



## Managing Drug-Drug Interactions With Boceprevir and Telaprevir

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The treatment of chronic hepatitis C virus (HCV) genotype 1 infection has been revolutionized by the introduction of direct-acting antiviral (DAA) agents (boceprevir and telaprevir) in combination with peginterferon and ribavirin. Although improved antiviral efficacy and shorter durations of therapy are anticipated, there are also potentially severe drug-drug interactions involving protease inhibitors and other commonly used agents, and both practitioners and patients must familiarize themselves with these interactions before they use these agents.

### Drug Metabolism

The cytochrome P450s (CYPs) are a superfamily of genes composed of several isoenzymes expressed in the endoplasmic reticulum of the liver and other organs that are integrally involved in the oxidative metabolism (i.e., phase 1) of numerous drugs (Fig. 1). In particular, the CYP3A4 and CYP3A5 isoenzymes are involved in the metabolism of up to 40% of all marketed drugs.<sup>1,2</sup> In addition, the enzyme activity of CYP3A4 and CYP3A5 in the small intestine can also influence the bioavailability of some drugs. Multiple studies have demonstrated substantial interindividual variations (i.e., 4- to 10-fold) in the hepatic expression of CYP3A4; this can be explained in part by genetic polymorphisms, diet, and other environmental cofactors.<sup>3</sup> The P-glycoprotein transporter system, which is encoded by the multidrug resistance protein 2 gene and is localized in the plasma membranes of hepatocytes and enterocytes, is also involved in the elimination of various drugs and/or metabolites (i.e., phase 3). This enzyme family plays a key role in the elimination of many commonly used drugs and has also been shown to be both inducible and inhibitable like CYP3A with complex gene regulation.<sup>4</sup>

Drugs and herbal agents such as rifampin, efavirenz, and St. John's wort are known to induce the expression of CYP3A4 activity via the activation of nuclear receptors in the liver and lead to clinically significant reductions in the blood levels of cyclosporine and other CYP3A4 substrates with potentially deleterious clinical effects (Table 1).<sup>5,6</sup> Conversely, other commonly used medications such as alpha-1-adrenoreceptor antagonists and statins can competitively inhibit CYP3A4 activity.<sup>7</sup> When competitive inhibitors and substrates of CYP3A4 are coadministered, the drug levels of one or both agents may significantly increase, and this can lead to clinically significant drug-drug interactions and associated adverse events.

Both telaprevir and boceprevir are extensively metabolized in the liver and are potent CYP3A4 substrates and inhibitors. Telaprevir is also a P-glycoprotein substrate and inhibitor, whereas boceprevir is partially metabolized by hepatic aldo-keto reductase. Therefore, the coadministration of either of these agents with other drugs metabolized by CYP3A4 may lead to increased pharmacokinetic and pharmacodynamic effects of the other drugs via the competitive inhibition of their metabolism (Fig. 2). For example, the peak plasma concentration ( $C_{max}$ ) for atorvastatin was 10-fold higher when it was coadministered with telaprevir in healthy volunteers.<sup>8</sup> In addition,  $C_{max}$  for amlodipine was 1.3-fold higher when it was coadministered with telaprevir. On the basis of these results and other *in vitro* testing, the package inserts for both protease inhibitors provide lists of drugs that are absolutely contraindicated when a patient is receiving either agent because of the potential for serious or life-threatening adverse events (Table 1).<sup>8,9</sup> In addition, other drugs that are less dependent on CYP3A for elimination (e.g., amlodipine) should also be administered with caution to subjects

Abbreviations:  $C_{max}$ , peak plasma concentration; CYP, cytochrome P450; DAA, direct-acting antiviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus

