Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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### Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018)

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<th>Generic Name (Abbreviation)</th>
<th>Formulations</th>
<th>Dosing Recommendations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Elimination/Metabolic Pathway</th>
<th>Serum Half-Life</th>
<th>Adverse Events&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td><strong>Atazanavir (ATV)</strong> Reyataz</td>
<td>Reyataz:  • 150, 200, and 300 mg capsules;  • 50 mg single packet oral powder</td>
<td><strong>Reyataz:</strong>  • (ATV 300 mg plus RTV 100 mg) once daily; or  • ATV 400 mg once daily <strong>With TDF or in ARV-Experienced Patients:</strong>  • (ATV 300 mg plus RTV 100 mg) once daily <strong>With EFV in ARV-Naive Patients:</strong>  • (ATV 400 mg plus RTV 100 mg) once daily Take with food. For dosing recommendations with H2 antagonists and PPIs, refer to Table 19&lt;sup&gt;a&lt;/sup&gt;.</td>
<td>CYP3A4 inhibitor and substrate; weak CYP2C8 inhibitor; UGT1A1 inhibitor Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 8).</td>
<td>7 hours</td>
<td>• Indirect hyperbilirubinemia  • PR interval prolongation: First degree symptomatic AV block reported. Use with caution in patients who have underlying conduction defects or who are on concomitant medications that can cause PR prolongation.  • Hyperglycemia  • Fat maldistribution  • Cholelithiasis  • Nephrolithiasis  • Renal insufficiency  • Serum transaminase elevations  • Hyperlipidemia (especially with RTV boosting)  • Skin rash  • Increase in serum creatinine (with COBI)</td>
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<tr>
<td><strong>Evotaz</strong> (ATV/c)</td>
<td>Evotaz:  • (ATV 300 mg plus COBI 150 mg) tablet</td>
<td><strong>Evotaz:</strong>  • 1 tablet once daily  • Take with food. <strong>With TDF:</strong>  • <strong>Not recommended</strong> for patients with baseline CrCl &lt;70 mL/min (see Appendix B, Table 8 for the equation for calculating CrCl).</td>
<td>ATV: as above COBI: CYP3A inhibitor and substrate; CYP2D6 inhibitor</td>
<td></td>
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<tr>
<td>Darunavir (DRV) Prezista</td>
<td>Prezista: • 75, 150, 600, and 800 mg tablets • 100 mg/mL oral suspension</td>
<td>In ARV-Naive Patients or ARV-Experienced Patients with No DRV Mutations: • (DRV 800 mg plus RTV 100 mg) once daily In ARV-Experienced Patients with One or More DRV Resistance Mutations: • (DRV 600 mg plus RTV 100 mg) BID Unboosted DRV is not recommended. Take with food.</td>
<td>CYP3A4 inhibitor and substrate; CYP2C9 inducer</td>
<td>15 hours (when combined with RTV)</td>
<td>• Skin rash (10%): DRV has a sulfonamide moiety; Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythema multiforme have been reported. • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Increase in serum creatinine (with COBI)</td>
</tr>
<tr>
<td>(DRV/c) Prezcobix</td>
<td>Prezcobix: • (DRV 800 mg plus COBI 150 mg) tablet</td>
<td>Prezcobix: • 1 tablet once daily • Take with food. Not recommended for patients with 1 or more DRV resistance-associated mutations. With TDF: • Not recommended for patients with baseline CrCl &lt;70 mL/min (see Appendix B, Table 8 for the equation for calculating CrCl).</td>
<td>DRV: CYP3A4 inhibitor and substrate; CYP2C9 inducer COBI: CYP3A inhibitor and substrate; CYP2D6 inhibitor</td>
<td>7 hours (when combined with COBI)</td>
<td>• Hyperglycemia • Fat maldistribution • Increase in serum creatinine (with COBI)</td>
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<tr>
<td>(DRV/cTAF/FTC) Symtuza</td>
<td>Symtuza: • (DRV 800 mg plus COBI 150 mg plus TAF 10 mg plus FTC 200 mg) tablet</td>
<td>Symtuza: • 1 tablet once daily with food Not recommended for patients with 1 or more DRV resistance-associated mutations. Not recommended for patients with CrCl &lt;30 mL/min. Not recommended in patients with severe hepatic impairment.</td>
<td>DRV: CYP3A4 inhibitor and substrate; CYP2C9 inducer COBI: CYP3A inhibitor and substrate; CYP2D6 inhibitor</td>
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### Fosamprenavir (FPV, a prodrug of APV) <br>Lexiva

