

# Drug-Drug Interactions in the Treatment of HCV Among People Who Inject Drugs

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**Boceprevir and telaprevir are inhibitors and substrates of the cytochrome P450 3A4 family. With the use of these HCV protease inhibitors as part of standard therapy for chronic hepatitis C genotype 1 infection, drug-drug interactions with multiple medications being inducers, inhibitors, or substrates of cytochrome P450 3A4 can be expected. Due to the complexity of these interactions, predicting the expected magnitude and sometimes even the direction of the effect has proven to be difficult. Pharmacokinetic studies should be carried out to evaluate drugs with clinical relevance and possible interactions. This review focuses on the data available regarding drugs that are frequently used in the setting of addiction or used by patients with addiction. In addition to highlighting relevant drug-drug interactions, alternative drugs that can be safely used are suggested.**

**Keywords.** HCV; drug interactions; telaprevir; boceprevir; drugs; addiction; mental health.

Before the introduction of hepatitis C virus (HCV) protease inhibitors for the treatment of HCV drug interactions focused on additive toxicities. Interactions were most often observed in patients with human immunodeficiency virus (HIV) coinfection (eg, zidovudine and didanosine). Zidovudine may increase hemoglobin decline, leading to more frequent dose reductions in ribavirin [1]. Didanosine is associated with cases of hepatic decompensation in patients with liver cirrhosis [2]. Drug-drug interactions based on substantial changes in the metabolism of drugs are uncommon with dual therapy using pegylated interferon and ribavirin.

Telaprevir and boceprevir exhibit substantial interactions with the cytochrome P450 system, changing treatment substantially. Telaprevir and boceprevir are mainly metabolized by cytochrome P450 3A4 and simultaneously inhibits 3A4 and 3A5 isoenzymes. Boceprevir is also metabolized by the aldo-keto reductase pathway [3]. To add complexity, both drugs inhibit p-glycoprotein and telaprevir inhibits the organic anion

transporters OATP1B1 and OATP2B1, which are also involved in the uptake and excretion of drugs.

These interactions may affect all drugs metabolized by the cytochrome P450 3A isoenzymes, resulting in an extensive list of potential drug interactions (Table 1). Simeprevir and faldaprevir, which are expected to be the next generation of direct-acting antivirals against HCV, share interactions with the cytochrome P450 system as their predecessors, but to a lesser extent. The focus of this review is on drugs commonly used for and by people who inject drugs (PWID).

## BASICS OF DRUG-DRUG INTERACTIONS

Cytochrome P450 is the main enzyme system for oxidation of drugs in the gut and the liver, which is usually the first step of metabolism followed by conjugation. This process is primarily responsible for rendering drugs or other substances excretable by the kidneys or the biliary system. This process inactivates most, but not all, drugs.

Interactions may lead to a loss of efficacy, which is usually due to a decrease in trough levels or an increase in toxicity that is usually due to an increase in peak concentrations. For an interaction to be considered medically relevant, it should at least require dose adjustments. Changes in drug levels that cannot be compensated for by changes in dosage will result in a contraindication of concomitant use. The therapeutic

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**Table 1. Important Substrates, Inhibitors, and Inducers of Cytochrome P450 3A**

| Function  | Drug  |
|-----------|---|
| Substrate | Albendazole, Alprazolam, Amiodarone, Amlodipine, Amprenavir, Astemizole, Atazanavir, Atorvastatin, Betamethasone, Boceprevir, Bosentan, Bortezomib, Buprenorphin, Carbamazepine, Ciclosporine, Clarithromycin, Cyclophosphamide, Daunorubicin, Diazepam, Diltiazem, Doxepin, Doxorubicin, Efavirenz, Enalapril, Erythromycin, Escitalopram, Ethinylestradiol, Fentanyl, Imatinib, Itraconazole, Lopinavir, Maraviroc, Methadone, Midazolam, Mirtazapine, Nevirapine, Nisoldipine, Paclitaxel, Pioglitazone, Quetiapin, Rifampin, Ritonavir, saquinavir, Sildenafil, Simvastatin, Sirolimus, Tacrolimus, Terfenadin, Telaprevir, Triazolam, Voriconazole |
| Inhibitor | Amiodaron, Amitriptyline, Amlodipine, Amprenavir, Atazanavir, Boceprevir, Buprenorphin, Cimetidin, Clarithromycin, Ciclosporine, Diltiazem, Erythromycin, Fluconazole, Fluvoxamine, Fluoxetine, Grapefruit juice, Indinavir, Isoniazid, Itraconazole, Ketoconazole, Lidocaine, Lopinavir, Midazolam, Nelfinavir, Pioglitazone, Posaconazole, Ritonavir, Roxithromycin, Saquinavir, Tadalafil, Telaprevir, Verapamil, Voriconazole   |
| Inducer   | Bosentan, Carbamazepine, Dexamethasone, Efavirenz, Etravirine, Nevirapine, Phenobarbital, Phenytoin, Rifampicin, Rifabutin, St. John's wort   |

window of a drug is crucial for the magnitude of change in drug levels needed to cause an effect that is considered relevant.

