HCV-infected patients by 1.3- and 2.8-fold for those with CTP class B and C disease, respectively, indicating that sizable increases in simeprevir exposure can be expected among HCV-infected patients with severe hepatic impairment.<sup>1</sup>

Potential adverse effects related to increased simeprevir exposure include rash, pruritus, photosensitivity, and increased bilirubin level. Strategies for reducing simeprevir exposure include avoiding substantial drug-drug interactions and taking the drug on an empty stomach.

### Sofosbuvir

Sofosbuvir is a nucleotide analogue that prodrug is diphosphorylated in the liver to generate a nucleoside triphosphate analogue, and does not undergo traditional hepatic metabolism. Its primary (inactive) metabolite (GS-331007) undergoes renal elimination via glomerular filtration and active tubular secretion. Sofosbuvir is a substrate of P-gp and breast cancer resistance protein (BCRP). It has no appreciable inhibitory or induction effects on drug transporters or CYP450 enzymes. As shown in Table 2, drugs that reduce sofosbuvir levels by inducing P-gp include anti-

convulsants, antimycobacterials, ritonavir-boosted tipranavir, and St John's wort. Increases of 5-fold or greater in the AUC of the primary circulating metabolite are observed in patients with severe renal impairment or end-stage renal disease (ESRD).<sup>2</sup> Thus, sofosbuvir is not recommended for patients with ESRD or a glomerular filtration rate (GFR) of less than 30 mL/min/1.73m<sup>2</sup>. An ongoing study is evaluating lower doses of sofosbuvir (200 mg or 400 mg) in patients with severe renal impairment or ESRD.

### Ledipasvir

The nonstructural protein 5A (NS5A) inhibitor ledipasvir is primarily eliminated in the feces as unchanged parent drug, with approximately 1% eliminated in the urine. It has little to no effect on CYP450 enzymes and is a substrate and weak inhibitor of P-gp and BCRP. As with sofosbuvir, coadministration of ledipasvir with P-gp inducers (eg, anti-convulsants, antimycobacterials, and St John's wort) should be avoided. There is potential for ledipasvir to interact with P-gp and BCRP substrates (Table 3). For example, ledipasvir increases levels of rosuvastatin (a BCRP substrate), and concurrent administration should be avoided. Because digoxin is a P-gp substrate, digoxin levels should

be monitored. There are no substantial interactions between ledipasvir and the immunosuppressants cyclosporine and tacrolimus, making ledipasvir suitable for use in post-liver transplant patients.

Ledipasvir exhibits decreased solubility as gastric pH increases. Thus, ledipasvir should not be administered within 4 hours of antacids. Histamine 2 receptor antagonists should be administered simultaneously with ledipasvir or administration should be separated by 12 hours, with daily dose not exceeding the equivalent of famotidine 40 mg twice daily. Proton pump inhibitors should be administered simultaneously

**Table 2.** Drugs That Decrease Sofosbuvir Concentrations

<ul style="list-style-type: none"> <li>• Anticonvulsants               <ul style="list-style-type: none"> <li>- Carbamazepine</li> <li>- Oxcarbazepine</li> <li>- Phenobarbital</li> <li>- Phenytoin</li> </ul> </li> <li>• Antimycobacterials               <ul style="list-style-type: none"> <li>- Rifabutin</li> <li>- Rifampin</li> <li>- Rifapentine</li> </ul> </li> <li>• Ritonavir-boosted tipranavir</li> <li>• St John's wort</li> </ul>
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**Table 3.** P-gp and BCRP Substrates That Have Potential Interactions With Ledipasvir

