

## Perspective

# Clinically Significant Drug-Drug Interactions Between Hepatitis C Virus and HIV Treatments

*The potential for drug-drug interactions is an important consideration in the treatment of HIV/hepatitis C virus (HCV) coinfection. Regimens for HCV genotype 1 infection are discussed in the context of an individual on stable antiretroviral therapy, to determine which HCV treatments may be initiated without requiring a change in antiretroviral regimen or an increase in monitoring for potential drug-drug interactions. The effects of potential interactions between HCV drugs and other therapeutic classes of drugs are also discussed. This article summarizes a presentation by Jennifer J. Kiser, PharmD, at the IAS–USA continuing education program, Improving the Management of HIV Disease, held in Los Angeles, California, in April 2016.*

**Keywords:** HIV, HCV, hepatitis C, coinfection, drug-drug interactions, CYP3A4, tenofovir, HIV protease inhibitors, metabolic enzymes, drug transporters

An important consideration in the treatment of HIV/hepatitis C virus (HCV)-coinfected individuals is the potential for drug-drug interactions. Current HCV therapies generally have well-characterized pharmacology and manageable drug interaction profiles. However, there are a number of potential interactions for which clinicians should maintain vigilance.

## HCV Regimens in an Individual on Stable Antiretroviral Therapy

Consider the case of a 60-year-old man with a history of injection drug use who was diagnosed with HIV and HCV infections in 1997. His HIV infection is well controlled; he has an undetectable HIV viral load and a CD4+ cell count of 506/ $\mu$ L. His past antiretroviral regimens were zidovudine/lamivudine (slash indicates a coformulation) plus indinavir; zidovudine/lamivudine/abacavir plus ritonavir-boosted lopinavir; and tenofovir disoproxil fumarate (TDF)/lamivudine, abacavir, and ritonavir-boosted lopinavir. His current regimen is TDF/emtricitabine, ritonavir-boosted darunavir twice daily, and raltegravir. The changes in his antiretroviral regimen were “upgrades” to emerging standard treatment and not due to virologic failure.

He has HCV genotype 1a infection, which relapsed after prior treatment with 72 weeks of peginterferon alfa and ribavirin. His current HCV RNA level is 7.3 log<sub>10</sub> IU/mL, and recent transient elastography testing showed a liver stiffness measurement of 9.1 kPa. Clinical lab results include an estimated creatinine clearance of approximately 119 mL/min,

indicating normal renal function; a platelet count of 175 x 10<sup>9</sup>/L; and serum biomarker results consistent with the transient elastography result. His physicians want to start HCV treatment that does not require a change in his antiretroviral regimen or increased monitoring. Would an HCV regimen of any of: elbasvir/grazoprevir; paritaprevir/ritonavir/ombitasvir plus dasabuvir (PrOD) plus ribavirin; ledipasvir/sofosbuvir; sofosbuvir/daclatasvir; or sofosbuvir/velpatasvir meet this objective?

## Elbasvir/Grazoprevir

With regard to effects on enzymes and drug transporters, elbasvir and grazoprevir are each metabolized by cytochrome P450 3A (CYP3A), posing risk of interaction with drugs that inhibit or induce this enzyme. Grazoprevir is also a mild inhibitor of CYP3A4 and is a substrate of the organic anion-transporting polypeptide 1B1 (OATP1B1) uptake transporter in the liver. Elbasvir and grazoprevir are each substrates of P-glycoprotein (P-gp). There are several inhibitors of OATP1B1 that would cause increased plasma concentrations of grazoprevir. Elbasvir and grazoprevir each inhibit breast cancer resistance protein (BCRP), an efflux transporter in the liver.

Boosting agents should not be used with elbasvir/grazoprevir, as they can inhibit CYP3A and OATP1B1, resulting in increased levels of grazoprevir and increased risk of toxic effects. Because this individual is taking boosted darunavir, he cannot take elbasvir/grazoprevir. Among other antiretroviral drugs, efavirenz also interacts with this HCV regimen, as it induces CYP3A and thus reduces levels of elbasvir and grazoprevir. Although etravirine has not been studied in this regard, a similar interaction is assumed.

