



ART Drug-Drug Interactions

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| Table 2: Boosted Atazanavir (ATV) Interactions (also see drug package inserts) | | |
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| Class or Drug | Mechanism of Action | Clinical Comments |
| Proton pump inhibitors (PPIs) [Falcon and Kakuda 2008; Kiser, et al. 2008; Brooks, et al. 2017] | <ul style="list-style-type: none"> ATV requires an acidic gastric pH for absorption, and acid-reducing agents interfere with the absorption of ATV. May markedly reduce ATV concentration and AUC. | <ul style="list-style-type: none"> Do not coadminister if alternatives are possible; use alternative acid-reducing agent, or alternative PI, or boost ATV with RTV or COBI. Treatment-naïve: If use cannot be avoided, do not exceed omeprazole 20 mg per day or equivalent; administer 12 hours prior to ATV. Treatment-experienced: 1) Consult with an experienced HIV care provider or a GI specialist. 2) Administer at least 12 hours before RTV- or COBI-boosted ATV. |
| Histamine 2 receptor antagonist (H2RA) [Falcon and Kakuda 2008; Wang, et al. 2011; Brooks, et al. 2017] | <ul style="list-style-type: none"> ATV requires an acidic gastric pH for absorption, and acid-reducing agents interfere with the absorption of ATV. | <ul style="list-style-type: none"> Treatment-naïve: 1) Administer ATV 300 mg + RTV 100 mg simultaneously with, or at least 10 hours after H2RA. 2) Do not exceed famotidine 20 mg twice per day or equivalent [a] if patient is not taking TFV. 3) Do not exceed famotidine 40 mg twice per day or equivalent [a] if patient is taking TFV. Treatment-experienced: 1) In second and third trimesters of pregnancy [b], increase dose to 400 mg per day. 2) H2RA use is contraindicated if pregnant patient takes TFV + boosted ATV. 3) If patient is taking TFV, ATV is dosed at 400 mg when boosted; unboosted ATV is not recommended. 4) Give drugs at the same time, or give ATV more than 10 hours after H2RA. 5) Administer ATV 300 mg + COBI 150 mg or RTV 100 mg simultaneously with and/or ≥10 hours after dose of H2RA. H2RA dose equivalents twice per day: famotidine 20 mg (40 mg), ranitidine 150 mg (300 mg), nizatidine 150 mg (300 mg). The volume of distribution increases as duration of pregnancy increases, which damages the PK parameters of medications such as some PIs. PK boosting protects some of these PIs, but caution is required during the second and third trimesters of pregnancy to ensure adequate therapeutic concentrations. |
| Antacids [Brooks, et al. 2017] | ATV requires an acidic gastric pH for absorption, and acid-reducing agents interfere with the absorption of ATV. | Give ATV 2 hours before or 1 to 2 hours after antacids (and all buffered medications). |

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| Simvastatin, lovastatin [Chauvin, et al. 2013; Feinstein, et al. 2015] | <ul style="list-style-type: none"> • Simvastatin and lovastatin are substrates for CYP3A4, CYP2D6, OATP1B1, and the drug transporter P-gP. Greatly increases concentrations. • COBI is an inhibitor of CYP3A4, CYP2D6, OATP1B1, and P-gP. | <ul style="list-style-type: none"> • 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 ATV use. |
| Pravastatin [Kis, et al. 2013] | <ul style="list-style-type: none"> • Pravastatin is a substrate for OATP1B1. • ATV is an inhibitor for OATP1B1. | Use the lowest effective dose of pravastatin and monitor for adverse events, including myopathy and rhabdomyolysis. |
| Atorvastatin [Vildhede, et al. 2014] | <ul style="list-style-type: none"> • Atorvastatin is a substrate for CYP3A4 and OATP1B1. • Boosted ATV inhibits both CYP3A4 and OATP1B1. • May moderately increase concentrations. | <ul style="list-style-type: none"> • Use with lowest effective doses; monitor closely for safety and efficacy before increasing statin dose. • Avoid atorvastatin use when combined with COBI-boosted ATV due to an increased risk of rhabdomyolysis and myopathy. • If atorvastatin use is necessary, do not exceed dose of 20 mg per day. |
| Rosuvastatin [Busti, et al. 2008] | <ul style="list-style-type: none"> • Rosuvastatin is a substrate of OATP1B1/1B3. • ATV is an inhibitor of OATP1B1. • May moderately increase concentrations | <ul style="list-style-type: none"> • Use with lowest effective doses; monitor closely for safety and efficacy before increasing statin dose. • If rosuvastatin use is necessary, start with 10 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. |
| Pitavastatin, pravastatin | Although moderate increases are possible, low doses are considered safe when used with boosted PIs. | Use with lowest effective doses; dose adjustments are not necessary when using these statins with boosted EVG. |
| Anticoagulants, factor Xa inhibitors [Egan, et al. 2014] | <ul style="list-style-type: none"> • Boosted PIs inhibit most factor Xa inhibitors (not dabigatran) via CYP3A or P-gP. • ATV is a minor inhibitor of CYP2C8. • Apixaban is a substrate of 2C8. • Dabigatran is a P-gP substrate. • RTV and COBI are inhibitors of P-gP. • Warfarin: Could potentially decrease (or more rarely) increase metabolism of warfarin. • Rivaroxaban, dabigatran, apixaban: May increase concentrations, increasing bleeding risk. | <ul style="list-style-type: none"> • 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; 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 renal impairment (CrCl <50 ml/min). • Warfarin: Use cautiously with warfarin, and if use is necessary, increase monitoring of INR. Decrease dose if INR increases. Increase dose slowly if INR decreases. |

