## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

**Updated:** September 12, 2024
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This table provides information on the known or predicted interactions between protease inhibitors (PIs) and non-antiretroviral (ARV) drugs. The term "PI" refers to atazanavir (ATV) or darunavir (DRV) boosted with either ritonavir (RTV or r) or cobicistat (COBI or c). This table does not include interactions for unboosted ATV, fosamprenavir (FPV), lopinavir (LPV), nelfinavir (NFV), or tipranavir (TPV). For information regarding interactions between PIs and other ARV drugs, including dosing recommendations, refer to Tables 24c, 25a, and 25b.

Recommendations for managing particular drug interactions may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgment to select the most appropriate alternative medication.

**Note:** Unboosted ATV, FPV, LPV/r, NFV, and TPV are no longer commonly used in clinical practice in the United States and are **not** included in this table. Please refer to the U.S. Food and Drug Administration product labels for information regarding drug interactions between these PIs and concomitant medications. Information regarding these agents may also be found in archived versions of this guideline.

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Acid Reducers** | | | |
| **Antacids** | ATV/c, ATV/r | **When Given Simultaneously**<br>• ↓ ATV expected | Administer ATV at least 2 hours before or 2 hours after antacids or buffered medications. |
| **H2 Receptor Antagonists** | ATV/c, ATV/r | ↓ ATV expected | H2RA dose should not exceed a dose equivalent to famotidine 40 mg twice daily in ART-naive patients or famotidine 20 mg twice daily in ART-experienced patients.<br>Give ATV 300 mg (plus COBI 150 mg **or** RTV 100 mg) with food simultaneously with and/or ≥10 hours after the dose of H2RA. |

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|---|---|---|---|
| | | | If using TDF and H2RA in ART-experienced patients, administer ATV 400 mg plus RTV 100 mg with food simultaneously with and/or ≥10 hours after the dose of H2RA.<br>**Do not coadminister** ATV/c with TDF and H2RA in ART-experienced patients. |
| | DRV/c, DRV/r | **With Ranitidine**<br>• ↔ DRV/r | No dose adjustment needed |
| **Proton Pump Inhibitors** | ATV/c, ATV/r | **With Omeprazole 40 mg**<br>• ATV AUC ↓ 76%<br>**When Omeprazole 20 mg Is Given 12 Hours Before ATV/c or ATV/r**<br>• ATV AUC ↓ 42% | PPI dose should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naive patients.<br>PPIs should be administered at least 12 hours before ATV/c or ATV/r.<br>**Do not coadminister** in PI-experienced patients. |
| | DRV/c | ↔ PI expected | No dose adjustment needed |
| | DRV/r | ↔ DRV/r<br>Omeprazole AUC ↓ 42% | Consider alternative ARV or acid reducer. If coadministered, monitor for omeprazole effectiveness. If the patient does not experience symptomatic relief, increase the dose to no more than omeprazole 40 mg daily. |
| **Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia** | | | |
| **Alfuzosin** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ alfuzosin expected | **Contraindicated** |
| **Doxazosin** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ doxazosin possible | Initiate doxazosin at lowest dose and titrate. Monitor blood pressure. Dose reduction may be necessary. |

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| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Tamsulosin** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ tamsulosin expected | **Do not coadminister** unless benefits outweigh risks**.** If coadministered, monitor blood pressure. |
| **Terazosin** | ATV/c, ATV/r, DRV/c, DRV/r | ↔ or ↑ terazosin possible | Initiate terazosin at lowest dose and titrate. Monitor blood pressure. Dose reduction may be necessary. |
| **Silodosin** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ silodosin expected | **Contraindicated** |
| **Antibacterials—Antimycobacterials** | | | |
| **Bedaquiline** | ATV/c, ATV/r, DRV/c, DRV/r | • ↑ bedaquiline possible | **Do not coadminister** unless benefits outweigh risks. If coadministered, consider therapeutic drug monitoring and monitor for bedaquiline-related adverse effects, including hepatotoxicity and QTc prolongation. |
| **Rifabutin** | ATV/r | **Compared With Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Once Daily) Plus ATV/r**<br>• Rifabutin AUC ↑ 110% and metabolite AUC ↑ 2,101% | Recommended dose is rifabutin 150 mg once daily.<br>Monitor for antimycobacterial activity and consider therapeutic drug monitoring. Monitor for rifabutin-related adverse events, including neutropenia and uveitis.<br>PK data in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in patients with HIV than in healthy study participants. |
| | DRV/r | **Compared With Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Every Other Day) Plus DRV/r**<br>• ↔ rifabutin AUC and metabolite AUC ↑ 881% | |
| | ATV/c, DRV/c | ↑ rifabutin expected<br>↓ COBI expected | **Do not coadminister.** |

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| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Rifampin** | ATV/c, ATV/r, DRV/c, DRV/r | ↓ PI concentration by >75% | **Contraindicated.** Increasing the dose of RTV does not overcome this interaction and may increase hepatotoxicity. Increasing the COBI dose **is not recommended.** Consider rifabutin if a rifamycin is indicated. |
| **Rifapentine** | ATV/c, ATV/r, DRV/c, DRV/r | **Daily and Weekly Dosing**<br>• ↓ PI expected | **Do not coadminister.** |
| **Antibacterials—Macrolides** | | | |
| **Azithromycin** | ATV/c, ATV/r | ↑ azithromycin possible | No dose adjustment needed |
| | DRV/c, DRV/r | ↔ azithromycin expected | No dose adjustment needed |
| **Clarithromycin** | ATV/c, ATV/r, DRV/c | ↑ clarithromycin expected<br>↑ ATV/r and PI/c expected | Consider alternative ARV or azithromycin. |
| | DRV/r | DRV/r ↑ clarithromycin AUC 57%<br>RTV 500 mg twice daily ↑ clarithromycin 77% | Consider alternative ARV or azithromycin.<br>If use of clarithromycin is necessary in a patient with impaired renal function, reduce clarithromycin dose by 50% in patients with CrCl 30 to 60 mL/min. In patients with CrCl <30 mL/min, reduce clarithromycin dose by 75%.<br>Monitor for clarithromycin-related adverse events, including QTc prolongation. |
| **Erythromycin** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ erythromycin expected<br>↑ PI expected | Consider alternative ARV or use azithromycin. |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Anticoagulants** | | | |
| **Apixaban** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ apixaban expected | **Do not coadminister** in patients who require apixaban 2.5 mg twice daily.<br>**In Patients Requiring Apixaban 5 mg or 10 mg Twice Daily**<br>• Reduce apixaban dose by 50%. |
| **Dabigatran** | ATV/c, ATV/r | **With COBI 150 mg Alone**<br>• Dabigatran AUC ↑ 110% to 127%<br>**With ATV/r**<br>• ↑ dabigatran expected | **Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation in Adult Patients**<br>• CrCl >30 mL/min: no dose adjustment needed<br>• CrCl ≤30 mL/min: do not coadminister.<br>**Treatment and Reduction in the Risk of Recurrence of DVT and PE or Prophylaxis of DVT and PE Following Hip Replacement Surgery in Adult Patients**<br>• CrCl ≥50 mL/min: no dose adjustment needed<br>• CrCl <50 mL/min: do not coadminister. |
| | DRV/c, DRV/r | **With DRV/c**<br>• Single dose DRV/c: dabigatran AUC ↑ 164%<br>• After 14 days of DRV/c: dabigatran AUC ↑ 88%<br>**With DRV/r**<br>• Single dose DRV/r: dabigatran AUC ↑ 72%<br>• After 14 days of daily DRV/r: dabigatran AUC ↑ 18% | |
| **Edoxaban** | ATV/c, ATV/r, DRV/c | ↑ edoxaban expected | **Treatment of Nonvalvular Atrial Fibrillation**<br>• No dose adjustment needed<br>**Treatment of DVT and PE**<br>• Reduce edoxaban dose to 30 mg once daily. |

