Drug Class Review

HIV Protease Inhibitors
8:18.08.08 HIV Protease Inhibitors

Atazanavir (Reyataz®)
Atazanavir/Cobicistat (Evotaz®)
Darunavir (Prezista®)
Darunavir/Cobicistat (Prexcobix®)
Fosamprenavir (Lexiva®)
Indinavir (Crixivan®)
Lopinavir/Ritonavir (Kaletra®)
Nelfinavir (Viracept®)
Ritonavir (Norvir®)
Saquinavir (Invirase®)
Tipranavir (Aptivus®)

Final Report
August 2015
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Executive Summary

Introduction: Agents used in the treatment of human immunodeficiency virus (HIV) infection include nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), entry inhibitors, fusion inhibitors and integrase inhibitors. Successful treatment of an HIV infection involves combination therapy with multiple direct antiviral agents. This report evaluates the safety and efficacy of the HIV protease inhibitors. Currently, 8 single agent protease inhibitors, one combination agent containing two protease inhibitors and two combination agents containing a protease inhibitor with a pharmacologic booster are available for use in the US: atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir and tipranavir, lopinavir/ritonavir, atazanavir/cobicistat and darunavir/cobicistat.

HIV, the virus that causes acquired immune deficiency syndrome (AIDS), is a worldwide health challenge and is the world’s leading cause of death from infection. The virus causes a chronic infection with a gradual onset of clinical symptoms starting with general malaise and illness, progressing to the development of opportunistic diseases and ultimately death. The goal of HIV therapy is to decrease viral load, increase CD4+ T cell count and prevent opportunistic infections. The biggest challenge to treatment of HIV/AIDS infection is the development of resistance to drug therapy. To prevent viral resistance, an approach called highly active antiretroviral therapy (HAART), combining agents from at least two different drug classes, is recommended for treatment of HIV infection. In general, standard combination therapy consists of two nucleoside reverse transcriptase inhibitors (NRTI) combined with a third antiretroviral agent from one of the other direct-acting antiviral drug classes, such as a protease inhibitor. The US Department of Health and Human Services recommends darunavir/ritonavir in combination with tenofovir and lamivudine or emtricitabine as their preferred PI-based regimen.

Clinical Efficacy: One meta-analysis and 20 comparative clinical trials comparing the efficacy of the HIV protease inhibitors were identified for evaluation. Of the 20 clinical trials identified, 14 evaluated the efficacy of the PI agents in treatment-naïve patients and 6 evaluated the efficacy of the agents in treatment-experienced patients. Each of the HIV protease inhibitors was studied in at least one comparative clinical trial. Overall, the evidence suggests, when used in combination regimens, the protease inhibitors are efficacious in the treatment of HIV-1. The combination protease therapies demonstrated efficacy in treatment-naïve and treatment-resistant patients with treatment durations ranging from 6-192 weeks.

Special Populations: The HIV protease inhibitors demonstrated safety and efficacy in the treatment of HIV in special populations. The PI agents have differing indications but, in general, are recommended in pediatric patients (age <18 years), older adults (age >50 years), pregnant women and in patients with co-infections (hepatitis, tuberculosis, etc.) Of note, adverse events may occur more frequently in pediatric patients and older adults and careful monitoring of bone, kidney, metabolic, cardiovascular and liver health in these patient populations is recommended.

Adverse Drug Reactions: The protease inhibitors are associated with short- and long-term toxicities, which may limit use. The most common adverse events reported with protease inhibitor therapy vary between the agents and may include gastrointestinal irritation, skin
reactions and metabolic disturbances. The metabolic disturbances reported with PI use include hyperlipidemia, lipodystrophy and impaired glucose tolerance. Some of the agents cause unconjugated hyperbilirubinemia which is asymptomatic and not generally associated with serious hepatic disease. Clinicians should monitor patients receiving protease inhibitors carefully for adverse events, especially those at risk for altered lipid and glucose metabolism.

**Summary:** The HIV PI agents are recommended for use in the treatment of HIV/AIDS as part of a comprehensive combination therapy regimen. All patients with HIV should receive Antiretroviral Therapy (ART) to reduce the risk of disease progression and to prevent transmission. Before initiation of ART, genotypic drug-resistance testing is recommended to help guide therapy decisions. In an attempt to reduce or avoid drug-resistance, patients should receive education outlining the benefits and risks of therapy and the importance of adherence before initiation of therapy.
Introduction

Human immunodeficiency virus (HIV) is a lentivirus within the family of mammalian retroviruses.\textsuperscript{1} The virus causes a chronic infection with a gradual onset of clinical symptoms starting with general malaise and illness, progressing to the development of opportunistic diseases and ultimately death.\textsuperscript{1} Successful treatment of HIV infection involves combination therapy with direct antiviral agents. Agents used in the treatment of HIV infection include nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), entry inhibitors, fusion inhibitors and integrase inhibitors.\textsuperscript{2,3} This report will evaluate the safety and efficacy of the HIV protease inhibitors. Currently, there are 8 single agent protease inhibitors (atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir and tipranavir), one combination agent containing two protease inhibitors (lopinavir/ritonavir) and two combination agents containing a protease inhibitor with a pharmacologic booster (atazanavir/cobicistat and darunavir/cobicistat).\textsuperscript{2,3} Table 1 provides a summary of the agents included in this drug class review.
# Table 1. Comparison of the HIV Protease Inhibitor Agents