## PrOD Plus Ribavirin

Paritaprevir, ombitasvir, and dasabuvir are substrates of CYP3A4 and P-gp. Dasabuvir is also a substrate of CYP2C8 and CYP2D6. All 3 drugs inhibit UDP-glucuronosyltransferase 1A1 (UGT1A1), paritaprevir and ombitasvir inhibit CYP2C8, and ritonavir inhibits CYP3A4. Paritaprevir inhibits P-gp, OATP1B1/3, and BCRP, and dasabuvir also inhibits BCRP. Ribavirin is used for individuals with HCV genotype 1a infection. Ribavirin is not metabolized by CYP enzymes and has a low potential for interactions with antiretroviral drugs. However, it does have an intracellular interaction with didanosine, which is seldom used in the treatment of HIV infection, and this combination should be avoided. Zidovudine should also be avoided with ribavirin, as both drugs can cause anemia.

Data are available on interactions between PrOD and several antiretroviral drugs.<sup>1</sup> There do not appear to be concerns

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regarding use of PrOD with TDF, emtricitabine, dolutegravir, or raltegravir; however, increased levels of rilpivirine have been observed when coadministered with PrOD, which could theoretically increase the risk for prolongation of the corrected QT interval.

With regard to HIV PIs, atazanavir at a dose of 300 mg can be used with PrOD, but it should be administered simultaneously with the coformulated tablet of ritonavir-boosted paritaprevir and ombitasvir, and separate tablets of ritonavir as a boosting agent should be held for the duration of treatment with PrOD. Lopinavir should not be used with PrOD owing to the fact that it is coformulated with ritonavir, and PrOD already contains ritonavir as a boosting agent.

Use of PrOD with ritonavir-boosted darunavir resulted in an approximately 50% reduction in darunavir trough concentrations in individuals not infected with HIV or HCV. Based on this study, the prescribing information for PrOD in the United States as well as guidelines from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America do not recommend use of ritonavir-boosted darunavir with PrOD.<sup>2,3</sup>

Data from a small study indicate this combination may be acceptable for individuals taking once-daily ritonavir-boosted darunavir provided they have no darunavir-associated resistance mutations.<sup>4</sup> Twenty-two HIV/HCV-coinfected individuals receiving once-daily darunavir were randomly assigned to continue once-daily or switch to twice-daily boosted darunavir, and were then treated with 12 weeks of PrOD plus ribavirin. When used concurrently with PrOD, the median darunavir trough concentrations among those taking once- and twice-daily darunavir were 1045 ng/mL and 2590 ng/mL, respectively.<sup>5</sup> These trough concentrations are lower than historical estimates of approximately 2200 ng/mL and 3300 ng/mL with once- and twice-daily darunavir, respectively. However, the lower trough concentrations did not appear to compromise HIV suppression, as no participants required changes in their antiretroviral regimen during treatment with PrOD. Five participants had HIV RNA levels between 40 and 79 copies/mL during treatment with PrOD, but there was no

clear association between darunavir trough concentrations and these HIV “blips.”

Use of PrOD in the individual under discussion would not be advisable, as he is HIV treatment experienced and is taking twice-daily ritonavir-boosted darunavir.

### Ledipasvir/Sofosbuvir

Ledipasvir has a much lower potential for interactions with antiretroviral drugs than elbasvir/grazoprevir and PrOD, but it is not devoid of interactions. Ledipasvir does appear to undergo some metabolism by CYP3A4, as efavirenz reduces levels of ledipasvir by approximately 30%. Ledipasvir is a substrate of P-gp and an inhibitor of P-gp (eg, increasing digoxin levels), BCRP (involved in the transport of rosuvastatin), and OATP1B1/3.