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| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| | DRV/r | ↑ edoxaban expected | **Treatment of Nonvalvular Atrial Fibrillation**<br>• No dose adjustment needed<br>**Treatment of DVT and PE**<br>• No dose adjustment needed |
| **Rivaroxaban** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ rivaroxaban expected | **Do not coadminister.** |
| **Warfarin** | ATV/c, DRV/c | ↑ warfarin possible | Monitor INR closely when stopping or starting PI/c or PI/r and adjust warfarin dose accordingly.<br>If switching between RTV and COBI, the effect of COBI on warfarin is not expected to be equivalent to RTV's effect on warfarin. |
| | ATV/r, DRV/r | ↓ warfarin possible | |
| **Antidepressants, Anxiolytics, and Antipsychotics**<br>Also see the Sedative/Hypnotics section below | | | |
| ***Antidepressants, Anxiolytics*** | | | |
| **Bupropion** | ATV/r, DRV/r | ↓ bupropion possible | Titrate bupropion dose based on clinical response. |
| | ATV/c, DRV/c | ↔ bupropion expected | No dose adjustment needed |
| **Buspirone** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ buspirone expected | Administer lowest dose of buspirone with caution and titrate buspirone dose based on clinical response. Dose reduction may be necessary. Monitor for buspirone-related adverse events. |
| **Desvenlafaxine** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ desvenlafaxine possible | No dose adjustment needed |

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| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Duloxetine** | ATV/c, DRV/c | ↑ duloxetine possible | No dose adjustment needed |
| | ATV/r, DRV/r | ↑ or ↓ duloxetine possible | |
| **Mirtazapine** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ mirtazapine possible | Monitor for mirtazapine-related adverse events. Mirtazapine dose reduction may be necessary. |
| **Nefazodone** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ nefazodone expected<br>↑ PI possible | Monitor for nefazodone-related adverse events and PI tolerability. |
| **Selective Serotonin Reuptake Inhibitors** (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vortioxetine) | DRV/r | Paroxetine AUC ↓ 39%<br>Sertraline AUC ↓ 49% | Titrate SSRI dose based on clinical response. |
| | ATV/c, ATV/r, DRV/c | ↑ or ↓ SSRI possible | Titrate SSRI dose using the lowest available initial or maintenance dose. |
| **Trazodone** | ATV/c, ATV/r, DRV/c, DRV/r | **RTV 200 mg Twice Daily (For 2 Days)**<br>• Trazodone ↑ AUC 240% | Administer lowest dose of trazodone and titrate dose based on clinical response. Monitor for trazodone-related adverse events, including CNS and CV adverse events. |
| **Tricyclic Antidepressants** (e.g., amitriptyline, doxepin, nortriptyline) | ATV/c, ATV/r, DRV/c, DRV/r | ↑ TCA expected | Administer lowest possible TCA dose and titrate based on clinical assessment and/or drug concentrations. Monitor for TCA-related adverse events. |
| **Venlafaxine** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ venlafaxine and O-desmethylvenlafaxine expected | Monitor for venlafaxine-related adverse events. Consider venlafaxine dose reduction. |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| ***Antipsychotics*** | | | |
| **Aripiprazole** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ aripiprazole expected | Administer 25% of the usual aripiprazole dose. Titrate dose based on clinical monitoring for effectiveness/adverse events. Refer to aripiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6-poor metabolizers. |
| **Brexpiprazole** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ brexpiprazole expected | Administer 25% of the usual brexpiprazole dose. Titrate the dose based on clinical monitoring for effectiveness/adverse events. Refer to brexpiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6-poor metabolizers. |
| **Cariprazine** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ cariprazine expected | **Starting Cariprazine in a Patient Who Is Already Receiving a PI**<br>• Administer cariprazine 1.5 mg on Day 1 and Day 3, with no dose given on Day 2. From Day 4 onward, administer cariprazine 1.5 mg daily. Dose can be increased to a maximum of cariprazine 3 mg daily. If the PI is withdrawn, cariprazine dose may need to be increased.<br>**Starting a PI in a Patient Who Is Already Receiving Cariprazine**<br>• For patients receiving cariprazine 3 mg or cariprazine 6 mg daily, reduce the dose by half. For patients taking cariprazine 4.5 mg daily, the dose should be reduced to cariprazine 1.5 mg or cariprazine 3 mg daily. For patients taking cariprazine 1.5 mg daily, change to cariprazine 1.5 mg every other day. If PI is withdrawn, the cariprazine dose may need to be increased. |