This review is based on a limited number of studies of pharmacokinetic interactions and some assumptions based on known pharmacodynamic properties of drugs. It does not provide a complete review of all relevant drugs and their possible interactions; however, it does highlight potentially problematic interactions and presumably safe choices as alternative options. In general, pharmacokinetic effects of telaprevir and boceprevir point in the same direction with a smaller effect caused by boceprevir.

### ANTIDEPRESSANTS, SEDATIVES, AND ANTIPSYCHOTICS

Antidepressants, sedatives, and antipsychotics are frequently used for or by PWID. Citalopram and escitalopram are 2 of the most frequently used selective serotonin reuptake inhibitors and both are metabolized by multiple isoenzymes (CYP450 2C19, 3A4, and 2D6). The inhibition of a single isoenzyme may not appreciably decrease their clearance. Escitalopram area under the curve (AUC) was reduced approximately –35% by telaprevir and had no relevant effects on telaprevir concentration [4]. No relevant interaction with boceprevir was observed [5]. Therefore, escitalopram can be used with both HCV protease inhibitors. Due to similar degradation pathways, it is likely that citalopram can be considered safe also.

Sedatives that show a marked change in AUC and that should not be coadministered include midazolam (orally area-under-the-concentration vs time-curve, AUC +796% with telaprevir, orally AUC +430% with boceprevir) and alprazolam (AUC +35% with telaprevir) [6, 7]. In contrast, zolpidem shows a drug-level reduction when given with telaprevir (AUC –47%) and can be considered safe [7].

Pimozid is an antipsychotic with the risk of cardiac arrhythmia and a clearance via cytochrome P4503A4. It should not be coadministered with boceprevir and telaprevir. CYP3A is also involved in the metabolism of sertraline and mirtazepine. In contrast, olanzapine is metabolized by the cytochrome P4501A2 isoenzyme and, as a result, considered not to have an interaction. Fluoxetine and paroxetine are mainly metabolized by CYP2D6 and therefore considered to be safe when used with boceprevir and telaprevir.

### ANTICONSULSANTS

Older anticonvulsants such as phenytoin, carbamazepine, and phenobarbital are strong inducers of cytochrome P450 3A4 and are likely to reduce the drug levels of boceprevir and telaprevir. Newer anticonvulsants such as gabapentin, levetiracetam, and pregabalin have no involvement with the cytochrome P450 system and can be given without the risk of interactions.

### OPIOID SUBSTITUTION TREATMENT

Methadone is metabolized mainly by CYP450 3A4 and has high protein binding. Telaprevir decreased the AUC by –29% by displacing protein-bound methadone [8]; the active free methadone remains unchanged. Dose adjustment of methadone is not recommended except in individual cases. For boceprevir a reduction of methadone AUC was shown to be –22% [9]. Data from clinical studies do not suggest major interactions [10].

Buprenorphine is metabolized by CYP450 3A4 und 3A5 and an inhibitor of CYP450 3A4. Despite this profile, telaprevir reduced the AUC of buprenorphine only by –4% without a substantial effect of buprenorphine on telaprevir levels [11]. Buprenorphine AUC increased (+19%) during boceprevir treatment without clinical significance [9].

Heroin, which is a 3,6-diacetyl derivative of morphine, is metabolized mainly by CYP450 3A4 [12], and an increase in drug levels is possible. Unfortunately no pharmacokinetic data are available.

### RECREATIONAL AND ILLICIT DRUG USE

Not unexpectedly, few pharmacokinetic studies on recreation and illicit drugs have been performed. However, the practical importance among PWID is evident.

Tetrahydrocannabinol is metabolized by CYP450 2C9, 2C19, and, to a lesser extent, 3A4 [12]. Because of the multiple pathways a profound interaction is not likely. Amphetamine and ecstasy are metabolized by CYP450 3A4, CYP450 2D6, and monoamine oxidases. Because overdosing can be fatal due to hyperthermia, cardiac arrhythmia, or liver failure, a concomitant use should be avoided. The same is true for cocaine, which is hydrolyzed by multiple CYP450 enzymes, resulting in degradation and partial activation of toxic metabolites [12]. In addition, cocaine acts as an inhibitor of CYP450 2D6. Because the metabolism of cocaine is complex, the effect of concomitant use with boceprevir or telaprevir is difficult to predict and should be avoided. This is also true for “crack.” Barbiturates and benzodiazepines are generally metabolized by CYP450 3A4 and are strong inducers of CYP450 3A4. Interactions are likely to result in a significant increase in the level of barbiturates and a marked decrease in the levels of telaprevir and boceprevir.