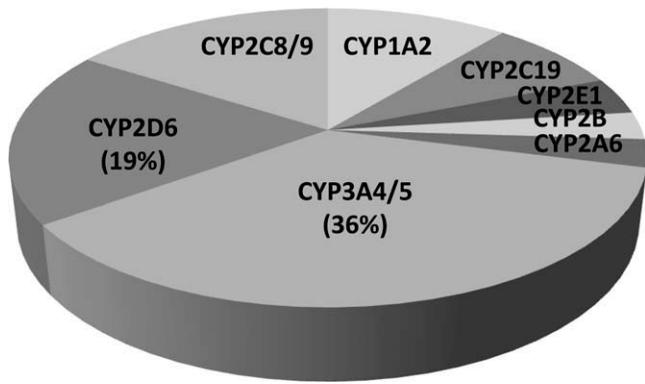
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Potential conflict of interest: Nothing to report.

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doi: 10.1002/cld.10



**FIGURE 1.** Proportions of commonly used drugs metabolized by CYP isoenzymes in the human liver.

**TABLE 1.** Drugs Absolutely Contraindicated With the Prescription of Telaprevir or Boceprevir Because of Potentially Serious Adverse Events

Drug Class	Examples	Potentially Serious or Life-Threatening Adverse Events
<b>CYP3A substrates/inhibitors</b>		
Alpha-1-adrenoreceptor antagonists	Alfuzosin	Hypotension, dizziness
Ergot derivatives	Dihydroergotamine Ergonovine Ergotamine Methylethergonovine	Peripheral vasospasm or ischemia
Gastrointestinal motility agents	Cisapride	Cardiac arrhythmia, QT prolongation
3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins)	Atorvastatin* Lovastatin Simvastatin	Myopathy, rhabdomyolysis
Neuroleptics	Pimozide	Cardiac arrhythmia
Oral contraceptives†	Drospirenone	Hyperkalemia
Phosphodiesterase type 5 enzyme inhibitors†	Sildenafil Tadalafil	Visual abnormalities, hypotension, prolonged erection, syncope
Sedatives	Midazolam Triazolam	Prolonged sedation, respiratory depression
<b>CYP3A inducers</b>		
Anticonvulsants†	Carbamazepine Phenobarbital Phenytoin	Reduced DAA levels with potentially reduced antiviral efficacy and increased drug resistance
Antimycobacterials	Rifampin	
Herbal products	St. John's wort	

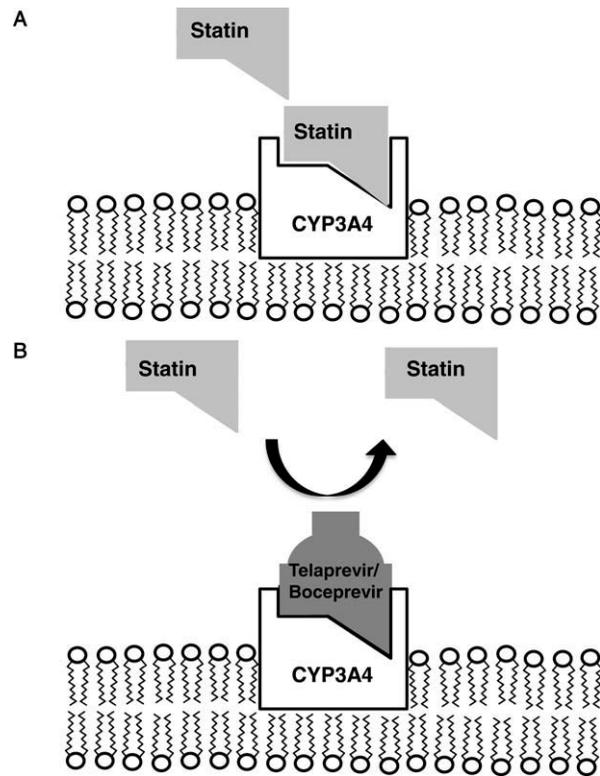
The information in this table was obtained from package inserts for boceprevir and telaprevir (February 2012).<sup>8,9</sup>

\*For telaprevir only.

†For boceprevir only.