P-gp Substrates	BCRP Substrates
<ul style="list-style-type: none"> <li>• Antineoplastics</li> <li>• Colchicine</li> <li>• Digoxin</li> <li>• Calcium channel blockers               <ul style="list-style-type: none"> <li>- Diltiazem</li> <li>- Verapamil</li> </ul> </li> <li>• Immunosuppressants               <ul style="list-style-type: none"> <li>- Cyclosporine</li> <li>- Tacrolimus</li> </ul> </li> <li>• Methotrexate</li> <li>• Rivaroxaban</li> <li>• Statins               <ul style="list-style-type: none"> <li>- Atorvastatin     - Pravastatin</li> <li>- Lovastatin       - Simvastatin</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Antineoplastics</li> <li>• Ciprofloxacin</li> <li>• Methotrexate</li> <li>• Nucleoside analogue reverse transcriptase inhibitors               <ul style="list-style-type: none"> <li>- Lamivudine</li> <li>- Zidovudine</li> </ul> </li> <li>• Statins               <ul style="list-style-type: none"> <li>- Pravastatin</li> <li>- Rosuvastatin</li> </ul> </li> </ul>

Abbreviations: BCRP, breast cancer resistance protein; P-gp, p-glycoprotein.

with ledipasvir, with daily dose not exceeding the equivalent of omeprazole 20 mg.

Ledipasvir undergoes little metabolism, and only a slight reduction in ledipasvir  $C_{max}$  has been observed as degree of hepatic impairment increases. Thus, ledipasvir is considered safe for patients with varying degrees of hepatic impairment.

### Paritaprevir, Ritonavir, and Ombitasvir Plus Dasabuvir

The fixed-dose combination of ritonavir-boosted paritaprevir (an HCV protease inhibitor) with ombitasvir (an NS5A inhibitor) and dasabuvir (a nonnucleoside polymerase inhibitor) was recently approved by the US Food and Drug Administration. This fixed-dose combination of paritaprevir, ritonavir, and ombitasvir plus dasabuvir (PrOD) slightly increased digoxin  $C_{max}$  and AUC, suggesting a minimal effect on drugs that are P-gp substrates.

In a study of pravastatin used as an OATP substrate, pravastatin exposure was increased by approximately 2-fold when coadministered with PrOD, indicating that pravastatin dose should be halved when used with this combination. Levels of rosuvastatin, a substrate of both OATP and BCRP, showed increases of 2.6-fold in AUC and 7-fold in  $C_{max}$  when coadministered with PrOD; therefore, rosuvastatin dosage should likely be limited to 10 mg daily.

The greatest effect of cyclosporine (an inhibitor of P-gp, BCRP, and OATP) on PrOD was a 2-fold increase in paritaprevir AUC, which is not considered clinically significant. However, this regimen substantially increases cyclosporine exposure (see below). Similarly, the greatest effect of ketoconazole (a CYP3A4 and P-gp inhibitor) on PrOD was a 2-fold increase in paritaprevir AUC. Increased ketoconazole exposure with coadministration of this regimen requires that the ketoconazole dose be limited to 200 mg. Caution should be used when administering PrOD with azoles, as increased paritaprevir levels can be expected.

When considering drug-drug interactions with PrOD, an important factor is the inclusion of ritonavir (a substrate of P-gp, CYP3A, and CYPD6; an inducer of CYP1A2, CYP2C8, CYP2C9, and CYP2C19; and an inhibitor of P-gp, CYP3A, CYP2D6, multirug resistance protein 1 [MRP1], OATP, and BCRP). Table 4 lists drugs that should be avoided or used with caution in patients receiving ritonavir. Based on other studies of PrOD pharmacokinetics, no dose adjustments are likely to be recommended for digoxin, duloxetine, fixed-dose emtricitabine and tenofovir disoproxil fumarate, escitalopram, methadone, progestin-only contraceptives, or raltegravir.<sup>3</sup> It is recommended that coadministration of carbamazepine (or other CYP450 inducing anticonvulsants) and gemfibrozil

(which increases dasabuvir exposure) be avoided with this regimen. Dose adjustments for amlodipine and other calcium channel blockers are also likely to be recommended when coadministered with this regimen.

