Resource: ART Drug-Drug Interactions

April 2023

Table 4: Boosted Darunavir (DRV) Interactions (also see drug package inserts)

Class or Drug	Mechanism of Action	Clinical Comments
Simvastatin, lovastatin [Feinstein, et al. 2015; Chauvin, et al. 2013]	• Simvastatin and lovastatin are substrates for CYP3A4, CYP2D6, OATP1B1, and drug transporter P-gP; boosted DRV greatly increases concentrations. • COBI inhibits CYP3A4, CYP2D6, OATP1B1, and P-gP.	• Concomitant use is contraindicated due to potential for myopathy, including rhabdomyolysis. • Consider using low doses of alternative statins less likely to be affected by boosted DRV.
Pravastatin [Kellick, et al. 2014; Aquilante, et al. 2012]	• When combined with DRV, pravastatin levels are significantly increased. • Pravastatin is an OATP1B1 substrate. • COBI and RTV may modestly inhibit OATP1B1. • Although moderate increases are possible, low doses are considered safe when used with boosted PIs.	If use is necessary, use lowest effective dose and monitor for signs of toxicity.
Atorvastatin [McKeage, et al. 2009]	• Atorvastatin is a substrate for CYP3A4. • Boosted DRV inhibits CYP3A4. • Boosted DRV may moderately increase concentrations.	• When administered with RTV-boosted DRV, use lowest effective dose; do not exceed 20 mg daily. • If concomitant use is necessary, monitor closely for signs of myopathy and rhabdomyolysis.
Pitavastatin	• Boosted DRV is less likely to interact compared to other statins. • When administered with RTV-boosted DRV, pitavastatin AUC is decreased by 26%.	No dose adjustments are necessary.
Rosuvastatin [Custodio, et al. 2014; Samineni, et al. 2012]	• Rosuvastatin is a substrate of OATP1B1 and OATP1B3. • COBI inhibits OATP. • Boosted DRV may moderately increase concentrations.	• When possible, avoid concomitant use. • If 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 coadminister. If use is required, use lowest effective dose; monitor closely for safety and efficacy before increasing statin dose.
Anticoagulants, factor Xa inhibitors [Egan, et al. 2014]	• Boosted PIs inhibit most factor Xa inhibitors (except dabigatran) via CYP3A or P-gP. • ATV is a minor inhibitor of CYP2C8. • RTV and COBI inhibit P-gP. • **Apixaban** is a substrate of CYP2C8. • **Dabigatran** is a substrate of P-gP. • **Warfarin:** Metabolism of warfarin could potentially decrease (or more rarely) increase. • **Rivaroxaban, dabigatran, apixaban:** Concentrations may increase, increasing bleeding risk.	• **Avoid concomitant use** or use lowest effective dose of factor Xa inhibitor to avoid increased bleeding risk. • **Apixaban:** Reduce apixaban dose to 2.5 mg twice per day; 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. – RTV boosting of PIs may be safer than COBI boosting with concomitant dabigatran [Kakadiya, et al. 2018]. – Avoid dabigatran in patients with renal impairment (CrCl <50 mL/min) who are taking boosted PIs.