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| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Iloperidone** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ iloperidone expected | Decrease iloperidone dose by 50%. |
| **Lumateperone** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ lumateperone expected | **Do not coadminister.** |
| **Lurasidone** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ lurasidone expected | **Contraindicated** |
| **Olanzapine, Olanzapine/Samidorphan** | ATV/c, DRV/c | ↔ olanzapine expected<br>↑ samidorphan possible | No dose adjustment needed |
| | ATV/r, DRV/r | ↓ olanzapine possible | Monitor for therapeutic effectiveness of olanzapine. |
| **Other Antipsychotics**<br>**CYP3A4 and/or CYP2D6 substrates** (e.g., clozapine, perphenazine, risperidone, thioridazine) | ATV/c, ATV/r, DRV/c, DRV/r | ↑ antipsychotic possible | Titrate the antipsychotic dose using the lowest initial dose or adjust the maintenance dose accordingly. Monitor for adverse events, including QTc prolongation. |
| **Pimavanserin** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ pimavanserin expected | Reduce pimavanserin dose to 10 mg once daily. |
| **Pimozide** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ pimozide expected | **Contraindicated** |
| **Quetiapine** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ quetiapine expected | **Starting Quetiapine in a Patient Receiving a PI**<br>• Initiate quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine effectiveness and adverse events, including QTc prolongation. |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| | | | **Starting a PI in a Patient Receiving a Stable Dose of Quetiapine**<br>• Consider alternative ARV. If coadministered, reduce quetiapine dose to 1/6 of the current dose. Closely monitor for quetiapine effectiveness and adverse events, including QTc prolongation. |
| **Ziprasidone** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ ziprasidone expected | Monitor for ziprasidone-related adverse events, including QTc prolongation. |
| **Antifungals** | | | |
| **Fluconazole** | ATV/c, ATV/r, DRV/c, DRV/r | ↔ PI expected<br>↔ fluconazole expected | No dose adjustment needed |
| **Isavuconazole** | ATV/c, DRV/c | ↑ isavuconazole expected<br>↓ PI possible | **Contraindicated** |
| | ATV/r, DRV/r | ↑ isavuconazole expected<br>↓ PI possible | If coadministered, monitor isavuconazole concentrations and monitor for isavuconazole-related adverse events. Monitor for PI tolerability. |
| **Ibrexafungerp** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ ibrexafungerp expected | Reduce ibrexafungerp dose to 150 mg twice daily. |
| **Itraconazole** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ itraconazole expected<br>↑ PI expected | Itraconazole doses >200 mg/day **are not recommended** unless dosing is guided by itraconazole concentrations. |
| **Posaconazole** | ATV/r | ATV AUC ↑ 146%<br>↔ posaconazole possible | If coadministered, monitor for PI-related adverse events. |
| | ATV/c, DRV/c, DRV/r | ↑ PI expected<br>↔ posaconazole possible | |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

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|---|---|---|---|
| **Voriconazole** | ATV/c, DRV/c | No data | **Do not coadminister** voriconazole and RTV or COBI unless benefits outweigh risks. If coadministered, monitor voriconazole concentration and adjust dose accordingly. |
| | ATV/r, DRV/r | RTV 100 mg twice daily<br>↓ voriconazole AUC 39% | |
| **Antimalarials** | | | |
| **Artemether/Lumefantrine** | ATV/c, DRV/c | ↑ lumefantrine expected<br>↑ artemether possible | Clinical significance is unknown. If coadministered, monitor closely for antimalarial effectiveness and lumefantrine-related adverse events, including QTc prolongation. |
| | DRV/r | ↔ artemether expected<br>↔ DHA[a] expected<br>Lumefantrine AUC ↑ 175%<br>↔ DRV | |
| **Artesunate** | ATV/c | ↑ DHA[a] possible | Monitor for artesunate-related adverse effects. |
| | DRV/c | ↔ DHA[a] expected | No dose adjustment needed |
| | ATV/r, DRV/r | ↓ DHA[a] possible | Monitor for clinical response to artesunate. |
| **Atovaquone/Proguanil** | ATV/r, DRV/r | **With ATV/r**<br>• Atovaquone AUC ↓ 46%<br>• Proguanil AUC ↓ 41%<br>**With DRV/r**<br>• ↓ atovaquone/proguanil possible | Clinical significance is unknown. Consider alternative ARV or malaria prophylaxis. |
| | ATV/c, DRV/c | ↔ atovaquone/proguanil expected | No dose adjustment needed |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Mefloquine** | ATV/c, ATV/r, DRV/c, DRV/r | **With RTV 200 mg Twice Daily**<br>• RTV AUC ↓ 31% and $C_{min}$ ↓ 43%<br>• ↔ mefloquine<br>**With ATV (Unboosted), PI/c, or PI/r**<br>• ↑ mefloquine possible | Clinical significance is unknown. Consider alternative ARV or antimalarial drug. If coadministered, monitor for mefloquine-related adverse events, including psychiatric symptoms and QTc prolongation. Monitor virologic response. |
| **Antimigraine** | | | |
| **Ergot Derivatives** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ dihydroergotamine, ergotamine, and methylergonovine expected | **Contraindicated** |
| ***Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists*** | | | |
| **Atogepant** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ atogepant expected | Chronic migraine: **Do not coadminister.**<br>Episodic migraine: Administer atogepant at a dose of 10 mg once daily. |
| **Rimegepant** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ rimegepant expected | **Do not coadminister.** |
| **Ubrogepant** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ ubrogepant expected | **Contraindicated** |
| **Zavegepant** | ATV/r, ATV/c, DRV/c | ↑ zavegepant expected | **Do not coadminister.** |
| | DRV/r | ↔ zavegepant expected | No dose adjustment needed |

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| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| ***Serotonin 5-HT1B, 1D Receptor Agonists*** | | | |
| **Almotriptan** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ almotriptan expected | Administer single dose of almotriptan 6.25 mg. Maximum dose should not exceed 12.5 mg in a 24-hour period. |
| **Eletriptan** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ eletriptan expected | **Contraindicated** |
| **Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan, Zolmitriptan** | ATV/c, ATV/r, DRV/c, DRV/r | ↔ triptan expected | No dose adjustment needed |
| **Antiplatelets** | | | |
| **Clopidogrel** | ATV/c, ATV/r, DRV/c, DRV/r | Clopidogrel active metabolite AUC ↓ 69% in people with HIV on RTV or COBI-boosted regimens compared with healthy volunteers without HIV. Impaired platelet inhibition observed in people with HIV. | **Do not coadminister.** |
| **Prasugrel** | ATV/c, ATV/r, DRV/c, DRV/r | Prasugrel active metabolite AUC ↓ 52% in people with HIV on RTV or COBI-boosted regimens compared to healthy volunteers without HIV. Adequate platelet inhibition observed in people with HIV. | No dose adjustment needed |
| **Ticagrelor** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ ticagrelor expected | **Do not coadminister.** |
| **Vorapaxar** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ vorapaxar expected | **Do not coadminister.** |

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| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Antipneumocystis and Antitoxoplasmosis** | | | |
| **Atovaquone**<br>Oral suspension | ATV/r | ↔ atovaquone | No dose adjustment needed |
| | ATV/c, DRV/c, DRV/r | ↔ atovaquone expected | No dose adjustment needed |
| **Antiseizure** | | | |
| **Carbamazepine** | ATV/r | ↑ carbamazepine possible<br>May ↓ PI concentrations substantially | Consider alternative ARV or anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assess virologic response. Carbamazepine dose reduction may be necessary. |
| | DRV/r | Carbamazepine AUC ↑ 45%<br>↔ DRV | Monitor anticonvulsant concentration and adjust dose accordingly. |
| | ATV/c, DRV/c | ↑ carbamazepine possible<br>↓ COBI expected<br>↓ PI expected | **Contraindicated** |
| **Eslicarbazepine** | ATV/c, ATV/r, DRV/c, DRV/r | ↓ PI possible | Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor for virologic response. Consider monitoring anticonvulsant and PI concentrations. |
| **Ethosuximide** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ ethosuximide possible | Monitor for ethosuximide-related adverse events. |