## ANTIRETROVIRALS

Telaprevir AUC was decreased by ritonavir-boosted lopinavir by –54%, by ritonavir-boosted darunavir by –35%, by ritonavir-boosted fosamprenavir by –32%, and ritonavir-boosted atazanavir by –20% in healthy volunteers. Lopinavir AUC was unchanged by telaprevir, atazanavir AUC increased +17%, darunavir AUC decreased –40%, and fosamprenavir decreased –47% [13]. Efavirenz levels decreased –18% and telaprevir at a daily dose of 1125 mg thrice daily AUC decreased –20% compared with telaprevir at standard dose (750 mg thrice daily) without efavirenz [13]. However, data from clinical studies with HCV/HIV–coinfected patients suggest smaller decreases of telaprevir levels compared with data for healthy volunteer [14].

Etravirine reduced telaprevir AUC by –18%, with etravirine AUC remaining unchanged. Rilpivirine concentrations were significantly higher than without telaprevir: +93% for minimal concentration ( $C_{min}$ ) and +78% for 24-hour AUC [15]. With rilpivirine coadministration, telaprevir levels were not significantly changed. No interaction was observed for tenofovir and raltegravir.

Boceprevir has no interaction with tenofovir and raltegravir. In healthy volunteers coadministration with ritonavir-boosted atazanavir reduced atazanavir AUC by –35%; boceprevir remained unaffected. Darunavir AUC was reduced by –44% and lopinavir AUC was reduced by –34%, reducing boceprevir AUC by –32% and –45%, respectively. However, in a clinical study of HIV/HCV–coinfected patients, no association between HIV protease inhibitor use and breakthrough of HIV replication or failure of HCV therapy was observed [16].

Etravirine AUC decreased by –23% and boceprevir AUC increased by +10%. Efavirenz decreased boceprevir AUC –19% and  $C_{min}$  –44% with efavirenz AUC was increased +20%.

## OTHER DRUGS

Other drugs that have significant interactions with telaprevir and that may be used on occasion for patients with drug use include amlodipine (AUC +179%), atorvastatin (AUC +688%), ciclosporine (AUC +360%), digoxin (AUC +85%), and tacrolimus (AUC +6900%) [17, 18]. Boceprevir had substantial effects on tacrolimus (+1600%) and minimal effects on ciclosporine (+170%), with no substantial effect on the other drugs mentioned above [20, 21]. Attention must be paid to significant interactions with sildenafil, tadalafil, vardenafil, ethinylestradiol-containing oral contraceptives [22], grapefruit juice, and herbal compounds such as St. John’s wort and LIV 52. Esomeprazole is safe with boceprevir and telaprevir.

Extended reviews on drug–drug interactions with boceprevir and telaprevir and their management in clinical practice were recently published by Kiser et al [23] and Burger et al [24]. For additional information refer to the following: <http://www.drugs.com> and <http://www.hep-druginteractions.org>. All pharmacokinetic data without reference can be found in the prescribing information at [http://www.merck.com/product/usa/pi\\_circulars/v/victrelis/victrelis\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/v/victrelis/victrelis_pi.pdf) and [http://pi.vrtx.com/files/uspi\\_telaprevir.pdf](http://pi.vrtx.com/files/uspi_telaprevir.pdf).

## SIMEPREVIR AND FALDAPREVIR

Simeprevir (TMC435), a second-generation HCV protease inhibitor, is primarily metabolized by cytochrome P450 enzyme 3A. Therefore, significant drug interactions are likely with anti-epileptics, antituberculosis drugs, St. John’s Wort, systemic antifungals, antiarrhythmics, and antihistamines. In addition, opioid-substitution drugs such as methadone and buprenorphine, calcium channel blockers, lipid-lowering drugs, phosphodiesterase 5 inhibitors, and sedatives are likely to exhibit pharmacokinetic interactions with simeprevir.

There is limited data on drug–drug interactions with simeprevir. No relevant changes in the pharmacokinetic profiles of ethinylestradiol and norethindrone following 10 days of coadministration with simeprevir were observed in healthy female volunteers [25]. Systemic hormonal contraceptives may be considered as an effective method of contraception in combination with simeprevir.

Faldaprevir (BI201335) is a competitive inhibitor for Uridine 5′-diphospho-glucuronosyltransferase 1A1 (UGT1A1), which is the major enzyme for the conjugation of bilirubin, a moderate inhibitor of CYP450 3A4/5, and a weak inhibitor of CYP450 2C9. Interactions with some drugs that are exclusively metabolized by CYP450 3A4/5 are likely to occur. No published data on specific drug–drug interactions are available to date.

## CONCLUSION

Drug–drug interactions need to be considered when telaprevir and boceprevir are used to treat chronic HCV infection. These interactions lead to some contraindications of concomitant medications but are generally manageable during treatment. The prediction of some interactions such as the effect of concomitant use of recreational and illicit drugs have not been studied but rather rely on extrapolation from metabolic properties of the agents involved.

## Notes

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