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| PY2-antagonists [Egan, et al. 2014; Teng 2015] | <ul style="list-style-type: none"> • Ticagrelor is rapidly metabolized by CYP3A. • May result in decreased concentrations of clopidogrel's active metabolite. | <ul style="list-style-type: none"> • To avoid increased bleeding risk, do not use ticagrelor with strong inhibitors of CYP3A. • Do not use with clopidogrel unless an alternative antiplatelet drug cannot be used. |
| Aliskiren | Boosted PIs inhibit P-gP, which may decrease aliskiren elimination, increasing risk of adverse events. | Do not coadminister. |
| Atenolol | COBI-boosted PIs may increase atenolol concentrations via inhibition of MATE-1 elimination. Similar interaction is not seen with RTV-boosted PIs. | If atenolol must be used with boosted PIs, use RTV as the PK booster. |
| Calcium channel blockers (CCBs) | Boosted PIs may increase CCB concentrations by as much as 50%. | Decrease original dose of CCB by as much as 50% when using with boosted PIs and slowly titrate to effect. |
| Anti-arrhythmic drugs [Roden, et al. 2007] | Boosted PIs inhibit anti-arrhythmic drug metabolism via CYP3A and CYP2D6. | Avoid concomitant use to avoid increased risk of QT prolongation and other adverse events of anti-arrhythmic drugs. |
| Anti-mineral corticoid (eplerenone) [Keating and Plosker 2004] | ATV inhibits the hepatic CYP3A4 isoenzyme and can increase the serum concentrations of eplerenone. | Avoid concomitant use due to increased risk of hyperkalemia and hypotension. |
| Glyburide | Drug is mainly metabolized via CYP3A, so concentrations are increased with boosted ARVs. | Use the lowest effective dose of glyburide and monitor for signs of hypoglycemia. |
| Saxagliptin | Levels may be increased via inhibition of CYP3A. | Limit dose of saxagliptin to 2.5 mg once per day. |
| Canagliflozin | Could lead to reduced canagliflozin exposure as a result of ATV's induction of UGT enzymes. | With RTV-boosted ATV and inadequate glycemic control, consider increasing dose to 300 mg per day if patient is tolerating 100 mg and has GFR >60 ml/min/1.73 m ² . |
| GLP-1 agonists | Exenatide may inhibit gastric secretion, reducing absorption of ATV. | Consider taking ATV 4 hours before exenatide. |
| Long-acting beta agonists | Inhibition of CYP3A increases plasma concentrations of these agents. | <ul style="list-style-type: none"> • Concomitant use is contraindicated unless benefits outweigh the risks; consider use of alternative ARV agent. • If coadministration is necessary, monitor frequently for QT prolongation, palpitations, and sinus tachycardia. • Boosted PIs may also increase QT prolongation. |

