# ART Drug-Drug Interactions

**July 2021**

## Table 3: Boosted Darunavir (DRV) Interactions
(Also see drug package inserts)

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<tr>
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| Simvastatin, lovastatin [Chauvin, et al. 2013; Feinstein, et al. 2015] | • Simvastatin and lovastatin are substrates for CYP3A4, CYP2D6, OATP1B1, and the drug transporter P-gp.  
• COBI is an inhibitor of CYP3A4, CYP2D6, OATP1B1, and P-gp.  
• Greatly increases concentrations. | • Avoid concomitant use due to potential for myopathy, including rhabdomyolysis.  
• Consider use of low doses of alternative statins less likely to be affected by boosted DRV use.  
• Avoid concomitant use due to potential for myopathy, including rhabdomyolysis.  
• Consider use of low doses of alternative statins less likely to be affected by boosted DRV use. |
• Pravastatin is an OATP1B1 substrate.  
• COBI and RTV may modestly inhibit OATP1B1.  
• Moderate increases are possible; low doses are considered safe when used with boosted PIs. | If pravastatin use is necessary, use the lowest effective dose and monitor for signs of toxicity. |
• Boosted DRV inhibits CYP3A4.  
• May moderately increase concentrations. | • Use the lowest effective dose of atorvastatin when combined with RTV-boosted DRV.  
• If concomitant use of atorvastatin and boosted DRV is necessary, monitor closely for signs of myopathy and rhabdomyolysis. |
• COBI inhibits OATP.  
• May moderately increase concentrations. | • When possible, avoid concomitant use of rosuvastatin and boosted DRV.  
• If rosuvastatin use is necessary, start with 10 mg per day. Dose should not exceed 20 mg per day. |
| Fluvastatin | Interaction has not been studied, but potential for moderate increase is possible. | Do not use, but if clinical use is desired, use the lowest effective dose; monitor closely for safety and efficacy before increasing statin dose. |
| Factor Xa inhibitors [Egan, et al. 2014] | • Boosted PIs inhibit factor Xa inhibitors via CYP3A or P-gp.  
• DRV is a minor inhibitor of CYP2C8.  
• Apixaban: Substrate of CYP2C8.  
• Warfarin: Could potentially decrease (or more rarely) increase metabolism of warfarin. | • Avoid concomitant use, or use the lowest effective dose of the factor Xa inhibitor to avoid increased bleeding risk.  
• Apixaban: Reduce apixaban dose to 2.5 mg twice per day, and if patient is already taking 2.5 mg twice per day, avoid concomitant use.  
• Dabigatran:  
  – Separate doses of dabigatran and boosted PIs by at least 2 hours. |
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<td>Antiplatelet drugs and PY2-antagonists [Egan, et al. 2014; Teng 2015]</td>
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<tr>
<td>RTV-boosted PIs may be safer than COBI boosting when using concomitant dabigatran [Kakadiya, et al. 2018]. Avoid dabigatran in patients taking boosted PIs if the patient also has severe renal impairment.</td>
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<tr>
<td>Warfarin:</td>
<td>Use cautiously with warfarin, and if use is necessary, increase monitoring of INR. Decrease dose if INR increases. Increase dose slowly if INR decreases.</td>
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<tr>
<td>Cilostazol: Metabolized by CYP3A, and boosted PIs will increase concentrations of this drug.</td>
<td>Cilostazol: Monitor for antiplatelet effect. May be necessary to use an alternative antiplatelet drug or alternative ARV agent.</td>
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<tr>
<td>Dipyridamole: RTV-boosted PIs may induce UGT enzymes, which are responsible for metabolism of dipyridamole (not seen with COBI).</td>
<td>Dipyridamole: Monitor for antiplatelet effect. Use another ARV agent or boost with COBI if necessary.</td>
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<tr>
<td>Ticagrelor: Results in increased exposure to ticagrelor.</td>
<td>Ticagrelor: Do not used with boosted PIs.</td>
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<td>Clopidogrel: Results in decreased concentration of clopidogrel’s active metabolite.</td>
<td>Clopidogrel: Do not use with boosted PIs unless an alternative antiplatelet drug (or ARV agent) cannot be used.</td>
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<tr>
<td>Atenolol</td>
<td>Eliminated via OCT2 and MATE1, which are inhibited by DTG and BIC; limited potential for atenolol levels to increase if given with these INSTIs.</td>