**Note:** Generic is available.

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| Lexiva:      | In ARV-Naive Patients:            | APV is a CYP3A4 substrate, inhibitor, and inducer. | 7.7 hours (APV) | • Skin rash (reported in 12% to 19% of patients on FPV): FPV has a sulfonamide moiety.  
• Diarrhea, nausea, vomiting  
• Headache  
• Hyperlipidemia  
• Serum transaminase elevation  
• Hyperglycemia  
• Fat maldistribution  
• Possible increase in the frequency of bleeding episodes in patients with hemophilia  
• Nephrolithiasis |
| • 700 mg tablet  
• 50 mg/mL oral suspension | • FPV 1400 mg BID, or  
• (FPV 1400 mg plus RTV 100–200 mg) once daily, or  
• (FPV 700 mg plus RTV 100 mg) BID | Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 8). |                |                           |
| **Tablet:** | In PI-Experienced Patients (Once-Daily Dosing Not Recommended): | | | |
| | • (FPV 700 mg plus RTV 100 mg) BID | | | |
| | **With EFV:** | | | |
| | • (FPV 700 mg plus RTV 100 mg) BID, or  
• (FPV 1400 mg plus RTV 300 mg) once daily | | | |
| **Tablet:** | **Without RTV tablet:** Take without regard to meals.  
**With RTV tablet:** Take with meals.  
**Oral Suspension:** | | | |
| | **Take without food.** | | | |
| **Indinavir (IDV) Crixivan** | Crixivan: | CYP3A4 inhibitor and substrate | 1.5–2 hours | • Nephrolithiasis  
• GI intolerance, nausea  
• Hepatitis  
• Indirect hyperbilirubinemia  
• Hyperlipidemia  
• Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia  
• Hyperglycemia  
• Fat maldistribution  
• Possible increase in the frequency of bleeding episodes in patients with hemophilia |
| • 200 and 400 mg capsules | Crixivan: | Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 8). | | |
| **Crixivan:** | • IDV 800 mg every 8 hours  
• Take 1 hour before or 2 hours after meals; may take with skim milk or a low-fat meal.  
**With RTV:**  
• (IDV 800 mg plus RTV 100–200 mg) BID  
• Take without regard to meals.  
Drink at least 48 oz of water daily. | | | |

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Appendix B, Table 3. Characteristics of Protease Inhibitors *(Last updated October 25, 2018; last reviewed October 25, 2018)* (page 3 of 6)
### Lopinavir/Ritonavir (LPV/r)

**Kaletra**
- **Tablets:**
  - (LPV 200 mg plus RTV 50 mg), or
  - (LPV 100 mg plus RTV 25 mg)
- **Oral Solution:**
  - Each 5 mL contains (LPV 400 mg plus RTV 100 mg).
  - Oral solution contains 42% alcohol.

**Kaletra:**
- **Dosing Recommendations:**
  - Once-daily dosing **is not recommended** for patients with ≥3 LPV-associated mutations, pregnant women, or patients receiving EFV, NVP, FPV, NFV, carbamazepine, phenytoin, or phenobarbital.
  - **With EFV or NVP (PI-Naive or PI Experienced Patients):**
    - LPV/r 500 mg/125 mg tablets BID (use a combination of 2 LPV/r 200 mg/50 mg tablets plus 1 LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg), or
    - LPV/r 533 mg/133 mg oral solution BID
  - **Tablet:**
    - Take without regard to meals.
  - **Oral Solution:**
    - Take with food.

**Elimination/Metabolic Pathway:**
- CYP3A4 inhibitor and substrate

**Serum Half-Life:**
- 5–6 hours

**Adverse Events:**
- GI intolerance, nausea, vomiting, diarrhea
- Pancreatitis
- Asthenia
- Hyperlipidemia (especially hypertriglyceridemia)
- Serum transaminase elevation
- Hyperglycemia
- Insulin resistance/diabetes mellitus
- Fat maldistribution
- Possible increase in the frequency of bleeding episodes in patients with hemophilia
- PR interval prolongation
- QT interval prolongation and torsades de pointes have been reported; however, causality could not be established.