Of note, absorption of ledipasvir is pH dependent. Antacid doses should be separated from ledipasvir/sofosbuvir doses by 4 hours. Doses of histamine type 2 receptor blockers should not exceed the equivalent of famotidine 40 mg twice daily. There are conflicting data on whether use of proton pump inhibitors (PPIs) with ledipasvir/sofosbuvir compromises SVR rates.<sup>6,7</sup> If possible, PPIs should be discontinued during treatment with ledipasvir/sofosbuvir. If a PPI is given concurrently with ledipasvir/sofosbuvir, only doses comparable to omeprazole 20 mg given once daily should be administered simultaneously with ledipasvir/sofosbuvir under fasted conditions.

However, the individual under discussion is not taking a PPI. This individual is receiving ritonavir-boosted darunavir and TDF, and ledipasvir/sofosbuvir may increase tenofovir levels. Increases in levels of tenofovir are observed with ledipasvir/sofosbuvir in many TDF-containing antiretroviral regimens, although increases are usually within established safety standards. However, increases in levels of tenofovir observed with ledipasvir/sofosbuvir in individuals receiving antiretroviral regimens that contain a booster (ie, ritonavir or cobicistat) may exceed those for which there are established safety data. Thus, ledipasvir/sofosbuvir likely should not be used for this individual without a change in his antiretroviral regimen or additional monitoring.

Current guidelines for HCV treatment state that concurrent use of ledipasvir/sofosbuvir and TDF should be avoided in individuals with a creatinine clearance below 60 mL/min and that use of ledipasvir/sofosbuvir with TDF and boosted antiretroviral regimens should be avoided (pending further data) unless the antiretroviral regimen cannot be changed and the urgency of treatment is high.<sup>3</sup> For individuals in whom use of TDF and a boosted antiretroviral regimen cannot be avoided,

**Table 1. Daclatasvir Dosing With Concomitant CYP3A4 Inhibitors and Inducers**

Drugs That Strongly Inhibit CYP3A (Decrease Daclatasvir Dose to 30 mg)	Drugs That Moderately Inhibit CYP3A (Standard Daclatasvir Dose of 60 mg)	Drugs That Strongly Induce CYP3A (Daclatasvir Contraindicated)	Drugs That Moderately Induce CYP3A (Increase Daclatasvir Dose to 90 mg)
<ul style="list-style-type: none"> <li>– Ritonavir-boosted atazanavir</li> <li>– Clarithromycin</li> <li>– Itraconazole</li> <li>– Ketoconazole</li> <li>– Nefazodone</li> <li>– Nelfinavir</li> <li>– Posaconazole</li> <li>– Telithromycin</li> <li>– Voriconazole</li> </ul>	<ul style="list-style-type: none"> <li>– Ritonavir-boosted darunavir</li> <li>– Ritonavir-boosted lopinavir</li> <li>– Ciprofloxacin</li> <li>– Diltiazem</li> <li>– Erythromycin</li> <li>– Fluconazole</li> <li>– Fosamprenavir</li> <li>– Verapamil</li> </ul>	<ul style="list-style-type: none"> <li>– Rifamycins</li> <li>– St John’s wort</li> <li>– Anticonvulsants</li> </ul>	<ul style="list-style-type: none"> <li>– Bosentan</li> <li>– Dexamethasone</li> <li>– Efavirenz</li> <li>– Etravirine</li> <li>– Modafinil</li> <li>– Nafcillin</li> <li>– Rifapentine</li> </ul>

Abbreviations: CYP3A, cytochrome P450 3A.

**Table 2.** Drug Classes That Can Be Used, Can Be Used With Dosing Modification, or Cannot Be Used With Hepatitis C Virus Regimens<sup>a</sup>