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| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Lamotrigine** | ATV/r | Lamotrigine AUC ↓ 32% | A dose increase of lamotrigine may be needed; monitor lamotrigine concentration or consider alternative ARV or anticonvulsant. |
| | DRV/r | ↓ lamotrigine possible | |
| | ATV/c | No data | Monitor anticonvulsant concentration and adjust dose accordingly. |
| | DRV/c | ↔ lamotrigine expected | No dose adjustment needed. |
| **Oxcarbazepine** | ATV/c, ATV/r, DRV/c, DRV/r | ↓ PI possible | Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor for virologic response. Consider monitoring anticonvulsant and PI concentrations. |
| **Phenobarbital** | ATV/r, DRV/r | ↓ phenobarbital possible<br>↓ PI possible | Consider alternative anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assessing virologic response. |
| | ATV/c, DRV/c | ↓ COBI expected<br>↓ PI expected | **Contraindicated** |
| **Phenytoin** | ATV/r, DRV/r | ↓ phenytoin possible<br>↓ PI possible | Consider alternative anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assessing virologic response. |
| | ATV/c, DRV/c | ↓ COBI expected<br>↓ PI expected | **Contraindicated** |
| **Primidone** | ATV/c, ATV/r, DRV/c, DRV/r | ↓ PI expected | **Do not coadminister.** |
| **Valproic Acid** | ATV/c, ATV/r, DRV/c, DRV/r | ↓ or ↔ VPA possible | Monitor VPA concentrations and monitor for PI tolerability. |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Antivirals—Hepatitis C** | | | |
| **Elbasvir/Grazoprevir** | ATV/r | Elbasvir AUC ↑ 4.8-fold<br>Grazoprevir AUC ↑ 10.6-fold<br>Elbasvir ↔ ATV<br>Grazoprevir ↑ ATV AUC 43% | **Contraindicated**<br>May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition. |
| | DRV/r | Elbasvir AUC ↑ 66%<br>Grazoprevir AUC ↑ 7.5-fold<br>↔ DRV | |
| | ATV/c, DRV/c | ↑ grazoprevir expected | |
| **Glecaprevir/Pibrentasvir** | ATV/c, ATV/r | **With (ATV 300 mg Plus RTV 100 mg) Once Daily**<br>• Glecaprevir AUC ↑ 6.5-fold<br>• Pibrentasvir AUC ↑ 64% | **Contraindicated** |
| | DRV/c, DRV/r | **With (DRV 800 mg Plus RTV 100 mg) Once Daily**<br>• Glecaprevir AUC ↑ fivefold<br>• ↔ pibrentasvir | **Do not coadminister.** |
| **Ledipasvir/Sofosbuvir** | ATV/r | ATV AUC ↑ 33%<br>Ledipasvir AUC ↑ 113%<br>↔ sofosbuvir | No dose adjustment needed<br>Coadministration of ledipasvir/sofosbuvir with TDF and a PI/r results in increased exposure to TDF. The safety of the increased TDF exposure has not been established. Consider alternative HCV or ARV drugs to avoid increased risk of TDF toxicities. If coadministration is necessary, monitor for TDF-related adverse events. |
| | ATV/c, DRV/c, DRV/r | ↔ PI expected<br>↔ ledipasvir and sofosbuvir | |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Sofosbuvir/Velpatasvir** | ATV/r | ↔ ATV/r<br>↔ sofosbuvir<br>Velpatasvir AUC ↑ 2.4-fold | No dose adjustment needed |
| | DRV/r | ↔ DRV/r<br>Sofosbuvir AUC ↓ 28%<br>↔ velpatasvir | No dose adjustment needed |
| | ATV/c, DRV/c | ↔ sofosbuvir and velpatasvir expected | No dose adjustment needed |
| **Sofosbuvir/Velpatasvir/ Voxilaprevir** | ATV/c, ATV/r | **With ATV/r**<br>• Voxilaprevir AUC ↑ 4.3-fold<br>• Velpatasvir AUC ↑ 93%<br>• Sofosbuvir AUC ↑ 40% | **Do not coadminister.** |
| | DRV/c, DRV/r | **With DRV/r**<br>• Voxilaprevir AUC ↑ 2.4-fold<br>• ↔ DRV/r, velpatasvir, and sofosbuvir | No dose adjustment needed |
| **Antivirals—Miscellaneous (e.g., for CMV, Mpox)** | | | |
| **Brincidofovir** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ brincidofovir possible | Give PI dose at least 3 hours after administering brincidofovir and monitor for brincidofovir-related adverse events (i.e., elevations in ALT/AST and bilirubin and GI adverse events). |
| **Cidofovir** | ATV/c, ATV/r, DRV/c, DRV/r | ↔ cidofovir | No dose adjustment needed |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Tecovirimat** | ATV/c, ATV/r, DRV/c, DRV/r | ↔ tecovirimat | No dose adjustment needed |
| **Antivirals—SARS-CoV-2** | | | |
| **Molnupiravir** | ATV/c, ATV/r, DRV/c, DRV/r | ↔ molnupiravir | No dose adjustment needed |
| **Remdesivir** | ATV/c, ATV/r, DRV/c, DRV/r | ↔ remdesivir | No dose adjustment needed |
| **Ritonavir-Boosted Nirmatrelvir** | ATV/r, ATV/c, DRV/c, DRV/r | ↑ PI expected<br>↑ ritonavir-boosted nirmatrelvir expected | No dose adjustment needed. Monitor for increased ritonavir-boosted nirmatrelvir and PI-related adverse events. |
| **Beta-Agonists, Long-Acting Inhaled** | | | |
| **Arformoterol, Formoterol** | ATV/c, ATV/r | ↑ arformoterol possible | No dose adjustment needed |
| | DRV/c, DRV/r | ↔ arformoterol expected | No dose adjustment needed |
| **Indacaterol** | ATV/c, ATV/r, DRV/c, DRV/r | **With RTV 300 mg Twice Daily**<br>• Indacaterol AUC ↑ 1.7-fold | No dose adjustment needed in patients receiving indacaterol 75 mcg daily. |
| **Olodaterol** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ olodaterol expected | No dose adjustment needed |
| **Salmeterol** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ salmeterol possible | **Do not coadminister,** due to potential increased risk of salmeterol-related CV events. |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Cardiac Medications** | | | |
| ***Antiarrhythmics*** | | | |
| **Amiodarone** | ATV/r | ↑ amiodarone possible<br>↑ PI possible | **Contraindicated** |
| | ATV/c, DRV/c, DRV/r | ↑ amiodarone possible<br>↑ PI possible | **Do not coadminister** unless the benefits outweigh the risks. If coadministered, monitor for amiodarone-related adverse events and consider monitoring ECG and amiodarone drug concentration. |
| **Digoxin** | ATV/c, ATV/r, DRV/c, DRV/r | RTV 200 mg twice daily ↑ digoxin AUC 29% and ↑ half-life 43%<br>DRV/r ↑ digoxin AUC 36%<br>COBI ↑ digoxin $C_{max}$ 41% and ↔ AUC | Monitor digoxin concentrations. Digoxin dose may need to be decreased. Titrate initial digoxin dose. |
| **Disopyramide** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ disopyramide possible | **Do not coadminister.** |
| **Dofetilide** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ dofetilide possible | **Do not coadminister.** |
| **Dronedarone** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ dronedarone expected | **Contraindicated** |
| **Flecainide** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ flecainide possible | Consider alternative ARV or antiarrhythmic. If coadministered, monitor flecainide concentrations and for antiarrhythmic-related adverse events. |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Lidocaine** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ lidocaine possible | Consider alternative ARV or antiarrhythmic. If coadministered, monitor lidocaine concentrations and for antiarrhythmic-related adverse events. |
| **Mexiletine** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ mexiletine possible | Consider alternative ARV or antiarrhythmic. If coadministered, monitor mexiletine concentrations and for antiarrhythmic-related adverse events. |
| **Propafenone** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ propafenone possible | **Do not coadminister.** |