<td>Start at lower dose and adjust until desired clinical effect is achieved. If patient is already on atenolol but starting DTG or BIC, monitor for atenolol-related adverse events. Reduce dose of atenolol if necessary or switch to another ARV agent.</td>
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<tr>
<td>Calcium channel blockers (CCBs)</td>
<td>Boosted PIs may increase CCB concentrations by as much as 50%.</td>
<td>Decrease the original dose of CCB by as much as 50% when using with boosted PIs and slowly titrate to effect.</td>
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<tr>
<td>Eplerenone [Keating and Plosker 2004]</td>
<td>DRV inhibits the hepatic CYP3A4 isoenzyme and can increase the serum concentrations of eplerenone.</td>
<td>Avoid concomitant use to avoid increased risk of hyperkalemia and hypotension.</td>
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<tr>
<td>Antidiabetic drugs</td>
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<tr>
<td>Metformin: COBI is known to inhibit MATE1, which plays a role in the elimination of metformin, thus increasing metformin concentrations.</td>
<td>Metformin: Monitor for metformin-related adverse events and reduce dose as needed.</td>
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<tr>
<td>Glyburide: Mainly metabolized by CYP3A, and thus concentrations are increased by inhibitors of this enzyme.</td>
<td>Glyburide or alternative sulfonylureas: Use lowest effective doses with boosted PIs; monitor for signs of hypoglycemia.</td>
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<tr>
<td>Saxagliptin: Substrate of CYP3A, so levels may be increased.</td>
<td>Saxagliptin: Limit dose to 2.5 mg once per day.</td>
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<td></td>
<td>Canagliflozin: With RTV-boosted DRV and inadequate glycemic control, consider increasing dose to 300 mg per day if patient is tolerating 100 mg per day and has GFR &gt;60 mL/min/1.73 m².</td>
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<td></td>
<td>GLP-1 agonist: Consider taking DRV 4 hours before.</td>
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<td></td>
<td>TZDs: No dose adjustments necessary.</td>
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<td>Canagliflozin: Use DRV may decrease concentrations of canagliflozin.</td>
<td>• <strong>Canagliflozin</strong>: Use with DRV may decrease concentrations of canagliflozin. • <strong>GLP-1 agonists</strong>: Caution needed when coadministering DRV and GLP-1 agonists, such as exenatide, due to their potential to inhibit gastric secretion, thereby reducing the absorption of DRV. Furthermore, exenatide has the potential to slow gastric emptying. • <strong>TZDs, exenatide</strong>: No significant interactions expected.</td>
<td>Concomitant use is contraindicated unless benefits outweigh the risks; consider use of alternative ARV agents. If coadministration is necessary, monitor frequently for QT prolongation, palpitations, and sinus tachycardia. Boosted PIs may also increase QT prolongation.</td>
</tr>
<tr>
<td>Long-acting beta agonists</td>
<td>Inhibition of CYP3A increases plasma concentrations of these agents.</td>
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| Inhaled and injected corticosteroids [Daveluy, et al. 2009; Saberi, et al. 2013] | • **Boosted PIs are strong inhibitors of CYP3A and many corticosteroids are substrates of these enzymes. Risk of Cushing’s syndrome when coadministered with the following corticosteroids:**  
  − *Intranasal or inhaled*: Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone.  
  − *Systemic*: Betamethasone, budesonide, dexamethasone.  
  − *Injectable*: Betamethasone, triamcinolone. | • **Intranasal or inhaled fluticasone, mometasone, ciclesonide, budesonide, triamcinolone**: Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid, e.g., beclomethasone.  
  − This agent is less likely to be affected by boosted DRV use and thus is less likely to cause symptoms of Cushing’s syndrome and other systemic corticosteroid adverse events.  
  • **Systemic betamethasone, budesonide**: Do not coadminister unless potential benefits outweigh risk.  
  • **Systemic prednisolone, prednisone**: Contraindicated unless potential benefits outweigh risk; if use cannot be avoided, use for shortest effective duration.  
  • **Injectable betamethasone, triamcinolone**: Contraindicated unless benefits outweigh risk.  
  • **Systemic dexamethasone**: Contraindicated unless potential benefits outweigh risk; consider alternative corticosteroid. |
| Oral prednisone                    | • Prednisone is a CYP3A4 and P-gp substrate.  