Drug or Drug Class	Elbasvir/ Grazoprevir	Ledipasvir/ Sofosbuvir	Paritaprevir/Ritonavir/ Ombitasvir/Dasabuvir	Sofosbuvir/ Daclatasvir	Sofosbuvir/ Velpatasvir
Methadone	✓	✓	✓	✓	✓
Analgesics	✓	✓	?	✓	✓
Anxiolytics, sedative hypnotics, benzodiazepines	✓ <sup>b</sup>	✓	Δ, x	✓	✓
Selective serotonin reuptake inhibitors	✓	✓	?	✓	✓
Oral contraceptives	✓	✓	x <sup>c</sup>	✓	✓
Immunosuppressants	✓ <sup>d</sup>	✓	Δ	✓	✓, ? <sup>e</sup>
Anticonvulsants (old)	x	x	x	x	x
Statins	Δ, x	? <sup>f</sup>	Δ, x	Δ	Δ
Calcium channel blockers	Δ, x	?	Δ	✓	✓
Amiodarone	x	x	x	x	x

<sup>a</sup>✓ Indicates lack of a clinically significant interaction; Δ indicates that a dose change or reduction may be necessary for the concomitant medication; x indicates these drugs should not be used in combination; ? indicates lack of data. Regimens listed are all coformulations.

<sup>b</sup>Midazolam given orally increased area under the concentration time curve by 34%.

<sup>c</sup>Progestin-containing only; elevations on liver function tests observed with concurrent use of ethinyl estradiol.

<sup>d</sup>Cyclosporine is not recommended; tacrolimus is acceptable.

<sup>e</sup>Cyclosporine is acceptable; data on tacrolimus are lacking.

<sup>f</sup>Rosuvastatin is not recommended; other statins have not been studied.

estimated renal function, electrolyte levels (including phosphorus), and urinary protein and glucose levels should be assessed at baseline and monitored every 2 to 4 weeks during treatment.<sup>3</sup>

In a recent study of individuals receiving a ritonavir- or cobicistat-boosted antiretroviral regimen with TDF, average estimated glomerular filtration rate (eGFR) declined slightly with the initiation of ledipasvir/sofosbuvir; however, there was no difference in eGFR between those taking TDF plus a boosted antiretroviral regimen and those taking TDF without a boosted antiretroviral regimen, and no difference between the groups at end of treatment in those with eGFRs below 70 mL/min.<sup>8</sup> Although the study includes only a small data set, it provides some reassurance that the increased tenofovir levels observed may not have a substantial clinical impact during the relatively short period of HCV treatment.

Tenofovir alafenamide (TAF) is an alternative to TDF. In the circulation, TDF is converted to tenofovir; tenofovir is a substrate of the OAT1 uptake transporter in the kidney, posing increased risk for nephrotoxic effects. In contrast, intact TAF transits directly into target cells, with only a minor amount being converted to tenofovir. Within cells, TDF and TAF are each converted to the active tenofovir diphosphate form. Because there is less systemically available tenofovir with use of TAF and because TAF is not a substrate of OAT1, there is less tenofovir interacting with the kidney and therefore a reduced risk of nephrotoxic effects. In a study of uninfected individuals given an antiretroviral regimen of TAF/emtricitabine/cobicistat-boosted elvitegravir, the addition of sofosbuvir/ledipasvir resulted in a 27% increase in tenofovir levels, but the tenofovir area under the concentration time curve (AUC) was still only 20% of that seen with TDF administration.<sup>9</sup>

### Sofosbuvir/Daclatasvir

Of the potential HCV regimens listed above, sofosbuvir/daclatasvir is the best choice for this individual, to avoid changes in antiretroviral regimen or additional monitoring. Daclatasvir is highly reliant on CYP3A for metabolism and it is also a substrate of P-gp and an inhibitor of P-gp, BCRP, and OATP1B1/3. Initial findings indicated that daclatasvir level was markedly increased when used concomitantly with ritonavir-boosted atazanavir, raising concerns over potential interactions with other ritonavir-boosted HIV PIs and suggesting the need to reduce doses of daclatasvir. However, in one study, it was found that 9 of 12 participants who experienced viral relapse were receiving ritonavir-boosted darunavir with daclatasvir 30 mg, a dose reduced from the standard 60 mg.<sup>10</sup>

In a study of HCV-uninfected individuals, daclatasvir maximum concentration when given at 60 mg was reduced by 62%, and daclatasvir AUC was reduced by 30% when given at 30 mg with ritonavir-boosted darunavir.<sup>11</sup> It is now recommended that daclatasvir be used at the full dose when concurrently used with boosted darunavir or lopinavir, but that the daclatasvir dose be decreased to 30 mg when concurrently used with boosted atazanavir.<sup>3</sup> The recommended dose of daclatasvir when used with strong or moderate CYP3A4 inhibitors or inducers is shown in Table 1.