<table>
<thead>
<tr>
<th>Product</th>
<th>Route of Administration</th>
<th>Available Doses</th>
<th>Dosing</th>
<th>Generic Available</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single Agents</strong></td>
<td></td>
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<td>------------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Atazanavir</strong></td>
<td>Oral capsule</td>
<td>150 mg, 200 mg, 300 mg</td>
<td>Adult dosing (treatment naïve): &lt;ul&gt;&lt;li&gt;300 mg daily w/ritonavir 100 mg daily; 400 mg daily alone&lt;/li&gt;&lt;/ul&gt;</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Oral powder (packet)</td>
<td>50 mg per packet</td>
<td>Adult dosing (treatment experienced): &lt;ul&gt;&lt;li&gt;300 mg daily w/ritonavir 100 mg daily&lt;/li&gt;&lt;/ul&gt;</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Pediatric dosing (treatment naïve or experienced): &lt;ul&gt;&lt;li&gt;3 mo-5 yo&lt;/li&gt;&lt;li&gt;-10-14.9 kg: 200 mg powder daily w/ritonavir 80 mg daily&lt;/li&gt;&lt;li&gt;-15-24.8 kg: 250 mg powder daily w/ritonavir 80 mg daily&lt;/li&gt;&lt;li&gt;6-17 yo&lt;/li&gt;&lt;li&gt;-15-19.9 kg: 150 mg daily w/ritonavir 100 mg daily&lt;/li&gt;&lt;li&gt;-20-39.9 kg: 200 mg daily w/ritonavir 100 mg daily&lt;/li&gt;&lt;li&gt;-&gt;40 kg: 300 mg daily w/ritonavir 100 mg daily; 400 mg daily alone&lt;/li&gt;&lt;/ul&gt;</td>
<td></td>
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<tr>
<td><strong>Darunavir</strong></td>
<td>Oral tablet</td>
<td>75 mg, 150 mg, 400mg, 600mg, 800 mg</td>
<td>Adult dosing (treatment naïve): &lt;ul&gt;&lt;li&gt;800 mg daily w/ritonavir 100 mg daily&lt;/li&gt;&lt;/ul&gt;</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adult dosing (treatment experienced; w/o darunavir resistance substitution): &lt;ul&gt;&lt;li&gt;800 mg daily w/ritonavir 100 mg daily&lt;/li&gt;&lt;/ul&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral suspension</td>
<td>100 mg/mL</td>
<td>Adult dosing (treatment experienced; w/darunavir resistance substitution): &lt;ul&gt;&lt;li&gt;600 mg twice daily w/ritonavir 100 mg twice daily&lt;/li&gt;&lt;/ul&gt;</td>
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<td>Pediatric dosing (treatment naïve or experienced w/o darunavir resistance substitution): &lt;ul&gt;&lt;li&gt;3-17 yo&lt;/li&gt;&lt;li&gt;-10-10.9 kg: 350 mg daily w/ritonavir 64 mg daily&lt;/li&gt;&lt;/ul&gt;</td>
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<tr>
<td>Product</td>
<td>Route of Administration</td>
<td>Available Doses</td>
<td>Dosing</td>
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<tr>
<td><strong>Fosamprenavir</strong></td>
<td>Oral tablet</td>
<td>700 mg</td>
<td>Adult dosing (treatment naïve):</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• 1400 mg twice daily</td>
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<td></td>
<td>• Alternate: 1400 mg daily w/ritonavir 100-200 mg</td>
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<td></td>
<td></td>
<td></td>
<td>• Alternate: 700 mg daily w/ritonavir 100 mg twice daily</td>
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<td></td>
<td>Oral suspension</td>
<td>50 mg/mL</td>
<td>Adult dosing (treatment experienced):</td>
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<td></td>
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<td></td>
<td>• 700 mg twice daily w/ritonavir 100 mg</td>
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<td></td>
<td>Pediatric dosing (treatment naïve):</td>
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<td></td>
<td></td>
<td></td>
<td>• &gt;38 wk gestation, &gt;4wk old</td>
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<td>• &lt;11 kg: 45 mg/kg twice daily w/ritonavir 7 mg/kg twice daily</td>
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<td>• 11-14 kg: 30 mg/kg twice daily w/ritonavir 3 mg/kg twice daily</td>
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<td>• 15-19 kg: 23 mg/kg twice daily w/ritonavir 3 mg/kg twice daily</td>
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<td>• &gt;20 kg: 18 mg/kg (up to 700 mg) twice daily w/ritonavir 3 mg/kg</td>
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<td>• (up to 100 mg) twice daily</td>
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<td></td>
<td>• &gt;38 wk gestation, &gt;2 yo, w/o ritonavir</td>
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<td></td>
<td>Pediatric dosing (treatment experienced w/darunavir resistance substitution):</td>
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<td></td>
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<td></td>
<td>• 3-17 yo</td>
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<td></td>
<td>• 10-10.9 kg: 200 mg twice daily w/ritonavir 32 mg twice daily</td>
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<td></td>
<td>• 11-11.9 kg: 220 mg twice daily w/ritonavir 32 mg twice daily</td>
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<td></td>
<td>• 12-12.9 kg: 240 mg twice daily w/ritonavir 40 mg twice daily</td>
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<td></td>
<td>• 13-13.9 kg: 260 mg twice daily w/ritonavir 40 mg twice daily</td>
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<td></td>
<td>• 14-14.9 kg: 280 mg twice daily w/ritonavir 48 mg twice daily</td>
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<td>• 15-29 kg: 375 mg twice daily w/ritonavir 48 mg twice daily</td>
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<td></td>
<td>• 30-39 kg: 450 mg twice daily w/ritonavir 60 mg twice daily</td>
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<td></td>
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<td></td>
<td>• 600 mg twice daily w/ritonavir 100 mg twice daily</td>
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</tbody>
</table>

**Product**

- **Fosamprenavir** (LEXIVA®)

**Route of Administration**

- Oral tablet
- Oral suspension

**Available Doses**

- 700 mg
- 50 mg/mL

**Dosing**

- 11-11.9 kg: 385 mg daily w/ritonavir 64 mg daily
- 12-12.9 kg: 420 mg daily w/ritonavir 80 mg daily
- 13-13.9 kg: 455 mg daily w/ritonavir 80 mg daily
- 14-14.9 kg: 490 mg daily w/ritonavir 96 mg daily
- 15-29 kg: 600 mg daily w/ritonavir 100 mg daily
- 30-39 kg: 675 mg daily w/ritonavir 100 mg daily
- >40 kg: 800 mg daily w/ritonavir 100 mg daily

**Pediatric dosing (treatment experienced w/darunavir resistance substitution):**

- 3-17 yo
  - 10-10.9 kg: 200 mg twice daily w/ritonavir 32 mg twice daily
  - 11-11.9 kg: 220 mg twice daily w/ritonavir 32 mg twice daily
  - 12-12.9 kg: 240 mg twice daily w/ritonavir 40 mg twice daily
  - 13-13.9 kg: 260 mg twice daily w/ritonavir 40 mg twice daily
  - 14-14.9 kg: 280 mg twice daily w/ritonavir 48 mg twice daily
  - 15-29 kg: 375 mg twice daily w/ritonavir 48 mg twice daily
  - 30-39 kg: 450 mg twice daily w/ritonavir 60 mg twice daily
  - >600 mg twice daily w/ritonavir 100 mg twice daily