### Nelfinavir (NFV)

**Viracept**
- **250 and 625 mg tablets**

**Viracept:**
- **Dosing Recommendations:**
  - NFV 1250 mg BID, or
  - NFV 750 mg TID

**Elimination/Metabolic Pathway:**
- CYP2C19 and 3A4 substrate—metabolized to active M8 metabolite; CYP3A4 inhibitor

**Serum Half-Life:**
- 3.5–5 hours

**Adverse Events:**
- Diarrhea
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increase in the frequency of bleeding episodes in patients with hemophilia
- Serum transaminase elevation
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| **Ritonavir** *(RTV)*       | Norvir     | Norvir:  
|                             |            |  • 100 mg tablet  
|                             |            |  • 100 mg soft gel capsule  
|                             |            |  • 80 mg/mL oral solution  
|                             |            |  • 100 mg single packet oral powder  
|                             |            | Oral solution contains 43% alcohol.  
|                             |            | **As PK Booster (or Enhancer) for Other PIs:**  
|                             |            |  • RTV 100–400 mg per day in 1 or 2 divided doses (refer to other PIs for specific dosing recommendations).  
|                             |            | **Tablet:**  
|                             |            |  • Take with food.  
|                             |            | **Capsule and Oral Solution:**  
|                             |            |  • To improve tolerability, take with food if possible.  
|                             |            | CYP3A4 > 2D6 substrate; potent 3A4, 2D6 inhibitor; inducer of UGT1A1 and CYPs 1A2, 2C8, 2C9, and 2C19  
|                             |            | 3–5 hours  
|                             |            | • GI intolerance, nausea, vomiting, diarrhea  
|                             |            | • Paresthesia (circumoral and extremities)  
|                             |            | • Hyperlipidemia (especially hypertriglyceridemia)  
|                             |            | • Hepatitis  
|                             |            | • Asthenia  
|                             |            | • Taste perversion  
|                             |            | • Hyperglycemia  
|                             |            | • Fat maldistribution  
|                             |            | • Possible increase in the frequency of bleeding episodes in patients with hemophilia  
| **Saquinavir** *(SQV)*     | Invirase   | Invirase:  
|                             |            |  • 500 mg tablet  
|                             |            |  • 200 mg capsule  
|                             |            | **Invirase:**  
|                             |            |  • (SQV 1000 mg plus RTV 100 mg) BID  
|                             |            | Unboosted SQV is not recommended.  
|                             |            | Take with meals or within 2 hours after a meal.  
|                             |            | CYP3A4 substrate  
|                             |            | 1–2 hours  
|                             |            | • GI intolerance, nausea, and diarrhea  
|                             |            | • Headache  
|                             |            | • Serum transaminase elevation  
|                             |            | • Hyperlipidemia  
|                             |            | • Hyperglycemia  
|                             |            | • Fat maldistribution  
|                             |            | • Possible increase in the frequency of bleeding episodes in patients with hemophilia  
|                             |            | • PR interval prolongation  
|                             |            | • QT interval prolongation, torsades de pointes have been reported. Patients with pre-SQV QT interval >450 msec should not receive SQV.  

**Note:** Generic is available.

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*Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV*  
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### Tipranavir (TPV) Aptivus

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| • 250 mg capsule  
• 100 mg/mL oral solution | • (TPV 500 mg plus RTV 200 mg) BID  
Unboosted TPV is not recommended.  
With RTV Tablets:  
• Take with meals.  
With RTV Capsules or Solution:  
• Take without regard to meals. | CYP3A4 inducer and substrate  
CYP2D6 inhibitor; CYP3A4, 1A2, and 2C19 inducer  
Net effect of combining TPV and RTV is a CYP3A4 and 2D6 inhibitor | 6 hours after single dose of TPV/r | • Hepatotoxicity: clinical hepatitis (including hepatic decompensation and hepatitis-associated fatalities) has been reported; monitor patients closely, especially those with underlying liver diseases.  
• Skin rash: TPV has a sulfonamide moiety; use with caution in patients with known sulfonamide allergy.  
• Rare cases of fatal and nonfatal intracranial hemorrhages have been reported. Risks include brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism, and the use of anticoagulant or antiplatelet agents (including vitamin E).  
• Hyperlipidemia  
• Hyperglycemia  
• Fat maldistribution  
• Possible increase in the frequency of bleeding episodes in patients with hemophilia |

<sup>a</sup> For dose adjustments in patients with hepatic insufficiency, see Appendix B, Table 8.<br><sup>b</sup> Also see Table 15.

**Key to Acronyms:** APV = amprenavir; ARV = antiretroviral; ATV = atazanavir; AV = atrioventricular; BID = twice daily; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; EFV = efavirenz; FPV = fosamprenavir; FTC = emtricitabine; GI = gastrointestinal; IDV = indinavir; LPV = lopinavir; LPV/r = lopinavir/ritonavir; msec = millisecond; NAF = nelfinavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RTV = ritonavir; SQV = saquinavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = three times a day; TPV = tipranavir; UGT = uridine diphosphate glucuronosyltransferase