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		• **Edoxaban:** – For stroke prevention in patients with nonvalvular atrial fibrillation: No dose adjustments are necessary. – For patients with DVT and PE: Administer edoxaban 30 mg once daily. • **Rivaroxaban:** Do not coadminister. • **Warfarin:** Use cautiously with warfarin; if use is necessary, increase INR monitoring. – If INR increases, decrease warfarin dose. – If INR decreases, increase warfarin dose slowly.
Antiplatelet drugs and PY2-antagonists [Teng 2015; Egan, et al. 2014]	• **Cilostazol** is metabolized by CYP3A; thus, boosted PIs will increase concentrations of this drug. • **Dipyridamole:** RTV-boosted PIs may induce UGT enzymes, which are responsible for metabolism of dipyridamole (not seen with COBI). • **Ticagrelor:** Strong CYP3A4 inhibitors may increase ticagrelor exposure. • **Clopidogrel:** Boosted DRV may decrease production of clopidogrel's active metabolite. • **Prasugrel:** Boosted DRV may decrease prasugrel's active metabolite; however, adequate antiplatelet activity is maintained. • **Vorapaxar:** Increased vorapaxar levels are expected.	• **Cilostazol:** Monitor for antiplatelet effect; may be necessary to use alternative antiplatelet drug or alternative ARV. • **Dipyridamole:** Monitor for antiplatelet effect; use alternative ARV or boost with COBI if necessary. • **Ticagrelor:** To avoid increased bleeding risk, do not use ticagrelor with strong CYP3A inhibitors, particularly COBI and RTV. • **Clopidogrel, vorapaxar:** Do not coadminister. • **Prasugrel:** No dose adjustments are necessary.
Alpha-adrenergic antagonists for benign prostatic hyperplasia	DRV boosted with COBI or RTV inhibits CYP3A4 and other transporters.	• **Alfuzosin, silodosin:** Concomitant use is contraindicated. • **Doxazosin, terazosin:** PIs may be used concurrently; potential increases in doxazosin and terazosin levels are possible. Dose reduction may be necessary. • **Tamsulosin:** Avoid unless benefits outweigh risk. If used together, monitor for tamsulosin-associated adverse effects, such as hypotension.
Aliskiren	Boosted PIs inhibit P-gP, which may decrease aliskiren elimination, increasing risk of adverse effects.	Do not coadminister.
Atenolol	• COBI-boosted PIs may increase atenolol via inhibition of MATE1 elimination. • Similar interaction is not seen with RTV-boosted PIs.	• Start at lowest possible dose and titrate slowly to achieve clinical effect while monitoring for adverse effects. • If patient is already using atenolol but starting COBI-boosted PI, monitor for atenolol-related adverse effects and reduce atenolol dose as needed. • RTV is the preferred PK booster when patient is also using atenolol.

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Calcium channel blockers (CCBs)	Boosted PIs may increase CCB concentrations by as much as 50%.	When using with boosted PIs, decrease original CCB dose by as much as 50% and titrate slowly to achieve clinical effect.
Eplerenone [Keating and Plosker 2004]	DRV inhibits hepatic CYP3A4 isoenzyme and can increase serum concentrations of eplerenone.	Avoid concomitant use to avoid increased risk of hyperkalemia and hypotension.
Antidiabetic drugs	• **Metformin:** COBI is known to inhibit MATE1, which is involved in metformin elimination, thus increasing metformin concentrations. • **Glyburide** is mainly metabolized by CYP3A; thus, concentrations are increased by inhibitors of this enzyme. • **Saxagliptin** is a substrate of CYP3A, so levels may be increased. • **Canagliflozin:** Use with DRV may decrease canagliflozin concentrations. • **GLP-1 agonists:** Caution is needed when coadministering DRV and GLP-1 agonists, such as exenatide, due to their potential to inhibit gastric secretion, thereby reducing DRV absorption. Furthermore, exenatide may slow gastric emptying. • **TZDs, exenatide:** No significant interactions are expected.	• **Metformin:** Monitor for metformin-related adverse effects; reduce dose as needed. • **Glyburide or alternative sulfonylureas:** Use lowest effective doses with boosted PIs; monitor for signs of hypoglycemia. • **Saxagliptin:** Limit dose to 2.5 mg once per day. • **Canagliflozin:** If the patient already tolerates canagliflozin 100 mg daily, increase dose to 200 mg daily. If the patient already tolerates canagliflozin 200 mg daily and requires additional glycemic control, the management strategy should be based on renal function. – In patients with eGFR ≥60 mL/min/1.73 m^2, canagliflozin dose may be increased to 300 mg daily. – In patients with eGFR <60 mL/min/1.73 m^2, consider adding another antihyperglycemic agent. • **GLP-1 agonists:** May recommend DRV dosing 4 hours before. • **TZDs:** No dose adjustments are necessary.
Long-acting beta agonists	CYP3A inhibition increases plasma concentrations of these agents.	• Concomitant use is contraindicated unless benefits outweigh risks; consider alternative ARV. • If coadministration is necessary, monitor frequently for QT prolongation, palpitations, and sinus tachycardia. • Boosted PIs may also increase QT prolongation.
Inhaled and injected corticosteroids [Saberi, et al. 2013; Daveluy, et al. 2009]	• Boosted PIs are strong inhibitors of CYP3A and many corticosteroids are substrates of these enzymes. • Risk of Cushing's syndrome occurs when boosted DRV is coadministered with following corticosteroids: – Intranasal or inhaled: Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone – Systemic: Betamethasone, budesonide, dexamethasone – Injectable: Betamethasone, triamcinolone	• **Use beclomethasone if possible.** Because this agent is less likely to be affected by boosted PIs, it is less likely to cause symptoms of Cushing's syndrome and other systemic corticosteroid adverse effects. • **Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone (intranasal or inhaled):** Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid (e.g., beclomethasone). • **Betamethasone, budesonide (systemic):** Do not coadminister unless potential benefits outweigh risk. • **Prednisolone, prednisone (systemic):** Concomitant use is contraindicated unless potential benefits outweigh risk; if use cannot be avoided, use for shortest effective duration.