**Generic Available**

- No
<table>
<thead>
<tr>
<th>Product</th>
<th>Route of Administration</th>
<th>Available Doses</th>
<th>Dosing</th>
<th>Generic Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indinavir (CRIXIVAN®)</td>
<td>Oral capsule</td>
<td>200 mg, 400 mg</td>
<td>- 11-19 kg: 30 mg/kg twice daily&lt;br&gt;- &gt;20 kg: 30 mg/kg (up to 1400 mg) twice daily</td>
<td>No</td>
</tr>
<tr>
<td>Nelfinavir (VIRACEPT®)</td>
<td>Oral tablet</td>
<td>250 mg, 625 mg</td>
<td>Adult dosing (treatment naive):&lt;br&gt;• 800 mg every 8 hours&lt;br&gt;Adult dosing (treatment experienced):&lt;br&gt;• 800 mg every 8 hours&lt;br&gt;Pediatric dosing:&lt;br&gt;• Limited experience, no current recommendation</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Oral powder</td>
<td>50 mg/g</td>
<td>Adult dosing (treatment naive):&lt;br&gt;• 1250 mg twice daily or 750 mg three times daily&lt;br&gt;Adult dosing (treatment experienced):&lt;br&gt;• 1250 mg twice daily&lt;br&gt;• Alternate: 750 mg three times daily&lt;br&gt;Pediatric dosing:&lt;br&gt;• 2-13 yo&lt;br&gt;  • 45-55 mg/kg twice daily&lt;br&gt;  • Alternate: 25-35 mg/kg three times daily&lt;br&gt;  • Max: 2500 mg/day&lt;br&gt;• &gt;13 yo&lt;br&gt;  • 1250 mg twice daily&lt;br&gt;  • Alternate: 750 mg three times daily</td>
<td>No</td>
</tr>
<tr>
<td>Ritonavir (NORVIR®)</td>
<td>Oral capsule</td>
<td>100 mg</td>
<td>Adult dosing:&lt;br&gt;• 600 mg twice daily&lt;br&gt;• Not preferred as primary PI&lt;br&gt;• Start at 300 mg twice daily and titrate up</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Oral tablet</td>
<td>100 mg</td>
<td>Pediatric dosing:</td>
<td></td>
</tr>
<tr>
<td>Product</td>
<td>Route of Administration</td>
<td>Available Doses</td>
<td>Dosing</td>
<td>Generic Available</td>
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<td></td>
<td></td>
<td></td>
<td><strong>Oral solution</strong> 80 mg/mL</td>
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</tbody>
</table>
| **Saquinavir** (INVIRASE®)    | Oral capsule            | 200 mg          | **Adult dosing (treatment naïve):**  
- 1000 mg twice daily w/ritonavir 100 mg twice daily  
**Adult dosing (treatment experienced):**  
- 1000 mg twice daily w/ritonavir 100 mg twice daily  
**Pediatric dosing:**  
- >16 yo; 1000 mg twice daily w/ritonavir 100 mg twice daily | No                |
|                               | Oral tablet             | 500 mg          |                                                                                                                                                                                                                                                                          |                   |
| **Tipranavir** (APTIVUS®)     | Oral capsule            | 250 mg          | **Adult dosing (treatment naïve):**  
- 500 mg twice daily w/ritonavir 200 mg twice daily  
**Adult dosing (treatment experienced):**  
- 500 mg twice daily w/ritonavir 200 mg twice daily  
**Pediatric dosing (treatment experienced):**  
- 2-18 yo  
- 14 mg/kg twice daily w/ritonavir 6 mg/kg twice daily  
- Alternate: 375 mg/m² twice daily w/ritonavir 150 mg/m² twice daily  
- Max: tipranavir 1000 mg/day; ritonavir: 400 mg/day | No                |
|                               | Oral solution           | 100 mg/mL       |                                                                                                                                                                                                                                                                          |                   |
| **Dual Protease Inhibitor**   |                         |                 | **Lopinavir and Ritonavir** (KALETRA®)  
- Oral tablet 100mg/25mg; 200mg/50mg  
**Adult dosing (treatment naïve or experienced; w/o efavirenz, nelfinavir, or nevirapine):**  
- 400 mg/100 mg twice daily  
**Adult dosing (treatment naïve or experienced; if given w/efavirenz, nelfinavir, or nevirapine; or w/lopinavir resistance substitutions):**  
- Tablet: 500 mg/125 mg twice daily  
- Suspension: 533 mg/133 mg twice daily  
**Pediatric dosing (w/o efavirenz, nelfinavir, or nevirapine):**  
- 80mg/20mg per mL  | No                |
<p>|                               | Oral suspension         | 80mg/20mg per mL|                                                                                                                                                                                                                                                                          |                   |</p>
<table>
<thead>
<tr>
<th>Product</th>
<th>Route of Administration</th>
<th>Available Doses</th>
<th>Dosing</th>
<th>Generic Available</th>
</tr>
</thead>
</table>
| **Atazanavir and Cobicistat (EVOTAZ®)** | Oral tablet             | 300 mg/150 mg   | Adult dosing (treatment naïve):  
• 300 mg/150 mg daily  
Adult dosing (treatment experienced):  
• 300 mg/150 mg daily  
Pediatric dosing:  
• Not currently recommended in pediatric patients                                                                                                                                                                                                                     | No                |
| **Darunavir and Cobicistat (PREXCOBIX®)** | Oral tablet             | 800 mg/150 mg   | Adult dosing (treatment naïve):  
• 800 mg/150 mg daily  
Adult dosing (treatment experienced w/o darunavir resistance substitution):  
• 800 mg/150 mg daily  
Pediatric dosing:  
• Not currently recommended in pediatric patients                                                                                                                                                                                                                  | No                |
Disease Overview

HIV, the virus that causes acquired immune deficiency syndrome (AIDS), is a worldwide health challenge with approximately 35 million people infected. HIV/AIDS is the world’s leading cause of death from infection. Of those infected, over 3 million are children (<15 years old) and the vast majority of those infected live in low- and middle-income countries, with sub-Saharan Africa the most affected region (24.7 million people). In the United States, an estimated 1.2 million people have HIV and up to 14% of those infected are unaware. Those who are unaware of being infected are a large source of disease transmission and are at risk for developing complications. The diagnosis of new HIV infections in the US has remained relatively constant at 50,000 per year. In Utah, over 100 new cases are diagnosed each year and, in total, nearly 3,000 people are infected. HIV is transmitted through exposure to infected blood, reproductive fluids, breast milk and the infection may be transmitted from mothers with an HIV infection to the child during the birthing process. Groups at highest risk of becoming infected with HIV include: men who have sex with men (MSM), African Americans and IV drug users (IDU).