### Sofosbuvir/Velpatasvir

Velpatasvir has pharmacologic characteristics similar to those of ledipasvir in that it exhibits pH-dependent absorption and results in increased tenofovir levels when used with TDF. Unlike ledipasvir/sofosbuvir, it is recommended that

sofosbuvir/velpatasvir be taken with food 4 hours before taking a PPI. Although tenofovir levels are increased when sofosbuvir/velpatasvir is given with TDF, the clinical significance of this increase is unknown. Fifty-six individuals who were taking TDF and a boosting agent (ritonavir or cobicistat) had no substantial changes in renal function during 12 weeks of treatment with sofosbuvir/velpatasvir in the ASTRAL-5 trial.<sup>12</sup> These data are reassuring, but all participants in the trial had good renal function. As with ledipasvir/sofosbuvir, it is recommended that use of sofosbuvir/velpatasvir be avoided with TDF and boosted antiretroviral drugs, or that renal function be monitored more frequently if coadministration cannot be avoided. Velpatasvir is more heavily reliant on CYP3A for metabolism than ledipasvir. A CYP3A inducer such as efavirenz will have a much greater effect on velpatasvir levels than it does on ledipasvir levels, for example. Thus, velpatasvir should not be used with efavirenz or other CYP3A inducers.

### Other Drug-Drug Interactions

Interactions of the HCV regimens discussed above with other classes of drugs are summarized in Table 2.<sup>13</sup> Methadone and buprenorphine do not interact with current HCV therapies. Analgesics may interact with PrOD, depending on the drug used. Anxiolytics, sedative hypnotics, and benzodiazepines may also interact with PrOD. There are few data on interactions between selective serotonin reuptake inhibitors and PrOD, but they do not appear to interact with other HCV regimens. Oral contraceptives can be used with HCV regimens; however, when used with PrOD, ethinyl estradiol-based contraceptives increased levels of liver enzymes and thus should not be used, although norethindrone-only-containing oral contraceptives are acceptable.

There are data available on how to modify doses of tacrolimus and cyclosporine in individuals receiving PrOD. These immunosuppressants can be used with ledipasvir/sofosbuvir and sofosbuvir/daclatasvir. Sofosbuvir/velpatasvir can be used with cyclosporine; however, there are currently no data on the effects of velpatasvir on tacrolimus. Levels of grazoprevir are substantially increased when coadministered with cyclosporine owing to its inhibition of CYP3A and OATP1B1 transporter.

Older anticonvulsants (eg, phenytoin, carbamazepine, or phenobarbital) are potent inducers of enzymes and drug transporters and should be avoided with all HCV regimens. Statin therapy may require dose reduction or therapeutic substitution in the case of simvastatin and lovastatin, as statins rely on CYP3A, OATP1B1, or BCRP for metabolism, and all of the HCV drugs above interact with at least 1 of these pathways. Calcium channel blockers also require adjustment or increased monitoring when used with elbasvir/grazoprevir or PrOD. Amiodarone should not be used with sobosbuvir-containing HCV regimens because of the risk of bradycardia.

### Conclusion

The most important consideration in the treatment of HIV/HCV coinfection is the potential for drug interactions. In

general, current HCV therapies have well-characterized pharmacology and manageable drug interaction profiles. A systematic approach to the identification and management of drug-drug interactions is essential. Although there are data available to inform treatment decisions, there are some interactions that should be committed to memory (more information on interactions is available from the University of Liverpool,<sup>14</sup> Toronto General Hospital,<sup>15</sup> and US Department of Health and Human Services<sup>16</sup>).

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