# HIV Antiretroviral Therapy

## Common Drug-Drug Interactions Tip Sheet

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### Overview of Drug Interaction by Class

<table>
<thead>
<tr>
<th>ARV</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Integrase inhibitors (INSTI)</strong></td>
<td><strong>Polyvalent cations</strong> <em>(E.g. Antacid, Ca²⁺, Fe²⁺, Mg²⁺, Zn²⁺ supplements)</em></td>
</tr>
<tr>
<td>- Bictegravir (BIC)</td>
<td><em>Mechanism: Chelate to INSTI and reduce oral absorption under fasting conditions</em></td>
</tr>
<tr>
<td>- Dolutegravir (DTG)</td>
<td>Administer INSTI 2 hours before or 4 hours after polyvalent cations; OR take both with food</td>
</tr>
<tr>
<td>- Elvitegravir/cobi (EVG/c)</td>
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<tr>
<td>- Raltegravir (RAL)</td>
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</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Protease Inhibitor (PI)</th>
<th><strong>CYP3A4 substrates</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Atazanavir (ATV)</td>
<td><em>Mechanism: PI and pharmacokinetic boosters are potent CYP3A4 inhibitors which may increase serum levels of CYP3A4 substrates or inhibit bioactivation</em></td>
</tr>
<tr>
<td>- Darunavir (DRV)</td>
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<tr>
<td>- Lopinavir/ritonavir (LPV/r)</td>
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</tbody>
</table>

**Pharmacokinetic boosters**  
- **Ritonavir (RTV)**                      |
| - **Cobicistat**                          |
|   w/ Darunavir (DRV/c)                    |
|   w/ Atazanavir (ATV/c)                   |

**PI**  
- **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

**Antiplaletets**:  
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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Updated 6/2020
**Protease Inhibitor (PI)**
- Atazanavir (ATV)
- Darunavir (DRV)
- Lopinavir/ritonavir (LPV/r)
- Ritonavir (RTV)

**Pharmacokinetic boosters**
- Cobicistat
  - w/ Darunavir (DRV/c)
  - w/ Atazanavir (ATV/c)

**CYP3A4 Inducers**
*Mechanism: Decrease PI plasma concentration*

- Rifampin/rifapentine/St. John’s wort: Do not co-administer
- Etravirine: Do not co-administer; If coadministration is necessary, consider atazanavir/darunavir boosted with ritonavir
- Efavirenz: Do not co-administer; If coadministration is necessary, consider ATV/DRV boosted with ritonavir

**CYP3A4 Inducers**
*Mechanism: Decrease PI plasma concentration*

- Rifampin/rifapentine/St. John’s wort: Do not co-administer
- Etravirine: Do not co-administer; If coadministration is necessary, consider atazanavir/darunavir boosted with ritonavir
- Efavirenz: Do not co-administer; If coadministration is necessary, consider ATV/DRV boosted with ritonavir

**Acid-lowering agents:**
*Mechanism: Atazanavir solubility decreases as pH increases which decreases oral absorption*

- **Antacids:**
  - Administer ATV at least 2 hours before or 1-2 hours after antacids or buffered medications
- **H2-receptor antagonists:**
  - Atazanavir alone
    - *Pl-naïve:* Max equivalent dose famotidine 20 mg twice daily
    - *Tx-experienced:* Do not co-administer
  - Atazanavir (boosted)
    - *Pl-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
      - If using TDF, use ATV 400 mg + ritonavir/cobicistat
- **Proton-pump inhibitors:**
  - *Pl-naïve:* Max equivalent dose omeprazole 20 mg twice daily and administer 12 hours prior to atazanavir dose
  - *Tx-experienced:* Do not co-administer

**Non-nucleoside/tide reverse transcriptase inhibitor (NNRTI)**
- Doravirine (DOR)
- Efavirenz (EFV)
- Etravirine (ETR)
- Rilpivirine (RPV)

**Acid-lowering agents:**
*Mechanism: Reduce the absorption of rilpivirine*

- **Antacids:**
  - Give antacids at least 2 hours before or at least 4 hours after RPV
- **H2-receptor antagonists:**
  - Give H2 receptor antagonists at least 12 hours before or at least 4 hours after RPV
- **Proton-pump inhibitors:**
  - Do not co-administer

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.*

**Carbamazepine, phenytoin and phenobarbital:**
Avoid coadministration with dorivirine, rilpivirine, and etravirine; If co-administration is necessary with efavirenz, closely monitor and consider monitoring drug levels

**CYP3A4 Inducers:**
*Mechanism: CYP3A4 inducers decrease NNRTI plasma concentration*

- **Rifampin or St. John’s wort:**
  - Do not co-administer; if co-administration is necessary with efavirenz, do not use 400 mg/day formulation (Symfi Lo®)
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

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

**Resources:**
Check for DDI’s using “Liverpool HIV Drug Interactions Checker” at [https://www.hiv-druginteractions.org/checker](https://www.hiv-druginteractions.org/checker)  
Check out up to date HIV/AIDs guidelines at [https://aidsinfo.nih.gov/](https://aidsinfo.nih.gov/)

Updated 6/2020
References:

3. Biktarvy® (bictegravir, emtricitabine, tenofovir alafenamide) prescribing information. Foster City, CA; Gilead Sciences; 2018.
4. Isentress® (raltegravir) prescribing information. Whitehouse Station, NJ; Merck Sharp & Dohme; 2015.
13. Descovy® (emtricitabine and tenofovir alafenamide) prescribing information. Foster City, CA; Gilead Sciences; 2016.