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		• **Betamethasone, triamcinolone (injectable):** Concomitant use is contraindicated unless benefits outweigh risk. • **Dexamethasone (systemic):** Concomitant use is 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 effects.
Benzodiazepines	The following benzodiazepines are substrates of CYP3A and may be increased in presence of strong inhibitors of this enzyme: • **Alprazolam:** Boosted ARVs may increase alprazolam concentrations via CYP3A4 inhibition. • **Diazepam:** CYP3A4 inhibition may reduce metabolism of diazepam.	• Consider alternative benzodiazepine (e.g., lorazepam, oxazepam, temazepam). If used, administer lowest effective dose; monitor closely for adverse effects. • **Diazepam:** Monitor for excess sedation.
Antipsychotics	• **Haloperidol:** Boosted PIs may moderately increase haloperidol concentrations. • **Aripiprazole, brexpiprazole:** RTV-boosted PIs may increase aripiprazole and brexpiprazole levels. • **Risperidone:** Boosted PIs may moderately increase risperidone levels. • **Clozapine:** Interaction has not been studied but boosted DRV may theoretically increase clozapine concentrations, increasing risk of adverse effects. • **Iloperidone, lumateperone, lurasidone, cariprazine:** Levels are likely to be increased by all PIs, whether boosted or not.	• **Quetiapine:** – Patients on stabilized quetiapine: Reduce dose to 1/6 if initiating ART; monitor for QT prolongation. – Patients stabilized on boosted PI: Use lowest dose and titrate slowly to achieve clinical effect; monitor for QT prolongation. • **Lurasidone:** No data available. Avoid coadministration; consider alternative antipsychotic or ARV. • **Haloperidol:** Monitor for QT prolongation. • **Iloperidone:** Decrease iloperidone dose by 50%. • **Aripiprazole:** Initiate at 25% of standard starting dose and titrate slowly to achieve clinical effect; monitor carefully for efficacy and adjust dose as necessary. • **Brexpiprazole:** Administer at 50% of brexpiprazole dose and adjust dose as necessary. • **Lumateperone:** Do not coadminister. • **Pimozide:** Concomitant use is contraindicated. • **Risperidone:** Initiate at low dose and titrate slowly to achieve clinical effect; monitor for adverse effects. • **Ziprasidone:** Monitor for adverse effects, including QTc prolongation. • **Cariprazine:** Consult DHHS guideline for full dosing recommendations and clinical comments [DHHS 2021]. • **Clozapine:** Monitor carefully for clozapine-related adverse effects.