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| <p>Inhaled, intranasal, and injected corticosteroids [Daveluy, et al. 2009; Saberi, et al. 2013]</p> | <p>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:</p> <ul style="list-style-type: none"> • Intranasal or inhaled: Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone. • Systemic: Betamethasone, budesonide, dexamethasone. • Injectable: Betamethasone, triamcinolone. | <ul style="list-style-type: none"> • Use beclomethasone if possible. This agent is less likely to be affected by boosted ATV use; thus is less likely to cause symptoms of Cushing’s syndrome and other systemic corticosteroid adverse events. • Intranasal or inhaled fluticasone, mometasone, ciclesonide, budesonide, and triamcinolone: Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid (e.g., beclomethasone). • 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 potential benefits outweigh risk. • Systemic dexamethasone: Contraindicated unless potential benefits outweigh risk; consider alternative corticosteroid. |
| <p>Oral prednisone</p> | <ul style="list-style-type: none"> • Prednisone is a CYP3A4 and P-gp substrate. • Boosted PIs are strong inhibitors of CYP3A4 and P-gp. | <ul style="list-style-type: none"> • Short-term use is not contraindicated. • For chronic use of prednisone, careful monitoring of immune function is warranted and dose adjustment may be considered with therapeutic efficacy and adverse events. |
| <p>Benzodiazepines</p> | <ul style="list-style-type: none"> • 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. | <ul style="list-style-type: none"> • Alprazolam, clonazepam, diazepam: Consider alternative benzodiazepine (e.g., lorazepam, oxazepam, temazepam). If used, administer lowest effective dose; monitor closely for adverse events. • Diazepam: Monitor for excess sedation. |
| <p>Antipsychotics</p> | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • Quetiapine: Reduce dose to 1/6 if initiating ARVs in patients on stabilized quetiapine; monitor for QT prolongation. If initiating in patient stabilized on boosted PI, use lowest dose and titrate slowly to desired effect; monitor for QT prolongation. • Lurasidone: No data; avoid coadministration; consider alternative anti-psychotic or ARV agent. • Haloperidol: Monitor for QT prolongation. • Aripiprazole: Initiate at 50% of standard starting |

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| | studied but may theoretically increase concentrations of clozapine, increasing risk of adverse events. | dose and titrate slowly; monitor carefully and adjust dose as necessary. <ul style="list-style-type: none"> • 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. |
| HCV PIs (“-previr” drugs) [Soriano, et al. 2017] | Inhibition of CYP3A4 and OATP1B1 by ATV 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. |
| Etravirine (ETR) [Orrell, et al. 2015] | <ul style="list-style-type: none"> • ETR is a substrate and inducer of CYP3A4. • COBI is a substrate/inhibitor of CYP3A4. • ATV is a substrate and inhibitor of CYP3A4. | <ul style="list-style-type: none"> • Use with RTV-boosted ATV results in decreases in ATV exposure, but the decrease is not considered relevant; can be administered together without dose adjustments. • Due to the potential for decreased ARV efficacy, avoid use of ETR with COBI. When these drugs are given together, concentrations of COBI are decreased. • When possible, avoid concomitant use of ETR and unboosted ATV. ETR with unboosted ATV results in significant decreases in ATV exposure. |
| Sleep medications [Kishi, et al. 2015] | <ul style="list-style-type: none"> • Suvorexant: CYP3A substrate. • COBI: Inhibitor of CYP3A. • Zolpidem, suvorexant: Potential for increased concentrations of zolpidem and suvorexant. • Ramelteon: RTV-boosted PIs may reduce efficacy. | <ul style="list-style-type: none"> • 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. • Ramelteon: Monitor efficacy in cigarette smokers. |
| Non-opioid pain medications | <ul style="list-style-type: none"> • Eletriptan: Metabolism inhibited by boosted PIs. • TCAs: PIs and TCAs can both cause QT prolongation. • Pregabalin: No significant interactions expected. | <ul style="list-style-type: none"> • 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. |
| Other antiplatelet drugs | <ul style="list-style-type: none"> • 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). | <ul style="list-style-type: none"> • 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. |