‡Used to treat pulmonary hypertension at high doses.

receiving telaprevir or boceprevir (Table 2). Although additional prospective studies are needed in HCV patients, boceprevir-treated patients in clinical trials who received a drug metabolized by CYP3A did not have an overall increased risk of an adverse event, although anemia and dysgeusia were more frequent with selective concomitant medications.<sup>10</sup>



**FIGURE 2.** Mechanism for the competitive inhibition of CYP3A enzyme activity. (A) Many commonly used drugs such as atorvastatin have a strong binding affinity for CYP3A4, which is located in the endoplasmic reticulum of hepatocytes. In the steady state, the drug is absorbed via the gastrointestinal tract, metabolized by CYP3A4 in the liver, and eliminated from the body. (B) When a drug with a similar or greater binding affinity to CYP3A4 (e.g., telaprevir or boceprevir) is coadministered with atorvastatin, it can displace atorvastatin from CYP3A4 and lead to greater local and systemic bioavailability of the parent compound. Increased bioavailability of the drug can lead to a greater pharmacodynamic effect (e.g., hypolipidemia) as well as an increased incidence or severity of adverse events (e.g., myopathy) because of reduced drug metabolism.

The serum levels of the DAAs themselves may also be affected when they are coadministered with certain drugs (Table 3). For example, the azole antifungal agents, which are strong binders of CYP3A, are expected to lead to potentially significant elevations in the serum levels of both boceprevir and telaprevir. As a result, telaprevir-treated patients receiving one of these drugs may experience more frequent or severe rashes, myelotoxicity, or gastrointestinal symptoms. Similarly, boceprevir-treated patients may have more frequent or severe anemia and/or dysgeusia when they are receiving one of these drugs. Therefore, practitioners must advise their patients to contact them if they develop an intercurrent illness that may require treatment and to report all concomitant medications. In addition, the treating physician may preferentially select an antibiotic, analgesic, or antidepressant that is less

**TABLE 2.** Selected Drugs That Should Be Used With Caution in Subjects Receiving Boceprevir or Telaprevir Because of Altered Metabolism

Drug Class	Examples	Potential Impact
<b>CYP3A substrates</b>		
Antiarrhythmics	Amiodarone Digoxin Lidocaine Quinidine	Increased arrhythmia
Antidepressants	Escitalopram*	Decreased efficacy of antidepressant
Antidepressants	Desipramine Trazodone	Increased sedation, dry mouth
Azole antifungals	Itraconazole Ketoconazole Posaconazole	Increased vomiting, diarrhea, hypertension
Antigout agents	Colchicine	Increased diarrhea
Calcium channel blockers	Amlodipine Diltiazem Nifedipine Verapamil	Increased hypotension, bradycardia
Corticosteroids	Budesonide Fluticasone Methylprednisolone Prednisone	Increased hyperglycemia, osteoporosis, insomnia, acne
HIV protease inhibitors <sup>†</sup>	Atazanavir	Increased vomiting, diarrhea
HIV reverse transcriptase inhibitors	Tenofovir	Increased nephrotoxicity
Hormonal contraceptives	Ethinyl estradiol	Decreased efficacy
Immunosuppressants	Cyclosporine Sirolimus Tacrolimus	Increased nephrotoxicity, hypertension, neurotoxicity
Inhaled beta-agonists	Salmeterol	Increased tachycardia
Macrolide antibiotics	Clarithromycin Erythromycin Telithromycin	Increased diarrhea, QT prolongation
<b>CYP3A inducers</b>		
HIV protease inhibitors <sup>†</sup>	Atazanavir Darunavir Fosamprenavir Lopinavir	Reduced DAA levels with potentially reduced antiviral efficacy and increased drug resistance
HIV reverse transcriptase inhibitors	Efavirenz	
Narcotic analgesics	Methadone	
Sedatives	Zolpidem	

The information in this table was obtained from package inserts for boceprevir and telaprevir.<sup>8,9</sup>

\*Only reported with telaprevir.

<sup>†</sup>When coadministered with ritonavir.