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HCV PIs ("-previr" drugs) [Soriano, et al. 2017]	Inhibition of CYP3A4, P-gP, and OATP1B1 by boosted PIs may increase plasma concentrations of other PIs.	Avoid concomitant use to avoid adverse effects of NS3/4A PIs.
Daclatasvir [Soriano, et al. 2017]	Boosted PIs inhibit daclatasvir metabolism via CYP3A4.	Decrease daclatasvir dose to 30 mg per day.
Sleep medications [Kishi, et al. 2015]	• COBI inhibits CYP3A. • **Suvorexant** is a substrate of CYP3A. • **Zolpidem, suvorexant:** Boosted PIs may increase zolpidem and suvorexant concentrations. • **Ramelteon:** RTV-boosted PIs may reduce ramelteon efficacy.	• **Zolpidem:** Administer lowest effective dose; monitor for adverse effects, including excess sedation. • **Eszopiclone:** Start with 1 mg per day and titrate slowly to achieve clinical effect; monitor for adverse effects, including excess sedation. • **Suvorexant:** Coadministration is not recommended (may increase somnolence, dizziness, and risk of sleep hangover); use alternative sleep medication or ARV. • **Ramelteon:** Monitor for 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 are expected.	• **Eletriptan:** Do not coadminister; use alternative triptan medication. • **TCAs:** With concomitant use of high-dose TCAs and PIs, consider monitoring for QT prolongation and other cardiac adverse effects or consider alternative medications.
Omeprazole	No clinically significant interactions reported.	Do not exceed omeprazole 40 mg per day.
Trazodone	Boosted DRV may increase trazodone concentrations.	Monitor for antidepressant and/or sedative effects.
Anticonvulsants	• **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin:** Coadministration may significantly reduce concentrations of ARVs through induction of CYP450 system. • **Zonisamide:** CYP3A4 inhibition may increase zonisamide concentrations.	• **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin:** – Coadministration is not recommended; use alternative anticonvulsant. – If benefit of use outweighs risk, monitor carefully for efficacy and toxicity. – Perform TDM. • **Zonisamide:** Monitor for efficacy and adverse effects; adjust dose as needed.
Opioid analgesics	Complex mechanisms of metabolism and 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; dose these analgesics accordingly.
Tramadol	Tramadol exposure is increased with CYP3A inhibition, but this reduces conversion to more potent active metabolite seen when tramadol is metabolized by CYP2D6.	When tramadol is given with COBI or RTV, monitoring for tramadol-related adverse effects and analgesic effect may be required as clinically indicated; adjust tramadol dose if indicated.
Hormonal contraceptives	• **RTV-boosted DRV:** Combination appears to decrease oral norethindrone concentrations. • **COBI-boosted DRV:** Combination has not been studied, but since COBI does not induce glucuronidation, it is expected to increase norethindrone concentration.	• **Norethindrone:** Consider alternative or additional contraceptive methods or alternative ARV. • **Etonogestrel:** No data available. Consider alternative or additional contraceptive methods or alternative ARV.