  • Boosted PIs are strong inhibitors of CYP3A4 and P-gp.                                                                                      | Avoid concomitant use unless risk outweighs benefits because of increased risk of corticosteroid-related adverse events. |
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| Benzodiazepines | The following benzodiazepines are substrates of CYP3A4 and may be increased in the presence of strong inhibitors of this enzyme:  
- **Alprazolam**: Boosted ARVs may increase alprazolam concentrations via CYP3A4 inhibition.  
- **Diazepam**: Metabolism of diazepam may be reduced via inhibition of CYP3A4. | Consider alternative benzodiazepine (e.g., lorazepam, oxazepam, temazepam).  
- If used, administer lowest effective dose; monitor closely for adverse events.  
- **Diazepam**: Monitor for excess sedation. |
| Antipsychotics | **Haloperidol**: Potential for moderately increased haloperidol concentrations with boosted PIs.  
- **Aripiprazole, brexpiprazole**: RTV-boosted PIs may increase levels of aripiprazole and brexpiprazole.  
- **Risperidone**: Potential for moderate increase in risperidone levels.  
- **Clozapine**: Interaction has not been studied but may theoretically increase concentrations of clozapine, increasing risk of adverse events. | Quetiapine: Reduce dose to 1/6 if initiating ARVs in patients on stabilized quetiapine.  
- **Lurasidone**: No data; avoid coadministration; consider alternative antipsychotic or ARV agent.  
- **Haloperidol**: Monitor for QT prolongation.  
- **Aripiprazole**: Initiate at 50% of standard starting dose and titrate slowly; monitor carefully and adjust dose as necessary.  
- **Brexpiprazole**: Monitor carefully and adjust dose as necessary.  
- **Risperidone**: Initiate at low dose; titrate slowly; monitor for adverse events.  
- **Clozapine**: Monitor carefully for adverse clozapine-related events.  
- **All other antipsychotics**: Use at the lowest dose possible in patients taking boosted ARVs, and monitor carefully for adverse events. |
| HCV PIs ("-previr" drugs) [Soriano, et al. 2017] | Inhibition of CYP3A4, P-gP, and OATP1B1 by boosted PIs may increase the plasma concentrations of other PIs. | Avoid concomitant use to avoid adverse events of NS3/4A PIs. |
| Sleep medications [Kishi, et al. 2015] | The following drugs are CYP3A substrates and may be increased by strong inhibitors of this enzyme:  
- **Zolpidem, suvorexant**: Potential for increased concentrations of zolpidem and suvorexant.  
- **Ramelteon**: RTV-boosted PIs may reduce efficacy.  
- **COBI**: Inhibitor of CYP3A. | Zolpidem: Administer lowest effective dose; monitor for adverse effects, including excess sedation.  
- **Eszopiclone**: Start with 1 mg per day; titrate slowly to effect; monitor for adverse effects, including excess sedation.  
- **Suvorexant**: Coadministration is not recommended; use alternative sleep medication or ARV agent (may increase somnolence, dizziness, and risk of sleep hangover).  
- **Ramelteon**: Monitor efficacy in cigarette smokers. |
| Nonopioid pain medications | **Eletriptan**: Metabolism inhibited by boosted PIs.  
- **TCAs**: PIs and TCAs can both cause QT prolongation.  
- **Pregabalin**: No significant interactions expected. | **Eletriptan**: Do not coadminister; use alternative triptan medication.  
- **TCAs**: When using high-dose TCAs and PIs, consider monitoring for QT prolongation or other cardiac adverse events or using alternative medications. |
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<td>Omeprazole</td>
<td>No significant interactions noted.</td>
<td>Do not exceed omeprazole 40 mg per day.</td>
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<tr>
<td>Trazadone</td>
<td>May increase trazodone concentrations.</td>
<td>Monitor antidepressant and/or sedative effects.</td>
</tr>
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| Carbazepine, oxcarbazepine, phenobarbital, phenytoin | Coadministration may significantly reduce concentrations of ARV agents through induction of CYP450 system. | • **Coadministration is not recommended; use alternative anticonvulsant.**  
  - If benefit of use outweighs risk, monitor carefully for efficacy and toxicity.  