The HIV virus causes infection by fusing with the host cell, sending RNA into the cytoplasm for replication and integrating the subsequent full-length double-stranded DNA virus copy into the host chromosome. Once integrated into the host cell, HIV causes a deficiency of helper T cells, a loss of cell mediated immunity and a profound immunodeficiency. Helper T cells with the CD4 molecule on the cell surface act as the primary cellular receptor for HIV. When CD4+ T cell count falls below 500/µL, patients are at a much higher risk of developing opportunistic infections. Opportunistic infections which may cause serious disease in patients with HIV infection include P. jiroveci, mycobacterium and cytomegalovirus (CMV).

Three key enzymes are required for successful HIV viral host infection: reverse transcriptase, integrase and protease. Reverse transcriptase converts the viral RNA into full-length double-stranded DNA, integrase is required for viral DNA insertion into the host genome and the protease enzymes cleave essential virus proteins required for host infection. These enzymes are the sites of action for HIV treatment therapy. To prevent viral resistance, an approach called highly active antiretroviral therapy (HAART), combining agents from at least two different drug classes, is recommended for treatment of HIV infection. In general, standard combination therapy in treatment-naïve patients with HIV consists of two nucleoside reverse transcriptase inhibitors (NRTI) combined with a third antiretroviral agent from one of the following classes: a non-nucleoside reverse transcriptase inhibitor (NNRTI), an integrase inhibitor (II) or a protease inhibitor (PI) boosted with ritonavir or cobicistat. Agents used to interfere with the virus' ability to enter the host cell (entry inhibitors and fusion inhibitors) may be considered as part of HAART. Table 2 provides a summary of the drug classes used in the treatment of HIV infection. Overall, the goal of HIV therapy is to decrease viral load, increase CD4+ T cell count and prevent opportunistic infections.
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agents in the class</th>
<th>Indications &amp; Use</th>
<th>Manufacturer &amp; Approval date</th>
<th>Safety</th>
</tr>
</thead>
</table>
| Nucleoside Reverse Transcriptase Inhibitors (NRTI) | Combivir®: lamivudine and zidovudine | Treatment of HIV infection Oral: one tablet twice daily Not recommended in patients requiring dosage reduction including pediatric patients <30 kg, renally-impaired patients with a creatinine clearance <50 mL/minute, patients with hepatic impairment | GlaxoSmithKline, 9/27/97; Generic Available | Black Box: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs in combination with other antiretrovirals. |}
<p>| | Emtriva®: emtricitabin (FTC) | Treatment of HIV infection in combination with at least two other antiretroviral agents Oral: Capsule- 200 mg once daily; Solution- 240 mg once daily | Gilead Sciences, 7/2/2003 | Black Box: Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued emtricitabine. |
| | Epivir®: lamivudine (3TC) | HIV: Treatment of HIV infection in combination with other antiretroviral agents Oral: 150 mg twice daily or 300 mg once daily HBV: Treatment of chronic hepatitis B associated with evidence of hepatitis B viral replication and active liver inflammation | GlaxoSmithKline, 11/17/1995; Generic Available | Black Box: Severe, acute exacerbations of hepatitis B have been reported in patients who are coinfected with hepatitis B virus (HBV) and HIV-1 and have discontinued lamivudine |
| | Epzicom®: abacavir and lamivudine | Treatment of HIV infections in combination with other antiretroviral agents Oral: One tablet (abacavir 600 mg and lamivudine 300 mg) once daily | GlaxoSmithKline, 8/2/2004 | Black Box: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir; Severe, acute exacerbations of hepatitis B have been reported in patients who are coinfected with hepatitis B virus (HBV) and HIV-1 and have discontinued lamivudine |</p>
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agents in the class</th>
<th>Indications &amp; Use</th>
<th>Manufacturer &amp; Approval date</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hivid®: zalcitabine, dideoxycytidine (ddC)</td>
<td>Treatment of HIV infection in conjunction with other antiretrovirals Oral: 0.75 mg every 8 hours</td>
<td>Hoffmann-La Roche, 6/19/1992</td>
<td>Black Box: Severe peripheral neuropathy reported; Pancreatitis reported rarely; Hepatic failure and death reported rarely</td>
<td></td>
</tr>
<tr>
<td>Retrovir®: zidovudine (ZDV, azidothymidine, AZT)</td>
<td>Treatment of HIV-1 infection in combination with at least two other antiretroviral agents; Prevention of perinatal HIV-1 transmission Oral: 300 mg twice daily, IV: 1 mg/kg/dose administered every 4 hours around-the-clock</td>
<td>GlaxoSmithKline, 3/19/1987; May be generic depending on product</td>
<td>Black Box: Zidovudine has been associated with hematologic toxicity, including neutropenia and severe anemia; Prolonged use of zidovudine has been associated with symptomatic myopathy</td>
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</tr>
<tr>
<td>Trizivir®: abacavir, zidovudine, and lamivudine</td>
<td>Treatment of HIV-1 infection in combination with other antiretroviral agents or alone in patients weighing more than 40 kg Oral: One tablet twice daily</td>
<td>GlaxoSmithKline, 11/14/2000; Generic Available</td>
<td>Black Box: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir; Zidovudine has been associated with hematologic toxicity; Prolonged use of zidovudine has been associated with symptomatic myopathy; Severe, acute exacerbations of hepatitis B have been reported in patients who are coinfected with hepatitis B virus (HBV) and HIV-1 and have discontinued lamivudine</td>
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<tr>
<td>Truvada®: tenofovir disoproxil fumarate and emtricitabine</td>
<td>Treatment of HIV-1 infection in combination with other antiretroviral agents in adults and pediatric patients ≥12 years of age Oral: One tablet (emtricitabine 200 mg and tenofovir 300 mg) once daily</td>
<td>Gilead Sciences, 8/2/2004</td>
<td>Black Box: Risk of drug resistance with use for preexposure prophylaxis</td>
<td></td>
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<tr>
<td></td>
<td>Pre-exposure prophylaxis (PrEP) for prevention of HIV-1 infection in adults who are at high risk for acquiring HIV Oral: One tablet (emtricitabine 200 mg and tenofovir 300 mg) once daily</td>
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<tr>
<td>Drug Class</td>
<td>Agents in the class</td>
<td>Indications &amp; Use</td>
<td>Manufacturer &amp; Approval date</td>
<td>Safety</td>
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</table>
| Videx®: didanosine (ddl) | Treatment of HIV-1 infection in combination with other antiretroviral agents  
Oral: <60 kg: 125 mg twice daily (preferred) or 250 mg once daily, ≥60 kg: 200 mg twice daily (preferred) or 400 mg once daily; Delayed release capsule (Videx EC): 25 kg to <60 kg: 250 mg once daily, ≥60 kg: 400 mg once daily | Bristol Myers-Squibb; 10/9/1991, enteric coated 10/31/2000; May be generic depending on product | Black Box: Fatal and nonfatal pancreatitis have occurred during therapy with didanosine used alone or in combination regimens |
| Viread®: tenofovir disoproxil fumarate (TDF) | Treatment of HIV-1 infection in combination with other antiretroviral agents in adults and pediatric patients ≥2 years of age  
Oral: 300 mg once daily  
Treatment of chronic hepatitis B virus (HBV) in patients ≥12 years of age | Gilead Sciences, 10/26/2001 |  |
| Zerit®: stavudine (d4T) | Treatment of HIV infection in combination with other antiretroviral agents  
Oral:  
<60 kg: 30 mg every 12 hours  
≥60 kg: 40 mg every 12 hours | Bristol Myers-Squibb, 6/24/1994; Generic Available | Black Box: Fatal and nonfatal pancreatitis has occurred during therapy when stavudine was part of a combination regimen that included didanosine |
| Ziagen®: abacavir sulfate (ABC) | Treatment of HIV-1 infection in combination with other antiretroviral agents  
Oral: 300 mg twice daily or 600 mg once daily | GlaxoSmithKline, 12/17/1998; May be generic depending on product | Black Box: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir therapy |
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agents in the class</th>
<th>Indications &amp; Use</th>
<th>Manufacturer &amp; Approval date</th>
<th>Safety</th>
</tr>
</thead>
</table>
| Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) | Edurant®: rilpivirine  | Treatment of HIV-1 infection in combination with other agents  
**Oral:** 25 mg once daily                                                                                       | Tibotec Therapeutics, 5/20/2011                           |                                                                                                                                                                                                                                                                                                                                                     |
|                                                | Intelence®: etravirine   | Treatment of HIV-1 infection in combination with at least two additional antiretroviral agents in treatment-experienced patients exhibiting viral replication with documented non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance  
**Oral:** 200 mg twice daily                                                                                                         | Tibotec Therapeutics, 1/18/2008                           |                                                                                                                                                                                                                                                                                                                                                     |
|                                                | Rescriptor®: delavirdine (DLV) | Treatment of HIV-1 infection in combination with at least two additional antiretroviral agents  
**Oral:** 400 mg 3 times/day                                                                                                           | Pfizer, 4/4/1997                                               |                                                                                                                                                                                                                                                                                                                                                     |
|                                                | Sustiva®: efavirenz (EFV) | Treatment of HIV-1 infection in combination with other antiretroviral agents in adults and pediatric patients at least 3 months old and weighing at least 3.5 kg  
**Oral:** 600 mg once daily                                                                                                          | Bristol Myers-Squibb, 9/17/1998                           |                                                                                                                                                                                                                                                                                                                                                     |
|                                                | Viramune®: nevirapine (NVP) | Treatment of HIV-1 infection in combination with additional antiretroviral agents  
**Oral:** Immediate release: 200 mg twice daily; Extended release: 400 mg once daily                                                                                  | Boehringer Ingelheim; 6/21/1996, XR 3/25/2011; Generic Available | **Black Box:** Severe, life-threatening, and, in some cases, fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with nevirapine; Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine; Patients must be monitored intensively during the first 18 weeks of therapy with nevirapine to detect potentially life-threatening hepatotoxicity or skin reactions                                                                                                                                                                                                 |