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Erectile and sexual dysfunction agents	• **PDE5 inhibitors:** Increased PDE5 inhibitor concentrations are expected. • **Flibanserin:** Increased flibanserin concentrations are expected	• **Sildenafil:** Start with 25 mg every 48 hours; monitor for adverse effects. • **Tadalafil:** Start with 5 mg and 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, flibanserin:** Do not coadminister.
Methadone, buprenorphine (BUP), naloxone (NLX), naltrexone	• **BUP:** RTV-boosted PIs may greatly increase BUP concentrations, but clinical significance of this effect is unknown because BUP dosing is based on Clinical Opiate Withdrawal Scale. • **BUP/NLX:** COBI-boosted DRV may increase BUP concentrations while decreasing NLX concentrations when given with sublingual BUP/NLX. • **Methadone:** – COBI does not appear to have any significant effect on methadone concentration. – RTV-boosted DRV taken twice per day may reduce methadone concentrations.	• **BUP:** When administering with RTV-boosted DRV, monitor for signs of increased opioid toxicity, including sedation, impaired cognition, and respiratory distress. • **BUP, BUP/NLX:** When administering with COBI-boosted DRV, titrate carefully to achieve clinical effect. • **Methadone:** – Based on efficacy and safety, initiate at lowest possible dose and titrate to achieve clinical effect; monitor for signs and symptoms of opiate withdrawal. – When administering with RTV-boosted DRV taken twice per day, monitor for signs of opiate withdrawal and increase methadone dose if necessary.
Immunosuppressants	**Everolimus, sirolimus, cyclosporine, tacrolimus:** Metabolism decreased by boosted PIs.	• **Everolimus, sirolimus:** Do not use with boosted DRV. • **Cyclosporine, tacrolimus:** Dose based on TDM; monitor closely for adverse effects.
Rifabutin, rifampin, rifapentine	• **Rifabutin** does not affect boosted PI levels, but when used concomitantly, bioavailability of rifabutin and its active metabolite is increased. • **Rifampin, rifapentine:** CYP3A induction reduces bioavailability of *all* PIs.	• **Rifabutin:** – RTV-boosted PIs: When used concomitantly, reduce rifabutin to 150 mg 3 times per week. – COBI-boosted PIs: Do not coadminister. • **Rifampin, rifapentine:** Concomitant use of PIs and rifampin or rifapentine is contraindicated.
COVID-19 therapeutics	• **Molnupiravir and monoclonal antibodies** do not affect CYP450, P-gP, or other drug metabolism transporters. • **Nirmatrelvir/RTV:** Inhibition of CYP3A4, P-gP, and other transporters may increase plasma concentrations of other PIs.	• **Molnupiravir, monoclonal antibodies:** Drug interactions are unlikely. • **Nirmatrelvir/RTV:** Patients on RTV- or COBI-containing regimens should continue treatment for COVID-19 and HIV as indicated without adjustment. Monitor for increased PI-related adverse effects.
Mpox treatments	• **Brincidofovir** is a substrate for OATP1B1 and OATP1B3. • **Tecovirimat** is a weak inducer of CYP3A and weak inhibitor of CYP2C8 and CYP2C19.	• **Brincidofovir:** Coadministration with PIs will likely increase brincidofovir levels. Consider avoiding concurrent PIs if possible. If unable to change PI, monitor for brincidofovir-related adverse effects, e.g., LFT elevations,

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		hyperbilirubinemia, diarrhea, or other GI adverse effects. Postpone PI dosing for at least 3 hours *after* brincidofovir administration. • **Tecovirimat** may reduce PI levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary. • **Cidofovir, VIGIV:** Drug interactions are unlikely.

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; AUC, area under the curve; BIC, bictegravir; COBI, cobicistat; CrCl, creatinine clearance; CYP, cytochrome P450; DHHS, U.S. Department of Health and Human Services; DTG, dolutegravir; DVT, deep vein thrombosis; GFR, glomerular filtration rate; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HCV, hepatitis C virus; INR, international normalized ratio; INSTI: integrase strand transfer inhibitor; LFT, liver function test; MATE, multidrug and toxin extrusion; NS3/4A, nonstructural protein 3/4A; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; PDE5, phosphodiesterase type 5; PE, pulmonary embolism; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir; TCA, tricyclic antidepressant; TDM, therapeutic drug monitoring; TZD, thiazolidinedione; UGT, uridine diphosphate glucuronosyltransferase; VIGIV, vaccinia immune globulin intravenous.

No significant interactions/no dose adjustments necessary: Common oral antibiotics (Table 19); acid-reducing agents (Table 25); polyvalent cations (Table 26); asthma and allergy medications (Table 27); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); gender-affirming hormones (Table 47).

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