| **Quinidine** | ATV/r | ↑ quinidine expected | **Contraindicated** |
| | ATV/c, DRV/c, DRV/r | ↑ quinidine possible | **Do not coadminister.** |
| **Sotalol** | ATV/c, ATV/r, DRV/c, DRV/r | ↔ sotalol expected | No dose adjustment needed |
| ***Beta-Blockers*** | | | |
| **Atenolol, Labetalol** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ beta-blockers possible | No dose adjustment needed |
| **Bisoprolol, Carvedilol, Metoprolol, Nebivolol** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ beta-blockers possible | May need to decrease beta-blocker dose; adjust dose based on clinical response.<br>Consider using beta-blockers that are not metabolized by CYP2D6 enzymes (e.g., atenolol, labetalol, nadolol). |
| ***Calcium Channel Blockers*** | | | |
| **Amlodipine, Diltiazem, Felodipine, Nifedipine, Verapamil** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ dihydropyridine possible<br>↑ verapamil possible | Titrate CCB dose and monitor closely. ECG monitoring is recommended when CCB is used with ATV. |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Diltiazem** | ATV/c, ATV/r | Unboosted ATV ↑ diltiazem AUC 125%<br>Greater ↑ of diltiazem AUC is likely with ATV/c or ATV/r | Decrease diltiazem dose by at least 50%. If starting diltiazem, start with the lowest dose and titrate according to clinical response and adverse events. ECG monitoring is recommended. |
| | DRV/c, DRV/r | ↑ diltiazem possible | Titrate diltiazem dose according to clinical response and adverse events. |
| ***Cardiac—Other*** | | | |
| **Bosentan** | ATV/c, ATV/r, DRV/c, DRV/r | **With ATV (Unboosted)**<br>• ↓ ATV expected<br>**With PI/r or PI/c**<br>• ↑ bosentan expected | **Do not coadminister** bosentan and unboosted ATV.<br>**In Patients on a PI (Other Than Unboosted ATV) >10 Days**<br>• Start bosentan at 62.5 mg once daily or every other day.<br>**In Patients on Bosentan Who Require a PI (Other Than Unboosted ATV)**<br>• Stop bosentan ≥36 hours before PI initiation and restart bosentan 10 days after PI initiation at 62.5 mg once daily or every other day.<br>**When Switching Between COBI and RTV**<br>• Maintain same bosentan dose. |
| **Eplerenone** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ eplerenone expected | **Contraindicated** |
| **Ivabradine** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ ivabradine expected | **Contraindicated** |
| **Mavacamten** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ mavacamten expected | **Contraindicated** |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Ranolazine** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ ranolazine expected | **Contraindicated** |
| **Corticosteroids** | | | |
| **Beclomethasone**<br>Inhaled or intranasal | DRV/r | ↔ 17-BMP (active metabolite) AUC<br>RTV 100 mg twice daily ↑ 17-BMP AUC 2-fold | No dose adjustment needed |
| | ATV/c, ATV/r, DRV/c | ↔ 17-BMP expected | No dose adjustment needed |
| **Budesonide, Ciclesonide, Fluticasone, Mometasone**<br>Inhaled or intranasal | ATV/c, ATV/r, DRV/c, DRV/r | ↑ glucocorticoids possible<br>RTV 100 mg twice daily ↑ fluticasone AUC 350-fold | **Do not coadminister** unless the potential benefits of inhaled or intranasal corticosteroid outweigh the risks of adverse events associated with corticosteroids. Coadministration can result in adrenal insufficiency and Cushing's syndrome. Consider alternative inhaled/intranasal corticosteroid (e.g., beclomethasone). |
| **Betamethasone, Budesonide**<br>Systemic | ATV/c, ATV/r, DRV/c, DRV/r | ↑ glucocorticoids possible<br>↓ PI possible | **Do not coadminister** unless the potential benefits of systemic corticosteroid outweigh the risks of adverse events associated with systemic corticosteroids. Coadministration can result in adrenal insufficiency and Cushing's syndrome. |
| **Dexamethasone**<br>Systemic | ATV/c, ATV/r, DRV/c, DRV/r | ↑ glucocorticoids possible<br>↓ PI possible | Consider alternative corticosteroid for long-term use. If coadministration is necessary, monitor virologic response to ART. |
| **Prednisone, Prednisolone**<br>Systemic | ATV/c, ATV/r, DRV/c, DRV/r | ↑ prednisolone possible | Coadministration may be considered if the potential benefits outweigh the risks of adverse events associated with systemic corticosteroids. If coadministered, monitor for adrenal insufficiency, Cushing's syndrome, and other corticosteroid-related adverse events. |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Betamethasone, Methylprednisolone, Triamcinolone**<br>Local injections, including intra-articular, epidural, or intra-orbital | ATV/c, ATV/r, DRV/c, DRV/r | ↑ glucocorticoids expected | **Do not coadminister.** Coadministration can result in adrenal insufficiency and Cushing's syndrome. |
| **Glucose-Lowering** | | | |
| **Canagliflozin** | ATV/c, DRV/c | ↔ canagliflozin | No dose adjustment needed |
| | ATV/r, DRV/r | ↓ canagliflozin expected | If a patient is already tolerating canagliflozin 100 mg daily, increase canagliflozin dose to 200 mg daily.<br>If a patient is already tolerating canagliflozin 200 mg daily and requires additional glycemic control, management strategy is based on renal function.<br>**In Patients With eGFR ≥60 mL/min/1.73 m$^2$**<br>• Canagliflozin dose may be increased to 300 mg daily.<br>**In Patients With eGFR <60 mL/min/1.73 m$^2$**<br>• Consider adding another antihyperglycemic agent. |
| **Saxagliptin** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ saxagliptin expected | Limit saxagliptin dose to 2.5 mg once daily. |
| **Dapagliflozin/Saxagliptin** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ saxagliptin expected | **Do not coadminister.** Dapagliflozin is only available as a coformulated drug that contains 5 mg of saxagliptin. When coadministered with EVG/c, the dose of saxagliptin should not exceed 2.5 mg once daily; thus, this combination **is not recommended.** |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Herbal Products** | | | |
| **St. John's Wort** | ATV/c, ATV/r, DRV/c, DRV/r | ↓ PI expected | **Contraindicated** |
| **Hormonal Therapies—Contraceptives** | | | |
| **Injectable Contraceptives**<br>Depot MPA | ATV/c, ATV/r, DRV/c, DRV/r | ↔ expected | No dose adjustment needed |
| **Oral Contraceptives**<br>(e.g., desogestrel, drospirenone, ethinyl estradiol, levonorgestrel, norgestimate, norethindrone) | ATV/c | Drospirenone AUC ↑ 130%<br>Ethinyl estradiol AUC ↓ 22% | **Contraindicated** with drospirenone-containing hormonal contraceptive due to potential for hyperkalemia. Use alternative ARV or alternative contraceptive methods. |
| | | ↔ ethinyl estradiol AUC and $C_{min}$ ↓ 25%<br>↔ levonorgestrel | No dose adjustment needed |
| | ATV/r | Ethinyl estradiol AUC ↓ 19% and $C_{min}$ ↓ 37%<br>Norgestimate AUC ↑ 85%<br>Norethindrone AUC ↑ 51% and $C_{min}$ ↑ 67% | Oral contraceptive should contain at least 35 mcg of ethinyl estradiol.[c] |
| | | ↑ drospirenone expected<br>↔ estetrol | Clinical monitoring is recommended due to the potential for hyperkalemia. Use alternative ARV or contraceptive methods. |