**Safety Note:**
- **Black Box:** Severe, life-threatening, and, in some cases, fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with nevirapine; Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine; Patients must be monitored intensively during the first 18 weeks of therapy with nevirapine to detect potentially life-threatening hepatotoxicity or skin reactions.
<table>
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<tbody>
<tr>
<td>Protease Inhibitors (PI)</td>
<td>Agenerase®: amprenavir (APV) *no longer marketed</td>
<td>Treatment of HIV Infection&lt;br&gt;Oral: 1.2 g once to twice daily</td>
<td>GlaxoSmithKline, 4/15/1999</td>
<td>Black Box: The oral solution is contraindicated in infants and children &lt;4 years of age, pregnant women, patients with hepatic or renal failure, and those receiving metronidazole or disulfiram and should be used with caution in others. In August 2007, the manufacturer of amprenavir announced that sales of the drug would be discontinued as of October 2007. This action was taken because demand for amprenavir had declined substantially and because of the availability of other treatment options.</td>
</tr>
<tr>
<td></td>
<td>Aptivus®: tipranavir (TPV)</td>
<td>Treatment of HIV-1 infection in combination with ritonavir and other antiretroviral agents; limited to treatment-experienced or multiprotease inhibitor resistance.&lt;br&gt;Oral: 500 mg twice daily</td>
<td>Boehringer Ingelheim, 6/22/2005</td>
<td>Black Box: Clinical hepatitis and hepatic decompensation, including some fatalities, have been reported; Both fatal and nonfatal intracranial hemorrhage have been reported.</td>
</tr>
<tr>
<td></td>
<td>Crixivan®: indinavir (IDV)</td>
<td>Treatment of HIV infection; should always be used as part of a multidrug regimen (at least 3 antiretroviral agents)&lt;br&gt;Oral: 800 mg two to three times daily</td>
<td>Merck, 3/13/1996</td>
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<td></td>
<td>Evotaz®: atazanavir and cobicistat</td>
<td>Treatment of HIV-1 infection in adults in combination with other antiretroviral agents&lt;br&gt;Oral: One tablet (atazanavir 300 mg/cobicistat 150 mg) once daily</td>
<td>Bristol-Myers Squibb, 1/29/2015</td>
<td></td>
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<tr>
<td></td>
<td>Invirase®: saquinavir mesylate (SQV; previously Fortovase®)</td>
<td>Treatment of HIV infection; used in combination with ritonavir and other antiretroviral agents&lt;br&gt;Oral: 1000 mg twice daily</td>
<td>Hoffmann-La Roche, 12/6/1995</td>
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<tr>
<td>Drug Class</td>
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<tr>
<td>Kaletra®: lopinavir and ritonavir (LPV/RTV)</td>
<td>Treatment of HIV-1 infection in combination with other antiretroviral agents</td>
<td>Oral: Lopinavir 400 mg/ritonavir 100 mg twice daily</td>
<td>Abbott Laboratories, 9/15/2000</td>
<td></td>
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<tr>
<td>Lexiva®: fosamprenavir calcium (FOS-APV)</td>
<td>Treatment of HIV infections in combination with at least two other antiretroviral agents</td>
<td>Oral: 700-1,400 mg once to twice daily</td>
<td>GlaxoSmithKline, 10/20/2003</td>
<td></td>
</tr>
<tr>
<td>Norvir®: ritonavir (RTV)</td>
<td>Treatment of HIV infection; should always be used as part of a multidrug regimen</td>
<td>Oral: 600 mg twice daily</td>
<td>Abbott Laboratories, 3/1/1996</td>
<td>Black Box: Coadministration with sedative hypnotics, antiarrhythmics, or ergot alkaloid preparations may result in potentially serious and/or life-threatening adverse reactions due to possible effects of ritonavir on the hepatic metabolism of certain drugs</td>
</tr>
<tr>
<td>Prezcobix®: darunavir and cobicistat</td>
<td>Treatment of HIV-1 infection, coadministered with other antiretroviral agents, in treatment-naive and in treatment-experienced patients without darunavir resistant-associated substitutions (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V) Oral: One tablet (darunavir 800 mg/cobicistat 150 mg) once daily</td>
<td>Janssen Therapeutics, 1/29/2015</td>
<td></td>
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<tr>
<td>Prezista®: darunavir</td>
<td>Treatment of HIV-1 infection, coadministered with ritonavir and other antiretroviral agents, in adults and pediatric patients 3 years and older Oral: 800 mg once daily</td>
<td>Tibotec Therapeutics, 6/23/2006</td>
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<td>Drug Class</td>
<td>Agents in the class</td>
<td>Indications &amp; Use</td>
<td>Manufacturer &amp; Approval date</td>
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</table>
|                                        | Reyataz®: atazanavir sulfate (ATV)        | Treatment of HIV-1 infections in combination with other antiretroviral agents in patients ≥3 months weighing ≥10 kg  
**Oral**: 300-400 mg once daily  | Bristol-Myers Squibb, 6/20/2003                                                              |                          |
|                                        | Viracept®: nelfinavir mesylate (NFV)      | Treatment of HIV infection in combination with other antiretroviral therapies  
**Oral**: 750 mg 3 times daily or 1250 mg twice daily  | Agouron Pharmaceuticals, 3/14/1997                                                              |                          |
| **Entry Inhibitors**                   | Selzentry®: maraviroc                     | Treatment of only CCR5-tropic HIV-1 infection, in combination with other antiretroviral agents  
**Oral**: 300 mg twice daily  | Pfizer, 8/6/2007                                                                 | **Black Box**: Hepatotoxicity has been reported with maraviroc use |
| **Fusion Inhibitors**                  | Fuzeon®: enfuvirtide (T-20)               | Treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy  
**SubQ**: 90 mg twice daily  | Hoffmann-La Roche & Trimeris, 3/13/2003                                                       |                          |
| **Integrase Inhibitors**               | Isentress®: raltegravir                    | Treatment of HIV-1 infection in combination with other antiretroviral agents in patients 4 weeks and older and weighing at least 3 kg  
**Oral**: Film-coated tablet: 400 mg twice daily; chewable tablet and oral suspension available for pediatric, weight-based dosing  | Merck & Co.: 10/21/2007                                                   |                          |
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agents in the class</th>
<th>Indications &amp; Use</th>
<th>Manufacturer &amp; Approval date</th>
<th>Safety</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Tivicay®: dolutegravir</td>
<td>Treatment of HIV-1 infection in combination with other antiretroviral agents in adults and children and adolescents ≥12 years of age and weighing ≥40 kg Oral: 50 mg once to twice daily</td>
<td>GlaxoSmithKline, 8/13/2013</td>
<td></td>
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<td></td>
<td>Vitekta®: Elvitegravir</td>
<td>Treatment of HIV-1 infection in combination with other antiretroviral agents Oral: 85–150 mg once daily</td>
<td>Gilead Sciences, 9/24/14</td>
<td></td>
</tr>
<tr>
<td>Multi-Class Combination Agents</td>
<td>Atripla®: efavirenz, emtricitabine, tenofovir disoproxil fumarate</td>
<td>Treatment of HIV-1 infection Oral: One tablet once daily Recommended as an initial regimen for antiretroviral-naive patients (HHS [adult], 2014)</td>
<td>Bristol-Myers Squibb, 7/12/2006</td>
<td>Moderate-to-severe renal OR hepatic impairment: Use not recommended</td>
</tr>
<tr>
<td></td>
<td>Complera®: emtricitabine, rilpivirine, tenofovir disoproxil fumarate</td>
<td>Treatment of HIV-1 infection Oral: One tablet once daily Recommended as a complete regimen in antiretroviral treatment-naive adult patients with HIV-1 RNA ≤100,000 copies/mL at the start of therapy and in certain virologically suppressed (HIV-1 RNA &lt;50 copies/mL) adult patients</td>
<td>Gilead Sciences, 8/10/2011</td>
<td>Dosage adjustment required for concomitant therapy with rifabutin</td>
</tr>
<tr>
<td></td>
<td>Stribild®: elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate</td>
<td>Treatment of HIV-1 infection Oral: One tablet once daily Recommended in adults who are antiretroviral treatment-naive and in certain virologically suppressed (HIV-1 RNA &lt;50 copies/mL) adult patients</td>
<td>Gilead Sciences, 8/27/2012</td>
<td>CrCl &lt;70 mL/minute: Use not recommended</td>
</tr>
<tr>
<td>Drug Class</td>
<td>Agents in the class</td>
<td>Indications &amp; Use</td>
<td>Manufacturer &amp; Approval date</td>
<td>Safety</td>
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<tr>
<td></td>
<td>Triumeq®: Abacavir, Dolutegravir, Lamivudine</td>
<td>Treatment of HIV-1 infection Oral: One tablet daily</td>
<td>ViiV Healthcare, 8/22/2014</td>
<td>Black Box: Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have been associated with abacavir; Severe, acute exacerbations of hepatitis B have been reported in patients who are coinfected with hepatitis B virus (HBV) and HIV-1 and have discontinued lamivudine</td>
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Both the United States Centers for Disease Control and Prevention (CDC)\textsuperscript{12} and the World Health Organization (WHO)\textsuperscript{13} have published staging systems for adolescent and adult patients with HIV/AIDS to help identify disease severity and guide treatment. See Table 3 for a summary of the disease classifications. Consideration of both the extent of immunosuppression and the current presenting symptoms are important when deciding therapeutic and prophylactic treatment therapies.\textsuperscript{12} Resistance to current HIV treatment in patients may manifest as lower CD4+ counts, thus prompting addition or change of therapy. Patients with additional bacterial and/or viral coinfections (such as hepatitis C virus (HCV), hepatitis B virus (HBV), tuberculosis (TB), etc.) may require specific drug therapies and additional monitoring. In addition, lower CD4+ levels increase risk of opportunistic infection, prompting initiation of prophylactic antimicrobial treatments.\textsuperscript{12-14}