With regard to the effect of PrOD on immunosuppressants, substantial increases in cyclosporine and tacrolimus exposure levels can be expected. These increases primarily reflect the effects of ritonavir inhibition of CYP3A4 and P-gp. In a phase II study in which the cyclosporine dose was reduced to 20% of the usual daily dose and tacrolimus was dosed at 0.5 mg per week or 0.2 mg every 3 days, cyclosporine levels were maintained within the desired range, and tacrolimus doses of 0.5 mg to 1 mg every 1 week or 2 weeks maintained adequate blood levels in most patients.<sup>4</sup> Thus, concomitant use of these agents requires close monitoring of drug levels.

Among patients with moderate hepatic impairment, ombitasvir, dasabuvir, and ritonavir drug exposure levels were comparable to those seen in controls, and paritaprevir AUC was increased by 62%. Among patients with severe hepatic impairment, ombitasvir AUC was reduced by 55%, ritonavir AUC was comparable to that seen in controls, paritaprevir AUC was increased by 920%, and dasabuvir AUC was increased by 320%.<sup>5</sup> PrOD is safe for use in patients with mild hepatic impairment, is not recommended for patients with moderate hepatic impairment, and is contraindicated for patients with severe hepatic impairment.

### Daclatasvir

The investigational NS5A inhibitor daclatasvir exhibits minimal renal clearance (5%) and is highly protein bound. It is metabolized by CYP3A4 and is a P-gp substrate and a moderate inhibitor of OATP1B1 and P-gp.

Daclatasvir is expected to be compatible with immunosuppressants. Coadministration of daclatasvir and cyclosporine resulted in no change in cyclosporine levels and an increase in daclatasvir levels (40% increase in AUC) that is likely clinically insignificant, and

**Table 4.** Drugs That Should Be Avoided or Used With Caution in Patients Receiving Ritonavir

Drugs That Should Not Be Used With Ritonavir	Drugs That Should Be Used With Caution With Ritonavir
<ul style="list-style-type: none"> <li>• Alfuzosin</li> <li>• Alprazolam</li> <li>• Amiodarone</li> <li>• Cisapride</li> <li>• Diazepam</li> <li>• Ergotamine</li> <li>• Flecainide</li> <li>• Lovastatin</li> <li>• Phenytoin</li> <li>• Pimozide</li> </ul>	<ul style="list-style-type: none"> <li>• Salmeterol</li> <li>• Simvastatin</li> <li>• Triazolam</li> <li>• Voriconazole</li> <li>• Rifampin</li> <li>• Rivaroxaban</li> </ul>
	<ul style="list-style-type: none"> <li>• Atorvastatin</li> <li>• Budesonide</li> <li>• Carbamazepine</li> <li>• Clarithromycin</li> <li>• Colchicine</li> <li>• Cyclosporine</li> <li>• Digoxin</li> <li>• Fentanyl</li> <li>• Fluticasone</li> <li>• Methadone (monitor)</li> <li>• Oral contraceptives</li> <li>• Phosphodiesterase type 5 inhibitors</li> <li>• Pravastatin</li> <li>• Quetiapine</li> <li>• Rifabutin</li> <li>• Rosuvastatin</li> <li>• Sirolimus</li> <li>• Tacrolimus</li> <li>• Trazodone</li> </ul>

no clinically significant changes were observed with coadministration of daclatasvir and tacrolimus.<sup>6</sup>

Daclatasvir dose adjustments will be necessary when administered with potent CYP3A inhibitors or inducers. For example, the daclatasvir dose should be decreased to 30 mg daily for patients also receiving ritonavir-boosted atazanavir (a CYP3A inhibitor) and increased to 90 mg daily for patients also receiving efavirenz (a CYP3A inducer).<sup>7</sup>

Increases of up to 2-fold in daclatasvir AUC were observed among patients with moderate or severe renal impairment. The increased exposure is considered to be within the safety range for the drug, suggesting it can be used for

patients with any degree of renal impairment.<sup>8</sup>

Among patients with hepatic impairment, although total daclatasvir levels increased with more severe impairment, the unbound levels of drug remained adequate and similar to levels in healthy controls, with clearance of the unbound fraction also remaining relatively unchanged.<sup>9</sup> Thus, daclatasvir use should be suitable for patients with any degree of hepatic impairment.