| | DRV/c | Drospirenone AUC ↑ 58%<br>Ethinyl estradiol AUC ↓ 30% | Clinical monitoring is recommended due to the potential for hyperkalemia. Use alternative ARV or contraceptive methods. |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| | DRV/r | Ethinyl estradiol AUC ↓ 44% and $C_{min}$ ↓ 62%<br>Norethindrone AUC ↓ 14% and $C_{min}$ ↓ 30% | **When Used for Contraception**<br>• Consider alternative ARV or contraceptive methods. If combined, consider using an oral contraceptive with at least 35 mcg of ethinyl estradiol.<br>**When Used for Other Clinical Indications (e.g., Acne, Menstrual Cycle Regulation)**<br>• Monitor for clinical effectiveness of hormonal therapy. |
| **Subdermal Implant Contraceptives** (e.g., etonogestrel, levonorgestrel) | ATV/c, ATV/r, DRV/c, DRV/r | ↑ etonogestrel, levonorgestrel expected | No dose adjustment needed |
| **Transdermal Contraceptives** (e.g., ethinyl estradiol/norelgestromin, ethinyl estradiol/levonorgestrel) | ATV/c, ATV/r, DRV/c, DRV/r | ↓ ethinyl estradiol possible with ritonavir<br>↑ ethinyl estradiol possible with cobicistat<br>↑ norelgestromin, levonorgestrel possible | No dose adjustment needed |
| **Vaginal Ring Contraceptives** (e.g., etonogestrel/ethinyl estradiol, segesterone/ethinyl estradiol) | ATV/r | Ethinyl estradiol AUC ↓ 26%<br>Etonogestrel AUC ↑ 79% | No dose adjustment needed with etonogestrel/ethinyl estradiol vaginal rings.<br>Use alternative ARV or contraceptive methods with segesterone/ethinyl estradiol vaginal rings. |
| | ATV/c, DRV/c, DRV/r | ↓ ethinyl estradiol possible with ritonavir<br>↑ ethinyl estradiol possible with cobicistat | |
| **Emergency Contraceptives** Levonorgestrel (oral) | ATV/c, ATV/r, DRV/c, DRV/r | ↑ levonorgestrel expected | No dose adjustment needed |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Hormonal Therapies—Miscellaneous** | | | |
| **5-Alpha Reductase Inhibitors** (e.g., dutasteride, finasteride) | ATV/c, ATV/r, DRV/c, DRV/r | ↑ dutasteride possible<br>↑ finasteride possible | Adjust dutasteride dose as needed based on clinical effects. No dose adjustment needed for finasteride. |
| **Estradiol** | ATV/c, DRV/c | ↓ or ↑ estradiol possible | Adjust estradiol dose as needed based on clinical effects. |
| | ATV/r, DRV/r | ↓ estradiol possible | |
| **Goserelin, Leuprolide Acetate, Spironolactone** | ATV/c, ATV/r, DRV/c, DRV/r | ↔ goserelin, leuprolide acetate, and spironolactone expected | No dose adjustment needed |
| **Menopausal Hormone Replacement Therapy** (e.g., conjugated estrogens, drospirenone, estradiol, MPA, progesterone) | ATV/c, ATV/r, DRV/c, DRV/r | ↓ or ↑ estrogen possible with estradiol or conjugated estrogen (equine and synthetic) | Adjust estrogen dose as needed based on clinical effects. |
| | ATV/c, ATV/r, DRV/c, DRV/r | ↑ drospirenone possible<br>↑ MPA<br>↑ micronized progesterone<br>See the Hormonal Therapies—Contraceptives section for other progestin-PI interactions. | Adjust progestin/progesterone dose as needed based on clinical effects. Drospirenone is not contraindicated with ATV/c products because it is prescribed at a lower dose for menopausal HRT than products used for hormonal contraceptives. |
| **Testosterone** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ testosterone possible | Adjust testosterone dose as needed based on clinical effects. |
| **Immunosuppressants** | | | |
| **Cyclosporine, Sirolimus, Tacrolimus** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ immunosuppressant expected | Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for immunosuppressant-related adverse events. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with a specialist as necessary. |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Everolimus** | DRV/c, DRV/r | ↑ immunosuppressant expected | **Do not coadminister.** |
| | ATV/c, ATV/r | ↑ immunosuppressant expected | Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for immunosuppressant-related adverse events. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with a specialist as necessary. |
| **Lipid-Modifying** | | | |
| **Atorvastatin** | ATV/r | ↑ atorvastatin possible | Administer the lowest effective atorvastatin dose while monitoring for adverse events. |
| | ATV/c | Atorvastatin AUC ↑ 9.2-fold and $C_{max}$ ↑ 18.9-fold | **Do not coadminister.** |
| | DRV/c | Atorvastatin AUC ↑ 3.9-fold and $C_{max}$ ↑ 4.2-fold | Administer the lowest effective atorvastatin dose while monitoring for adverse events. Do not exceed 20 mg atorvastatin daily. |
| | DRV/r | DRV/r plus atorvastatin 10 mg similar to atorvastatin 40 mg administered alone | Administer the lowest effective atorvastatin dose while monitoring for adverse events. Do not exceed 20 mg atorvastatin daily. |
| **Fluvastatin** | ATV/c, DRV/c | ↑ fluvastatin expected | Administer the lowest effective fluvastatin dose while monitoring for adverse events. |
| | ATV/r, DRV/r | ↑ or ↓ fluvastatin possible | |
| **Lomitapide** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ lomitapide expected | **Contraindicated** |
| **Lovastatin** | ATV/c, ATV/r, DRV/c, DRV/r | Significant ↑ lovastatin expected | **Contraindicated** |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Pitavastatin** | ATV/c, DRV/c | No data | No dose adjustment needed. Monitor for pitavastatin-related adverse events. |
| | ATV/r, DRV/r | **With ATV/r**<br>• ↔ pitavastatin expected<br>• ↔ ATV/r expected<br>**With DRV/r**<br>• ↓ pitavastatin AUC 26%<br>• ↔ DRV/r | No dose adjustment needed |
| **Pravastatin** | ATV/c, ATV/r | No data | Administer the lowest effective pravastatin dose while monitoring for adverse events. |
| | DRV/c, DRV/r | **With DRV/r**<br>• Pravastatin AUC ↑ 81% following single dose of pravastatin<br>• Pravastatin AUC ↑ 23% at steady state | Administer the lowest effective pravastatin dose while monitoring for adverse events. |
| **Rosuvastatin** | ATV/r | Rosuvastatin AUC ↑ 3-fold and $C_{max}$ ↑ 7-fold | Administer the lowest effective rosuvastatin dose while monitoring for adverse events. Do not exceed rosuvastatin 10 mg daily. |
| | ATV/c | Rosuvastatin AUC ↑ 3.4-fold and $C_{max}$ ↑ 10.6-fold | |
| | DRV/c | Rosuvastatin AUC ↑ 1.9-fold and $C_{max}$ ↑ 3.8-fold | Administer the lowest effective rosuvastatin dose while monitoring for adverse events. Do not exceed rosuvastatin 20 mg daily. |
| | DRV/r | Rosuvastatin AUC ↑ 48% and $C_{max}$ ↑ 2.4-fold | Administer the lowest effective rosuvastatin dose while monitoring for adverse events. |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Simvastatin** | ATV/c, ATV/r, DRV/c, DRV/r | Significant ↑ simvastatin expected | **Contraindicated** |
| **Narcotics and Treatment for Opioid Dependence** | | | |
| **Buprenorphine**<br>Sublingual, buccal, or implant | ATV/r | Buprenorphine AUC ↑ 66%<br>Norbuprenorphine (active metabolite) AUC ↑ 105% | Monitor for sedation and other signs or symptoms of overmedication. Buprenorphine dose reduction may be necessary. It may be necessary to remove implant and treat with a formulation that permits dose adjustments. |
