HIV Antiretroviral Therapy
Common Drug-Drug Interactions Tip Sheet

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Overview of Drug Interaction by Class

ARV	Recommendations
Integrase inhibitors (INSTI) - Bictegravir (BIC) - Dolutegravir (DTG) - Elvitegravir/cobi (EVG/c) - Raltegravir (RAL)	**Polyvalent cations** (E.g. Antacid, Ca^{2+}, Fe^{2+}, Mg^{2+}, Zn^{2+} supplements) *Mechanism: Chelate to INSTI and reduce oral absorption* ***under fasting conditions*** Administer INSTI 2 hours before or 4 hours after polyvalent cations; OR take both with food
	Metformin *Mechanism: DTG inhibits renal organic cation transport 2 (OCT2) and decreases metformin clearance* Monitor renal function during co-administration to prevent accumulation and lactic acidosis (max: 1000mg/day)
	CYP3A4 Inducers *Mechanism: Decreases INSTI plasma concentration* **Rifampin**: Increase DTG dose to 50 mg PO BID **Etravirine**: DTG - Add ritonavir boosted PI; RAL - dose 400 mg BID **Efavirenz**: May be given with DTG (if no INSTI resistance) or RAL
Protease Inhibitor (PI) - Atazanavir (ATV) - Darunavir (DRV) - Lopinavir/ritonavir (LPV/r) **Pharmacokinetic boosters** - Ritonavir (RTV) - Cobicistat w/ Darunavir (DRV/c) w/ Atazanavir (ATV/c)	**CYP3A4 substrates** *Mechanism: PI and pharmacokinetic boosters are potent CYP3A4 inhibitors which may increase serum levels of CYP3A4 substrates or inhibit bioactivation* **Statins**: Do not co-administer with simvastatin/lovastatin Atorvastatin (generally max 20 mg/day); avoid when on ATV/r Rosuvastatin (generally max 10 mg/day; 20mg/day for DRV/c) Pravastatin & pitavastatin does not require dose adjustment **Steroids**: Beclomethasone (Qvar®, Qnasl®) or flunisolide is preferred to avoid Cushing's syndrome **Antiplatelets**: Aspirin and prasugrel are preferred Do not co-administer with clopidogrel/ticagrelor **Anticoagulants**: Apixaban: Reduce dose by 50%; Do not co-administer in patients who require apixaban 2.5 mg BID Rivaroxaban: Do not co-administer with rivaroxaban Warfarin: Closely monitor INR and adjust warfarin dose **Antiepileptics**: Carbamazepine: Do not co-administer with carbamazepine **Rifabutin**: Adjust dose to 150 mg once daily or 150-300 mg three times a week Do not co-administer with PI boosted with cobicistat (not studied) **Macrolides**: Preferred: Azithromycin Clarithromycin: Reduce dose by 50% **Antiarrhythmics**: When an antiarrhythmic is indicated, may need to consider a non-PI based regimen

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<td>Protease Inhibitor (PI)
- Atazanavir (ATV)
- Darunavir (DRV)
- Lopinavir/ritonavir (LPV/r)
- Ritonavir (RTV)

Pharmacokinetic boosters
- Cobicistat
w/ Darunvir (DRV/c)
w/ Atazanavir (ATV/c)</td>
<td>CYP3A4 Inducers
Mechanism: Decrease PI plasma concentration

<u>Rifampin/rifapentine/St. John’s wort</u>: Do not co-administer
<u>Etravirine</u>: Do not co-administer; If coadministration is necessary, consider atazanavir/darunavir boosted with ritonavir
<u>Efavirenz</u>: Do not co-administer; If coadministration is necessary, consider ATV/DRV boosted with ritonavir</td>
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<td>Acid-lowering agents:
Mechanism: Atazanavir solubility decreases as pH increases which decreases oral absorption

<u>Antacids</u>:
Administer ATV at least 2 hours before or 1-2 hours after antacids or buffered medications
<u>H2-receptor antagonists</u>:
Atazanavir alone
- Administer atazanavir 2 hours before or >10 hours after
- PI-naïve: Max equivalent dose famotidine 20 mg twice daily
- Tx-experienced: Do not co-administer
Atazanavir (boosted)
- PI-naïve: Max equivalent dose famotidine 40 mg twice daily;
- Tx-experienced: Max equivalent dose famotidine 20 mg twice daily; Administer atazanavir+ritonavir with and/or >10 hours after
o If using TDF, use ATV 400 mg + ritonavir/cobicistat
<u>Proton-pump inhibitors</u>:
- PI-naïve: Max equivalent dose omeprazole 20 mg twice daily and administer 12 hours prior to atazanavir dose
- Tx-experienced: Do not co-administer</td>
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<td>Non-nucleoside/tide reverse transcriptase inhibitor (NNRTI)
- Doravirine (DOR)
- Efavirenz (EFV)
- Etravirine (ETR)
- Rilpivirine (RPV)</td>
<td>Acid-lowering agents:
Mechanism: Reduce the absorption of rilpivirine