### Asunaprevir

The investigational NS3 protease inhibitor asunaprevir, originally intended to be coformulated with daclatasvir, is

metabolized by CYP3A4 and is a substrate of P-gp and OATP1B1, a weak inducer of CYP3A4, a weak inhibitor of P-gp, and a moderate inhibitor of CYP2D6.<sup>10,11</sup>

Ketoconazole substantially increased asunaprevir levels, indicating that caution will be needed when coadministering asunaprevir with CYP3A4 or P-gp inhibitors. Caution may also be necessary when coadministering asunaprevir with CYP2D6 substrates, including antidepressants, antipsychotics, codeine, and dextromethorphan.<sup>12</sup>

Asunaprevir is suitable for patients with ESRD. However, studies of hepatic impairment showed AUC increases of 10-fold with CTP class B disease and of 32-fold with CTP class C disease, indicating that the drug should not be used for patients with moderate or severe hepatic impairment.<sup>10</sup>

### Summary


Table 5 provides a summary of inhibition, induction, and substrate profiles of the DAAs discussed here and recommendations for their use and dose adjustments as needed for patients with renal or hepatic impairment.<sup>13</sup> Prior to initiating treatment with HCV DAAs, patients' current medications must be reviewed for potential drug interactions

**Table 5.** Characteristics of Direct-Acting Antiviral Drugs and Dose Adjustments for Renal or Hepatic Impairment

Drug	Inhibition	Induction	Substrate	Renal Impairment	Hepatic Impairment
Asunaprevir <sup>a</sup>	Moderate inhibitor of CYP2D6	Weak inhibitor of CYP3A4 and P-gp	Substrate of CYP3A4, P-gp, and OATP1B1	No adjustment needed	Should likely be avoided in patients with CTP class B or C disease
Daclatasvir <sup>a</sup>	Moderate inhibitor of P-gp and OATP	NA	Substrate of CYP3A and P-gp	No adjustment needed	No adjustment needed
Ledipasvir	Mild inhibitor of P-gp, BCRP	NA	Substrate of P-gp	No adjustment needed	No adjustment needed
Paritaprevir, ritonavir, and ombitasvir plus dasabuvir	Inhibitor of CYP3A4, CYP2D6, P-gp, OATP, and BCRP	Inhibitor of CYP1A2, CYP2C8, CYP2C9, and CYP2C19 (based on ritonavir pharmacokinetics)	Substrate of CYP3A4, CYP2C8, and CYP2D6	Likely no adjustment needed	Not recommended in patients with CTP class B disease, and contraindicated in patients with CTP class C disease
Simeprevir	Mild inhibitor of intestinal CYP3A and CYP1A2; mild inhibitor of OATP and P-gp	NA	Substrate of CYP3A	No adjustment needed	Should be used with caution in patients with CTP class B or C disease
Sofosbuvir	NA	NA	Substrate of P-gp	Not recommended if GFR <30 mL/min/1.73m <sup>2</sup>	No adjustment needed

Abbreviations: BCRP, breast cancer resistance protein; CTP, Child-Turcotte-Pugh; CYP, cytochrome P450; GFR, glomerular filtration rate; NA, not available; OATP, organic anion-transporting polypeptide; P-gp, P-glycoprotein. Adapted from Kiser et al.<sup>13</sup>

<sup>a</sup>Investigational drug.

and adjusted if needed. When selecting the ideal regimen for a patient, other comorbidities such as renal impairment or degree of liver disease are important considerations. 

*Presented by Dr Hill in October 2014. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Hill in March 2015.*

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