<table>
<thead>
<tr>
<th>Classification System</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>U.S. Centers for Disease Control and Prevention (CDC)</strong></td>
<td>CD4+ T Cell Count</td>
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<tr>
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<td>&gt;500/µL</td>
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<tr>
<td></td>
<td>200-499/µL</td>
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<tr>
<td></td>
<td>&lt;200/µL</td>
</tr>
<tr>
<td><strong>World Health Organization (WHO) Clinical Staging and Disease Classification System</strong></td>
<td>Stage</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Asymptomatic, Persistent generalized lymphadenopathy</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Moderate unexplained weight loss, Recurrent respiratory infections, Herpes zoster, Angular cheilitis, Recurrent oral ulceration, Papular pruritic eruptions, Seborrheic dermatitis, Fungal nail infections</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Unexplained severe weight loss, Unexplained chronic diarrhea for &gt;1 month, Unexplained persistent fever for &gt;1 month, Persistent oral candidiasis, Oral hairy leukoplakia, Pulmonary tuberculosis, Severe presumed bacterial infections, Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis, Unexplained anemia, Neutropenia, Chronic thrombocytopenia</td>
</tr>
<tr>
<td>Stage 4</td>
<td>HIV wasting syndrome, Pneumocystis pneumonia, Recurrent severe bacterial pneumonia, Chronic herpes simplex infection, Esophageal candidiasis, Extrapulmonary tuberculosis, Kaposis sarcoma, Cytomegalovirus infection, Toxoplasmosis, Encephalopathy, Cryptococcosis, Disseminated nontuberculosis mycobacteria infection, Progressive multifocal leukoencephalopathy, Candida of the trachea/bronchi/lungs, Chronic cryptosporidiosis, Chronic isosporiasis, Disseminated mycosis, Recurrent nontypoidal Salmonella bacteremia, Lymphoma, Invasive cervical carcinoma, Atypical disseminated leishmaniasis, Symptomatic HIV-associated nephropathy/ cardiomyopathy, Reactivation of trypanosomiasis</td>
</tr>
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</table>