  - Perform therapeutic drug monitoring. |
| Zonisamide    | Zonisamide concentrations may be increased through CYP3A4 inhibition. | Monitor efficacy and adverse effects; adjust dose as needed. |
| Opioid analgesics | Complex mechanisms of metabolism and the formation of both active and inactive metabolites create interactions of unclear significance between these drugs and boosted PIs. | Monitor for signs of opiate toxicity and analgesic effect and dose these analgesics accordingly. |
| Tramadol      | Tramadol exposure is increased with inhibition of CYP3A, but this reduces conversion to the more potent active metabolite seen when tramadol is metabolized by CYP2D6. | When tramadol is given with COBI or RTV, monitoring for tramadol-related side effects and for the analgesic effect may be required as clinically indicated; adjust tramadol dosage if needed. |
| Hormonal contraceptives | • **RTV-boosted:** Combination appears to decrease oral norethindrone concentrations.  
  • **COBI-boosted:** Combination has not been studied, but since COBI does not induce glucuronidation, it is expected to increase concentration of norethindrone. | **Norethindrone:** Consider alternative or additional contraceptive method or alternative ARV agent. |
| Erectile and sexual dysfunction agents | • **PDE5 inhibitor:** Increased PDE5 inhibitor concentrations expected.  
  • **Flibanserin:** Increased flibanserin concentrations expected. | **Sildenafil:** Start with 25 mg every 48 hours; monitor for adverse effects.  
  **Tadalafil:** Start with 5 mg; do not exceed 10 mg every 72 hours; monitor for adverse effects.  
  **Vardenafil:** Administer 2.5 mg every 72 hours; monitor for adverse effects.  
  **Avanafil:** Do not coadminister.  
  **Flibanserin:** Do not coadminister. |
| Methadone, buprenorphine (BUP), naloxone (NLX), and naltrexone | • **RTV-boosted:** May greatly increase BUP concentrations, but the clinical significance of this is unknown because dosing of BUP is based on clinical opiate withdrawal scale.  
  • **RTV-boosted, taken twice per day:** May reduce methadone concentrations. | • **RTV-boosted:** Monitor BUP for signs of increased opioid toxicity, including sedation, impaired cognition, and respiratory distress.  
  • **RTV-boosted, taken twice per day:** Monitor methadone for signs of opiate withdrawal and increase dose of methadone if necessary.  
  • **COBI-boosted:**  
    - Use careful dose titration when giving BUP/NLX with COBI-boosted ARV. |
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| • **COBI-boosted:** | - May increase BUP concentrations while decreasing NLX concentrations when given with sublingual BUP/NLX.  
- COBI does not appear to have any significant effect on the concentration of methadone. | - Based on efficacy and safety, initiate methadone at lowest possible dose and monitor for signs and symptoms of opiate withdrawal and titrate dose to effect. |
| Immunosuppressants | • **Everolimus, sirolimus:** Metabolism decreased by boosted PIs.  
• **Cyclosporine, tacrolimus:** Metabolism decreased by boosted PIs. | • **Everolimus, sirolimus:** Do not use with boosted PIs.  
• **Cyclosporine, tacrolimus:** Dose based upon therapeutic drug monitoring.  
- Monitor closely for adverse events. |
| Rifabutin, rifampin, rifapentine | • **Rifabutin:** Does not affect levels of boosted PIs, but when used concomitantly, bioavailability of rifabutin and its active metabolite is increased.  
• **Rifampin, rifapentine:** Induction of CYP3A reduces bioavailability of ALL protease inhibitors. | • **Rifabutin:** When used concomitantly, reduce rifabutin dose to 150 mg 3 times per week.  
• **Rifampin, rifapentine:** Concomitant use of PIs and rifampin or rifapentine is contraindicated. |

**Abbreviations:** ARV, antiretroviral; BIC, bictegravir; BUP, buprenorphine; COBI, cobicistat; CYP, cytochrome P450; DTG, dolutegravir; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; HCV, hepatitis C virus; INR, international normalized ratio; INSTI: integrase strand transfer inhibitor; MATE, multidrug and toxin extrusion; NLX, naloxone; NS3/4A, nonstructural protein 3/4A; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir; TCA, tricyclic antidepressant; UGT, uridine diphosphate glucuronosyltransferase.

**No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 15); acid-reducing agents (Table 21); polyvalent cations (Table 22); asthma and allergy medications (Table 23); tobacco and smoking cessation products (Table 35); alcohol, disulfiram, and acamprosate (Table 36); gender-affirming hormones (Table 40).

**References**