| | DRV/r | ↔ buprenorphine<br>Norbuprenorphine (active metabolite) AUC ↑ 46% and $C_{min}$ ↑ 71% | No dose adjustment needed. Monitor for buprenorphine-related adverse events. When transferring buprenorphine from transmucosal delivery to implantation, monitor to ensure buprenorphine effect is adequate and not excessive. |
| | ATV/c, DRV/c | ↑ buprenorphine possible | Titrate buprenorphine dose using the lowest initial dose. Dose adjustment of buprenorphine may be needed. It may be necessary to remove implant and treat with a formulation that permits dose adjustments. Monitor for buprenorphine-related adverse events. |
| **Fentanyl** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ fentanyl possible | Monitor for fentanyl-related adverse events, including potentially fatal respiratory depression. |
| **Lofexidine** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ lofexidine possible | Monitor for lofexidine-related adverse events, including symptoms of orthostasis and bradycardia. |
| **Methadone** | ATV/c, DRV/c | No data | Titrate methadone dose using the lowest feasible initial dose. Dose adjustment of methadone may be needed. Monitor for methadone-related adverse events. |
| | ATV/r, DRV/r | ATV/r and DRV/r ↓ R-methadone[d] AUC 16% to 18% | Opioid withdrawal is unlikely but may occur. Monitor for opioid withdrawal and increase methadone dose as clinically indicated. |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Oxycodone** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ oxycodone expected | Monitor for opioid-related adverse events, including potentially fatal respiratory depression. Oxycodone dose reduction may be necessary. |
| **Tramadol** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ tramadol expected<br>↓ M1 (active metabolite) possible | Tramadol dose adjustments may be necessary. Monitor for clinical response and tramadol-related adverse events. |
| **PDE5 Inhibitors** | | | |
| **Avanafil** | ATV/c, ATV/r, DRV/c, DRV/r | RTV 600 mg twice daily (for 5 days) ↑ avanafil AUC 13-fold and ↑ $C_{max}$ 2.4-fold | **Do not coadminister.** |
| **Sildenafil** | ATV/c, ATV/r, DRV/c, DRV/r | DRV/r plus sildenafil 25 mg similar to sildenafil 100 mg alone<br>RTV 500 mg twice daily ↑ sildenafil AUC 1,000% | **For Treatment of Erectile Dysfunction**<br>• Start with sildenafil 25 mg every 48 hours and monitor for sildenafil-related adverse events.<br>**Contraindicated** for treatment of PAH. |
| **Tadalafil** | ATV/c, ATV/r, DRV/c, DRV/r | RTV 200 mg twice daily ↑ tadalafil AUC 124% | **For Treatment of Erectile Dysfunction**<br>*As-Needed Use*<br>• Start with tadalafil 5 mg and do not exceed a single dose of tadalafil 10 mg every 72 hours. Monitor for tadalafil-related adverse events.<br>*Once-Daily Use*<br>• Do not exceed tadalafil 2.5 mg once daily. Monitor for tadalafil-related adverse events.<br>**For Treatment of PAH**<br>*In Patients on a PI >7 Days*<br>• Start with tadalafil 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| | | | *In Patients on Tadalafil Who Require a PI*<br>• Stop tadalafil ≥24 hours before PI initiation. Seven days after PI initiation, restart tadalafil at 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability.<br>*In Patients Switching Between COBI and RTV*<br>• Maintain tadalafil dose.<br>**For Treatment of Benign Prostatic Hyperplasia**<br>• Maximum recommended daily dose is tadalafil 2.5 mg per day. Monitor for tadalafil-related adverse events. |
| **Vardenafil** | ATV/c, ATV/r, DRV/c, DRV/r | RTV 600 mg twice daily<br>↑ vardenafil AUC 49-fold | Start with vardenafil 2.5 mg every 72 hours and monitor for vardenafil-related adverse events. |
| **Sedative/Hypnotics** | | | |
| ***Benzodiazepines*** | | | |
| **Alprazolam, Clonazepam, Diazepam** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ benzodiazepine possible<br>RTV 200 mg twice daily (for 2 days) ↑ alprazolam half-life 222% and ↑ AUC 248% | Consider alternative benzodiazepines, such as lorazepam, oxazepam, or temazepam. |
| **Lorazepam, Oxazepam, Temazepam** | ATV/c, ATV/r, DRV/c, DRV/r | No data | These benzodiazepines are metabolized via non-CYP450 pathways and, therefore, have less interaction potential than other benzodiazepines. |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Midazolam** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ midazolam expected | Oral midazolam is **contraindicated** with PIs.<br>Parenteral midazolam can be used with caution when given in a monitored situation with appropriate medical management available in case of respiratory sedation and/or prolonged sedation. Consider dose reduction, especially if more than a single dose of midazolam is administered. |
| **Triazolam** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ triazolam expected<br>RTV 200 mg twice daily<br>↑ triazolam half-life 1,200% and<br>↑ AUC 2,000% | **Contraindicated** |
| ***Orexin Receptor Antagonist*** | | | |
| **Daridorexant, Lemborexant, Suvorexant** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ daridorexant, lemborexant, suvorexant expected | **Do not coadminister.** |
| ***Other Sedatives*** | | | |
| **Eszopiclone** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ eszopiclone expected | Start with lowest dose and increase to a maximum of 2 daily; monitor for eszopiclone-related adverse events. |
| **Zolpidem** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ zolpidem possible | Initiate zolpidem at a low dose and monitor for zolpidem-related adverse events. Dose reduction may be necessary. |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Miscellaneous** | | | |
| **Calcifediol** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ calcifediol possible | Dose adjustment of calcifediol may be required, and serum 25-hydroxyvitamin D, intact PTH, and serum calcium concentrations should be closely monitored. |
| **Cisapride** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ cisapride expected | **Contraindicated** |
| **Colchicine** | ATV/c, ATV/r, DRV/c, DRV/r | RTV 100 mg twice daily<br>↑ colchicine AUC 296% and $C_{max}$ ↑ 184%<br>Significant ↑ colchicine expected with all PIs, with or without COBI or RTV | **For Treatment of Gout Flares**<br>• Administer a single dose of colchicine 0.6 mg, followed by colchicine 0.3 mg 1 hour later. Do not repeat dose for at least 3 days.<br>**For Prophylaxis of Gout Flares**<br>• If original dose was colchicine 0.6 mg twice daily, decrease to colchicine 0.3 mg once daily. If dose was 0.6 mg once daily, decrease to 0.3 mg every other day.<br>**For Treatment of Familial Mediterranean Fever**<br>• Do not exceed colchicine 0.6 mg once daily or colchicine 0.3 mg twice daily.<br>**Contraindicated** in patients with hepatic (Child-Pugh Score A, B, or C) or renal impairment (CrCl <60 mL/min) |
| **Dronabinol** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ dronabinol possible | Monitor for dronabinol-related adverse events. |
| **Eluxadoline** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ eluxadoline expected | Administer eluxadoline at a dose of 75 mg twice daily and monitor for eluxadoline-related adverse events. |
| **Finerenone** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ finerenone expected | **Contraindicated** |

## Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Flibanserin** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ flibanserin expected | **Contraindicated** |
| **Naloxegol** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ naloxegol expected | **Contraindicated** |
| **Praziquantel** | ATV/c, ATV/r, DRV/c, DRV/r | ↑ praziquantel possible | Consider alternative ARV. If coadministration is necessary, monitor for praziquantel-related adverse events. |

[a] DHA is an active metabolite of artemether and artesunate.

[b] The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate: Lo Minastrin Fe; Lo Loestrin Fe; Loestrin 1/20, 1.5/30; Loestrin Fe 1/20, 1.5/30; Loestrin 24 Fe; Minastrin 24 Fe; Ortho Tri-Cyclen Lo. Generic formulations also may be available.

[c] The following products contain at least 35 mcg of ethinyl estradiol combined with norethindrone or norgestimate: Brevicon; Femcon Fe; Modicon; Norinyl 1/35; Ortho-Cyclen; Ortho-Novum 1/35, 7/7/7; Ortho Tri-Cyclen; Ovcon 35; Tri-Norinyl. Generic formulations also may be available.

[d] R-methadone is the active form of methadone.

**Key to Symbols**

↑ = increase
↓ = decrease
↔ = less than 20% change in AUC

**Key:** 17-BMP = beclomethasone 17-monopropionate; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; $C_{max}$ = maximum plasma concentration; $C_{min}$ = minimum plasma concentration; CCB = calcium channel blocker; CNS = central nervous system; COBI = cobicistat; CrCl = creatinine clearance; CMV = cytomegalovirus; CV = cardiovascular; CYP = cytochrome P; DHA = dihydroartemisinin; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DVT = deep vein thrombosis; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EVG/c = elvitegravir/cobicistat; GI = gastrointestinal; H2RA = H2 receptor antagonist; HCV = hepatitis C virus; HRT = hormone replacement therapy; INR = international normalized ratio; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MPA = medroxyprogesterone acetate; OATP = organic anion-transporting polypeptide; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; PE = pulmonary embolism; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; PK = pharmacokinetic; PPI = proton pump inhibitor; PTH = parathyroid hormone; QTc = QT corrected for heart rate; RTV = ritonavir; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TDF = tenofovir disoproxil fumarate; VPA = valproic acid