The US Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (2015)\textsuperscript{15} recommends all patients receive Antiretroviral Therapy (ART) to reduce the risk of disease progression and to prevent transmission. Before initiation of ART, genotypic drug-resistance testing is recommended to help guide therapy decisions. In an attempt to reduce or avoid drug-resistance, the guidelines recommend patients receive education outlining the benefits and risks of therapy and the importance of adherence before initiation of therapy. If the benefits do not outweigh the risks or if adherence will be a significant challenge, patients may decide to postpone therapy or providers may recommend deferring therapy. In treatment-naïve adults and adolescent patients with HIV, ART should consist of three active antiretroviral agents. Table 4 provides a summary of the ART combination therapy recommendations published by the most recent clinical practice guidelines. In general, both HIV-1 and HIV-2 infections are treated the same as they are transmitted in the same fashion and are associated with similar rates of
opportunistic infections and development of AIDS. Although HIV-2 infections tend to be associated with slower development of immunodeficiency, treatment should be initiated before disease progression. In treatment-experienced patients, a thorough evaluation of virologic failure including an assessment of HIV-RNA and CD4+ T cell count trends over time, treatment history, drug-resistance testing results, medication adherence and drug-drug/drug-food interactions is recommended. In these patients, an entirely new regimen including at least two, preferably three, antiretroviral agents should be initiated; simply adding an additional antiretroviral agent to the current regimen is not recommended as this may lead to increased resistance and drug inefficacy.\textsuperscript{15}

In general, the recommendations for initiation of ART and goals of therapy in adults and adolescents are the same for special populations of patients with HIV infection. Initiation of ART is recommended as soon as possible in all pregnant women to prevent perinatal transmission. Pharmacokinetic changes in pregnancy may lead to lower plasma levels of drugs and necessitate increased dosages, more frequent dosing, or boosting, especially of protease inhibitors. All patients >50 years of age should receive ART, regardless of CD4+ T cell count, due to increased risk of non-AIDS related complications and reduced response to ARV in this patient population.\textsuperscript{15} ART is recommended in patients with HIV-coinfections as the benefits of antiretroviral therapy almost always outweigh the risks (drug-induced liver injury, drug-drug interactions, etc.) In patients with HIV and a TB-coinfection, both ART and TB treatments should be initiated immediately. All patients with an HIV/HCV-coinfection, including those with cirrhosis, should receive ART, regardless of CD4+ T cell count. Patients with an HIV/HBV-coinfection should receive an ART regimen with an NRTI backbone including tenofovir (TDF) and either emtricitabine (FTC) or lamivudine (3TC), as this regimen has activity against both HIV and HBV infections. In pediatric patients, ART is recommended in all children < 12 months old and in children > 1 year old, depending on CDC stage and CD4+ T cell count.\textsuperscript{15,16} Table 4 provides a summary of the ART combination therapy recommendations in special populations.