**TABLE 3.** Drugs That Can Alter Serum Boceprevir and Telaprevir Levels

Drug Class	Examples	Impact on DAA Level	Potential Manifestation of Altered DAA Metabolism
<b>CYP3A substrates</b>			
Azole antifungals	Itraconazole Ketoconazole Posaconazole Voriconazole	Increase	Increased number of adverse events such as rash, myelotoxicity, and gastrointestinal side effects (telaprevir) or anemia and dysgeusia (boceprevir)
HIV protease inhibitors	Atazanavir Darunavir Fosamprenavir Lopinavir	Increase	
<b>CYP3A inducers</b>			
Anticonvulsants	Carbamazepine Phenobarbital Phenytoin	Decrease	Decreased antiviral efficacy with potential increase in drug-resistant variants
Antimycobacterials	Rifabutin	Decrease	
Corticosteroids	Dexamethasone	Decrease	
HIV reverse-transcriptase inhibitors	Efavirenz	Decrease	
HIV protease inhibitors*	Atazanavir Darunavir Fosamprenavir Lopinavir	Decrease	

The information in this table was obtained from package inserts for boceprevir and telaprevir (February 2012).<sup>8,9</sup>

\*When coadministered with ritonavir.

likely to lead to an interaction with the DAAs according to their known routes of elimination (Table 4). Similarly, subjects who receive a known CYP3A inducer such as rifampin or phenytoin may experience lower serum levels of DAAs and may have a greater risk of treatment failure and/or drug resistance (Fig. 3). Some studies have begun to explore the use of higher doses of telaprevir (i.e., 1125 mg by mouth three times a day) in human immunodeficiency virus (HIV)-coinfected patients receiving efavirenz, a CYP3A inducer, or the use of ritonavir boosting, but further studies are needed.<sup>11</sup>

## DAAs in Liver Transplant Recipients

Because of the known risk of accelerated fibrosis and graft failure from recurrent HCV infections, there is a great deal of interest in using DAAs in combination with peginterferon and ribavirin in liver transplant recipients. However, the coadministration of DAAs and calcineurin inhibitors is a very risky proposition. For example,  $C_{max}$  for a single dose of tacrolimus was 9.3-fold higher when it was coadministered with telaprevir in healthy volunteers, and the half-life was increased 5-fold.<sup>12</sup> In addition,  $C_{max}$  for cyclosporine was increased 1.4-fold in healthy volunteers, whereas the half-life was increased 3.5-fold.

Similar difficulties with immunosuppressive therapy have previously been reported for HIV-positive transplant recipients receiving antiretroviral agents that inhibit CYP3A4. For example, HIV-positive liver transplant recipients receiving the potent CYP3A inhibitors ritonavir and lopinavir required as little as 0.5 mg of tacrolimus per week to maintain therapeutic trough levels.<sup>13,14</sup> These data suggest that although DAAs are potentially dangerous, their use in liver transplant recipients with recurrent HCV on calcineurin inhibitors may