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| Antidiabetic drugs | <ul style="list-style-type: none"> • 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 ATV may decrease concentrations of canagliflozin. • GLP-1 agonists: Caution needed when coadministering ATV and GLP-1 agonists, such as exenatide, due to their potential to inhibit gastric secretion, thereby reducing the absorption of ATV. Furthermore, exenatide has the potential to slow gastric emptying. • TZDs, exenatide: No significant interactions expected | <ul style="list-style-type: none"> • 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 ATV 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 m². • GLP-1 agonist: Consider taking ATV 4 hours before. • TZDs: No dose adjustments necessary. |
| Trazodone | May increase trazodone concentrations. | Monitor antidepressant and/or sedative effects. |
| Anticonvulsants | <ul style="list-style-type: none"> • Carbamazepine, oxcarbazepine, phenobarbital, and phenytoin: Coadministration may significantly reduce concentrations of ARVs through induction of CYP450 system. • Zonisamide: Zonisamide concentrations may be increased through CYP3A4 inhibition. | <ul style="list-style-type: none"> • Carbamazepine, oxcarbazepine, phenobarbital, phenytoin: 1) Coadministration is not recommended; use alternative anticonvulsant. 2) If benefit of use outweighs risk, monitor carefully for efficacy and toxicity. 3) Perform therapeutic drug monitoring. • Zonisamide: 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 | <ul style="list-style-type: none"> • Complex drug interaction potential has been described. • Drospirenone: Potential for hyperkalemia. | <ul style="list-style-type: none"> • Etonogestrel: No data; consider alternative or additional contraceptive method or alternative ARV agent. • Ethinyl estradiol; norgestimate and metabolites: Dose with at least 35 mcg (no data on other progestins). • Drospirenone: Do not coadminister. |

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| Erectile and sexual dysfunction agents | <ul style="list-style-type: none"> • PDE5 inhibitor: Increased PDE5 inhibitor concentrations expected. • Flibanserin: Increased flibanserin concentrations expected. | <ul style="list-style-type: none"> • 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) | <ul style="list-style-type: none"> • RTV-boosted PIs: May greatly increase BUP concentrations, but clinical significance of this is unknown because BUP dosing is based on clinical opiate withdrawal scale. • COBI-boosted PIs: 1) May increase BUP concentrations while decreasing NLX concentrations when given with sublingual BUP/NLX. 2) Does not appear to have any significant effect on the concentration of methadone. | <ul style="list-style-type: none"> • RTV-boosted PIs: Monitor BUP for signs of increased opioid toxicity, including sedation, impaired cognition, and respiratory distress. • COBI-boosted PIs: 1) Use careful dose titration of BUP/NLX when administering with COBI-boosted ARVs. • Methadone: Based on efficacy and safety, initiate at lowest possible dose, and monitor for signs and symptoms of opiate withdrawal, and titrate dose to effect. |
| Immunosuppressants | <ul style="list-style-type: none"> • Everolimus, sirolimus: Metabolism decreased by boosted PIs. • Cyclosporine, tacrolimus: Metabolism decreased by boosted PIs. | <ul style="list-style-type: none"> • Everolimus, sirolimus: Do not use with boosted PIs. • Cyclosporine, tacrolimus: Dose based upon therapeutic drug monitoring. • Monitor closely for adverse events. |
| Rifabutin, rifampin | <ul style="list-style-type: none"> • Rifabutin: Does not affect levels of boosted PIs, but when used concomitantly, bioavailability of rifabutin and its active metabolite is increased. • Rifampin induction of CYP3A reduces bioavailability of ALL protease inhibitors. | <ul style="list-style-type: none"> • Rifabutin: When used concomitantly, reduce rifabutin dose to 150 mg 3 times per week. • Rifampin: Concomitant use of PIs and rifampin is contraindicated. |
| <p>Abbreviations: ARV, antiretroviral; ATV, atazanavir; BUP, buprenorphine; AUC, area under the curve; COBI, cobicistat; CrCl, creatinine clearance; CYP, cytochrome P450; EVG, elvitegravir; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; HCV, hepatitis C virus; INR, international normalized ratio; MATE, multidrug and toxin extrusion; NLX, naloxone; NS3/4A, nonstructural protein 3/4A; PK, pharmacokinetic; OATP, organic anion transporting polypeptide; PDE-5, phosphodiesterase type 5; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir; TCA, tricyclic antidepressant; TFV, tenofovir; TZD, thiazolidinedione; UGT, uridine diphosphate glucuronosyltransferase.</p> <p>No significant interactions/no dose adjustments necessary: Common oral antibiotics (Table 15); drugs used as antihypertensive medicines (Table 16); asthma and allergy medications (Table 23); tobacco and smoking cessation products (Table 35); alcohol, disulfiram, and acamprosate (Table 36); gender-affirming hormones (Table 40).</p> | | |