Boosted Darunavir (DRV) Interactions (also see drug package inserts)		NYSDOH AI Clinical Guidelines Program | www.hivguidelines.org
Class or Drug	**Mechanism of Action**	**Clinical Comments**
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.
Pravastatin [Aquilante, et al. 2012; Kellick, et al. 2014]	• When combined with DRV, pravastatin levels are significantly increased. • 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.
Atorvastatin [McKeage, et al. 2009]	• Atorvastatin is a substrate for CYP3A4. • 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.
Rosuvastatin [Samineni, et al. 2012; Custodio, et al. 2014]	• Rosuvastatin is a substrate of OATP1B1 and OATP1B3. • 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:** 1) Separate doses of dabigatran and boosted PIs by at least 2 hours. 2) RTV-boosted PIs may be safer than COBI boosting when using concomitant dabigatran [Kakadiya, et al. 2018]. 3) Avoid dabigatran in patients taking boosted PIs if the patient also has severe renal impairment. • **Warfarin:** 1) Use cautiously with warfarin, and if use is necessary, increase monitoring of INR. 2) Decrease dose if INR increases. 3) Increase dose slowly if INR decreases.
Antiplatelet drugs and PY2-antagonists [Egan, et al. 2014; Teng 2015]	• **Cilostazol:** Metabolized by CYP3A, and 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:** Results in increased exposure to ticagrelor. • **Clopidogrel:** Results in decreased concentration of clopidogrel's active metabolite.	• **Cilostazol:** Monitor for antiplatelet effect. May be necessary to use an alternative antiplatelet drug or alternative ARV agent. • **Dipyridamole:** Monitor for antiplatelet effect. Use another ARV agent or boost with COBI if necessary. • **Ticagrelor:** Do not used with boosted PIs. • **Clopidogrel:** Do not use with boosted PIs unless an alternative antiplatelet drug (or ARV agent) cannot be used.

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Atenolol	Eliminated via OCT2 and MATE1, which are inhibited by DTG and BIC; limited potential for atenolol levels to increase if given with these INSTIs.	• 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.
Calcium channel blockers (CCBs)	Boosted PIs may increase CCB concentrations by as much as 50%.	Decrease the original dose of CCB by as much as 50% when using with boosted PIs and slowly titrate to effect.
Eplerenone [Keating and Plosker 2004]	DRV inhibits the hepatic CYP3A4 isoenzyme and can increase the 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 plays a role in the elimination of metformin, thus increasing metformin concentrations. • **Glyburide:** Mainly metabolized by CYP3A, and thus concentrations are increased by inhibitors of this enzyme. • **Saxagliptin:** Substrate of CYP3A, so levels may be increased. • **Canagliflozin:** Use with DRV may decrease concentrations of canagliflozin. • **GLP-1 agonists:** 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. • **TZDs, exenatide:** No significant interactions expected.	• **Metformin:** Monitor for metformin-related adverse events and 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:** 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 >60 mL/min/1.73 m^2. • **GLP-1 agonist:** Consider taking DRV 4 hours before. • **TZDs:** No dose adjustments necessary.
Long-acting beta agonists	Inhibition of CYP3A increases plasma concentrations of these agents.	• 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.
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:** 1) Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid, e.g., beclomethasone. 2) 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.

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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.
Benzodiazepines	• These benzodiazepines are substrates of CYP3A 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. • **Clozaril:** Monitor carefully for adverse Clozaril-related events. • All other antipsychotics should be used at the lowest dose possible in patients taking boosted ARVs, and careful monitoring for adverse events is warranted.
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.
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]	• These 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 is an 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.
Non-opioid 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.
Omeprazole	No significant interactions noted.	Do not exceed omeprazole 40 mg per day.
Trazadone	May increase trazodone concentrations.	Monitor antidepressant and/or sedative effects.

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Class or Drug	**Mechanism of Action**	**Clinical Comments**
Carbamazepine, 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 concentrations 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. • **COBI-boosted:** 1) May increase BUP concentrations while decreasing NLX concentrations when given with sublingual BUP/NLX. 2) COBI does not appear to have any significant effect on the concentration of methadone.	• **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:** 1) Use careful dose titration when giving BUP/NLX with COBI-boosted ARV. 2) 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.

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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; acid-reducing agents; polyvalent cations; asthma and allergy medications; tobacco and smoking cessation products; alcohol, disulfiram, and acamprosate.

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