**TABLE 4.** Alternative Agents to Consider for Patients Receiving Telaprevir or Boceprevir

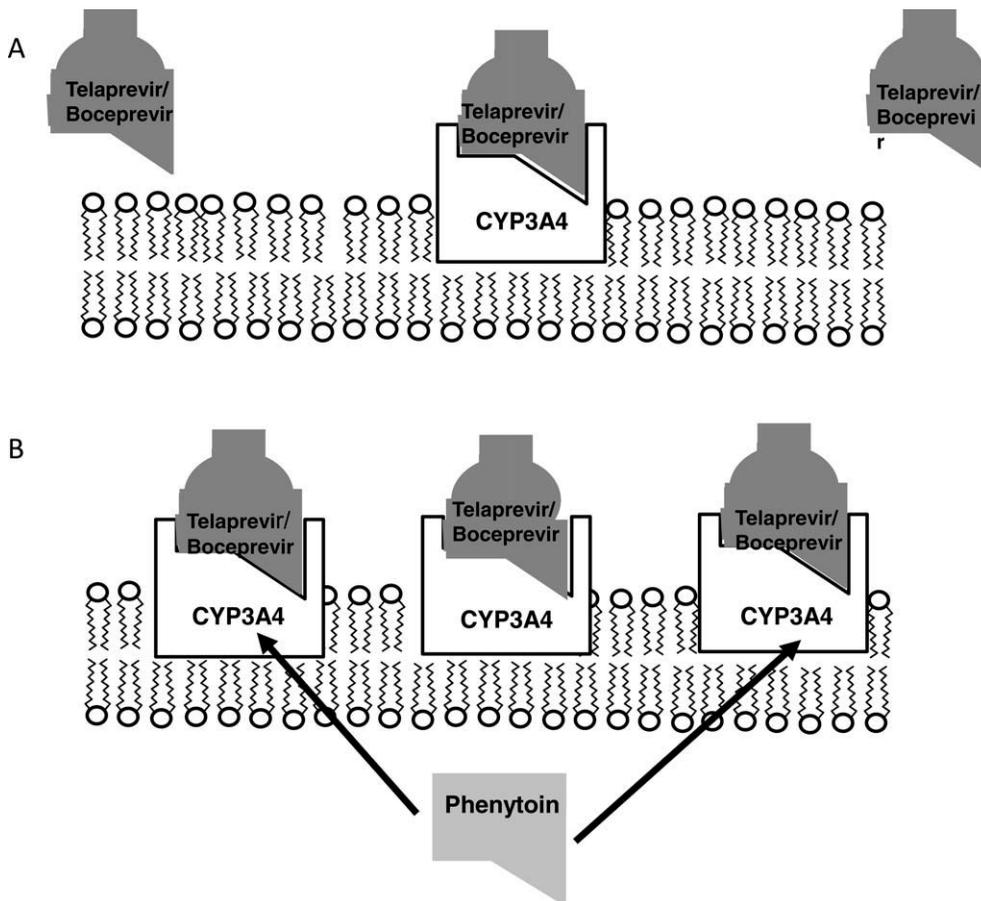
Antibiotics	Amoxicillin Cefazolin Clindamycin Trimethoprim-sulfamethoxazole Ciprofloxacin Levofloxacin Metronidazole Doxycycline
Analgesics	Acetaminophen Ibuprofen Tramadol Oxycodone
Antihypertensives	Metoprolol Hydrochlorothiazide Lisinopril Losartan
Antidepressants	Clonidine Bupropion Duloxetine
Antihistamines	Diphenhydramine Fexofenadine
Antidiabetic agents	Metformin Glipizide

The major metabolism/elimination route of these agents is not CYP3A-mediated. However, studies of prospective drug-drug interactions with DAAs in healthy volunteers and/or HCV patients have not been completed.

be possible; however, prospective safety and efficacy studies will be needed.

### Summary Recommendations

It is important that providers carefully review all medications before and during the treatment of their HCV genotype 1 patients who are receiving boceprevir or telaprevir. Furthermore, the education of patients receiving DAAs must include explicit instructions to discuss all new medications with the treating provider in a timely manner. Physicians must also remember to discontinue both contraindicated and unnecessary medications when they are initiating therapy with DAAs. A thorough knowledge of potential drug-drug interactions (or at least a quickly accessible and updated database of absolutely and relatively contraindicated drugs) will also be essential (e.g., [www.hep-druginteractions.org](http://www.hep-druginteractions.org) or [www.drug-interactions.com](http://www.drug-interactions.com)). In addition, a list of safe and effective alternative agents to be used for common ailments