<u>Antacids</u>:
Give antacids at least 2 hours before or at least 4 hours after RPV
<u>H2-receptor antagonists</u>:
Give H2 receptor antagonists at least 12 hours before or at least 4 hours after RPV
<u>Proton-pump inhibitors</u>:
Do not co-administer</td>
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<td>All NNRTIs are substrates of CYP3A4

INSTI (See INSTI section)
PI (See PI section)

Antiepileptics:
Mechanism: CYP inducers may reduce NNRTIs levels. Etravirine and efavirenz are CYP3A4 inducers and substrates which may also lower serum concentration of select antiepileptics.

<u>Carbamazepine, phenytoin and phenobarbital:</u>
Avoid coadministration with dorivirine, rilpivirine, and etravirine; If co-adminstration is necessary with efavirenz, closely monitor and consider monitoring drug levels

CYP3A4 Inducers<u>:</u>
Mechanism: CYP3A4 inducers decrease NNRTI plasma concentration

<u>Rifampin or St. John’s wort:</u>
Do not co-administer; if co-administration is necessary with efavirenz, do not use 400 mg/day formulation (Symfi Lo®)</td>
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Nucleoside/tide reverse transcriptase inhibitor (NRTI) - Abacavir (ABC) - Lamivudine (3TC) - Emtricitabine (FTC) - Tenofovir disoproxil fumarate (TDF) - Tenofovir alafenamide (TAF)	**Drug transporter inducers**: *Mechanism: TAF is a substrate of multiple drug transports, such as P-gp and BCRP. P-gp/BCRP induces may reduce intestinal absorption of TAF* **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin**: Do not co-administer with TAF **Rifampin/St. John's Wort**: Co-administration is not recommended with TAF
Entry Inhibitors - Maraviroc (MVC)	**CYP3A4 Inhibitor** *Mechanism: CYP inhibitor may increase MVC levels* - E.g. Clarithromycin With strong CYP3A4 inhibitor: dose MVC 150 mg BID
	CYP3A4 Inducer *Mechanism: CYP inducers may reduce MVC levels* - E.g. Rifabutin/Rifampin, carbamazepine, phenobarbital, phenytoin With strong CYP3A4 inducer: dose MVC 600 mg BID

Simplified Interaction Summary of Most Common Combination Pills

Brand	Components	Interaction Summary	
		Oral absorption	Hepatic metabolism
Biktarvy®	**BIC + TAF + FTC**	Polyvalent cations	P-gp substrate
Triumeq®	**DTG + ABC + 3TC**	Polyvalent cations	X
Symtuza®	**DRV/cobi + TAF + FTC**	X	CYP3A4 inhibitor and P-gp substrate
Stribild®	**EVG/cobi + TDF + FTC**	Polyvalent cations	CYP3A4 inhibitor & substrate
Genvoya®	**EVG/cobi + TAF + FTC**	Polyvalent cations	CYP3A4 inhibitor & substrate and P-gp substrate
Atripla®	**EFV + TDF + FTC**	X	CYP3A4 inducer & substrate
Complera®	**RPV + TDF + FTC**	Acid-reducers	X
Odefsey®	**RPV + TAF + FTC**	Acid-reducers	P-gp substrate
Juluca®	**DTG + RPV**	Polyvalent cations & Acid-reducers	X
Symfi®/ Symfi Lo®	**TDF + 3TC + EFV**	X	CYP3A4 inducer & substrate
Delstrigo®	**DOR + 3TC + TDF**	X	CYP3A4 substrate
Dovato®	**DTG + 3TC**	Polyvalent cations	X
Truvada®	**TDF + FTC**	X	X
Descovy®	**TAF + FTC**	X	P-gp substrate
Epzicom®	**ABC + 3TC**	X	X

Resources:

Check for DDI's using "Liverpool HIV Drug Interactions Checker" at https://www.hiv-druginteractions.org/checker

Check out up to date HIV/AIDs guidelines at https://aidsinfo.nih.gov/

References:

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