**FIGURE 3.** Mechanism of CYP3A4 induction and reduced bioavailability of telaprevir/boceprevir. (A) Telaprevir and boceprevir are metabolized in hepatocytes, which have a constitutive but inducible level of CYP3A4 enzyme activity. (B) The administration of select drugs such as phenytoin and efavirenz can lead to the induction of additional CYP3A4 gene expression via the activation of intracellular nuclear receptors. This induction leads to greater amounts of CYP3A4 protein expression in the endoplasmic reticulum, which can lead to enhanced metabolism and the elimination of telaprevir or boceprevir. The net effect of CYP3A4 induction includes a potential reduction in the local and systemic bioavailability of the DAAs and a higher rate of treatment failure and drug resistance in HCV genotype 1 patients.



and side effects of antiviral therapy that are not expected to cause drug-drug interactions is needed (Table 4). Lastly, although there are multiple new DAAs under development with favorable efficacy and side-effect profiles, the metabolism and elimination of each agent by itself and in combination with other commonly used drugs will need to be deter-

mined in order to maximize patient safety and optimize clinical outcomes.

#### CORRESPONDENCE

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## References

1. Zhou S, Yung Chan S, Cher Goh B, Chan E, Duan W, Huang M, et al. Mechanism-based inhibition of cytochrome P450 3A4 by therapeutic drugs. *Clin Pharmacokinet* 2005;44:279-304.
2. Zhou S, Chan E, Lim LY, Boelsterli UA, Li SC, Wang J, et al. Therapeutic drugs that behave as mechanism-based inhibitors of cytochrome P450 3A4. *Curr Drug Metab* 2004;5:415-442.
3. Fontana RJ, Lown KS, Paine MF, Fortlage L, Santella RM, Felton JS, et al. Effects of a char-grilled meat diet on expression of CYP3A, CYP1A, and P-glycoprotein levels in healthy volunteers. *Gastroenterology* 1999;117:89-98.
4. Evans WE, McLeod HL. Pharmacogenomics—drug disposition, drug targets and side effects. *N Engl J Med* 2003;348:538.
5. Waxman DJ. P450 gene induction by structurally diverse xenochemicals: central role of nuclear receptors CAR, PXR, and PPAR. *Arch Biochem Biophys* 1999;369:11-23.
6. Leichtman A, Watkins PB. The molecular basis of cyclosporin A metabolism, pharmacokinetics, and drug interactions. *Organ Cell Transplant* 1999;2:177-182.
7. Lee JE, van Heeswijk R, Alves K, Smith F, Garg V. Effect of the hepatitis C virus protease inhibitor telaprevir on the pharmacokinetics of amlodipine and atorvastatin. *Antimicrob Agents Chemother* 2011;55:4569-4574.
8. Telaprevir [package insert]. Boston, MA: Vertex Pharmaceuticals; 2011.
9. Boceprevir [package insert]. Whitehouse Station, NJ: Merck Laboratories; 2011.
10. Poordad F, Lawitz E, Gordon SC, Bourliere M, Vierling JM, Paynard T, et al. Concomitant medication use in patients with hepatitis C genotype 1 treated with boceprevir (BOC) combination therapy [abstract]. *Hepatology* 2011;54:799-800.
11. Sherman KE, Rockstroh J, Dietrich DT, Soriano V, Girard P, McCallister S, et al. Telaprevir in combination with peginterferon alfa-2a/ribavirin in HCV/HIV coinfecting patients: 24-week treatment interim analysis [abstract]. *Hepatology* 2011;54:1431-1432.
12. Garg V, van Heeswijk R, Lee JE, Alves K, Nadkarni P, Luo X. Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. *Hepatology* 2011;54:20-27.
13. Jain AK, Venkataramanan R, Shapiro R, Scantlebury VP, Potdar S, Bonham CA, et al. The interaction between antiretroviral agents and tacrolimus in liver and kidney transplant patients. *Liver Transpl* 2002;8:841-845.
14. Jain AB, Venkataramanan R, Eghtesad B, Marcos A, Ragni M, Shapiro R, et al. Effect of coadministered lopinavir and ritonavir (Kaletra) on tacrolimus blood concentration in liver transplantation patients. *Liver Transpl* 2003;9:954-960.