**Table 4. Most Current Clinical Practice Guidelines for the Treatment of HIV**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendations</th>
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| **Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (US Department of Health and Human Services; 2015)**\textsuperscript{15} | **Treatment naive patients, recommended regimens:**
- INSTI-based regimens:
  - DTG/ABC/(3TC or FTC) only for patients who are HLA-B*5701 negative
  - DTG plus TDF/(3TC or FTC)
  - AVG/c/TDF/(3TC OR FTC) only for patient with pre-treatment estimated CrCl ≥70 mL/min
  - RAL plus TDF/(3TC OR FTC)
- PI-based regimens:
  - DRV/r plus TDF/(3TC OR FTC)

**Treatment naive patients, alternative regimens:**
- NNRTI-based regimens:
  - EFV/TDF/(3TC OR FTC)
  - RPV/TDF/(3TC OR FTC) only for patients with pre-treatment HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm\(^3\)
- PI-based regimens:
  - ATV/c plus TDF/(3TC OR FTC) only for patients with pre-treatment estimated CrCl ≥70 mL/min |
- ATV/r plus TDF/(3TC OR FTC)
- (DRV/c or DRV/r) plus ABC/(3TC or FTC) only for patients who are HLA-B*5701 negative
- DRV/c plus TDF/(3TC OR FTC) only for patients with pre-treatment estimated CrCl ≥ 70 mL/min

**Treatment naive patients, other regimens:**

- INSTI-based regimen:
  - RAL plus ABC/(3TC or FTC) only for patient who are HLA-B*5701 negative
- NNRTI-based regimen:
  - EFV plus ABC/(3TC or FTC) only for patients who are HLA-B*5701 negative and pre-treatment HIV RNA < 100,000 copies/mL
- PI-based regimens:
  - (ATV/c or ATV/r) plus ABC/(3TC or FTC) only for patients who are HLA-B*5701 negative and pre-treatment HIV RNA < 100,000 copies/mL
  - LPV/r (once or twice daily) plus ABC/(3TC or FTC) only for patients who are HLA-B*5701 negative
  - LPV/r (once or twice daily) plus TDF/(3TC OR FTC)
- Other regimens when TDF or ABC cannot be used:
  - DRV/r plus RAL only for patients with pre-treatment HIV RNA < 100,000 copies/mL and CD4 cell count > 200 cells/mm³
  - LPV/r (twice daily) plus (3TC or FTC) (twice daily)

---

**Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection (National Institutes of Health Office of AIDS Research Advisory Council; 2015)**

**Pediatric initial therapy recommendations:**

- **2-NRTI backbone:**
  - < 3 months: AZT plus (3TC or FTC)
  - ≥ 3 months: ABC plus (3TC or FTC) OR AZT plus (3TC or FTC); ABC only if HLA-B*5701 negative
  - ≥ 12 years: ABC plus 3TC or plus FTC
  - Adolescents at Tanner Stage 4 or 5: ABC plus 3TC or plus FTC or TDF plus 3TC or plus FTC
- **Alternative 2-NRTI backbone:**
  - ≥ 2 weeks: ddi plus (3TC or FTC) OR AZT plus ddi
  - ≥ 3 months: AZT plus ddi
  - Children and adolescents at Tanner Stage 3: TDF plus (3TC or FTC)
  - ≥ 13 years: AZT plus (3TC or FTC)
- **Agents to combine with backbone:**
  - ≥ 42 weeks postmenstrual and > 14 days postnatal and children < 3 years: LPV/r
  - 3 to < 6 years: EFV or LPV/r
  - ≥ 6 years: ATV/r or EFV or LPV/r
- **Alternative agents to combine with backbone:**
  - > 14 days old: NVP
  - ≥ 3 months to < 6 months & ≥ 10 kg: ATV/r
  - ≥ 2 years: RAL
  - ≥ 3 years to < 12 years: DRV (twice daily)/r
  - ≥ 12 years: DRV (once daily)/r or DTG
### Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States (National Institutes of Health Office of AIDS Research Advisory Council; 2014)\(^7\)

- Generally, the same regimens used in non-pregnant adults are used in pregnant women unless there are known risks to the fetus or mother during pregnancy
- Avoid EFV containing regimens until after 8 weeks gestation (may be continued if started if woman present in first trimester and it is achieving virologic suppression)
- Avoid combination of d4T and ddI
- PI-based regimens present a small risk of preterm birth

### Antiretroviral therapy for HIV infection in infants and children: towards universal access (World Health Organization; 2010)\(^8\)

**Infants, first-line treatment:**
- No prior exposure to ARVs:
  - NVP + 2 NRTIs
- Prior exposure to NVP or other NNRTIs:
  - LPV/r + 2 NRTIs
- Unknown ARV exposure status:
  - NVP + 2 NRTIs

**Children, first-line treatment:**
- 12-24 months, not exposed to NNRTIs:
  - NVP + 2 NRTIs
- 12-24 months, prior exposure to NVP or other NNRTIs:
  - LPV/r + 2 NRTIs
- 24 months-3 years:
  - NVP + 2 NRTIs
- 3 years plus:
  - (NVP or EFV) + 2 NRTIs

**Preferred NRTI backbones:**
1. 3TC + AZT
2. 3TC + ABC
3. 3TC + d4T

### Guide for HIV/AIDS Clinical Care (Health Resource and Services Administration (HRSA); 2011)\(^9\)

**Treatment naive patients, preferred regimens:**
- INSTI-based regimens:
  - RAL + TDF/(FTC or 3TC)
  - Elvitegravir/cobicistat/TDF/(FTC or 3TC) only if CrCl ≥70 mL/min
  - Dolutegravir (once daily) +ABC/(FTC or 3TC) only for patients who are HLA-B*5701 negative and pre-treatment HIV RNA <100,000 copies/mL
  - Dolutegravir (once daily) + TDF/(FTC or 3TC)
- PI-based regimens:
  - ATV/r + TDF/(FTC or 3TC)
  - DRV (once daily) + TDF/(FTC or 3TC)
- NNRTI-based regimens:
  - EFV/TDF/FTC

**Treatment naive patients, alternative regimens:**
- NRTI-based regimens:
  - EFV + ABC/(FTC or 3TC) only for patients who are HLA-B*5701 negative; caution with pre-treatment HIV RNA <100,000 copies/mL
  - Rilpivirine/TDF/(FTC or 3TC) only for patients with pre-treatment HIV RNA
<100,000 copies/mL and CD4 cell count >200 cells/mm³
- Rilpivirine + ABC/(FTC or 3TC) only for patients with CD4 cell count >200 cells/mm³ and are HLA-B*5701 negative; caution with pre-treatment HIV RNA <100,000 copies/mL
- PI-based regimens:
  - ATV + ABC (FTC or 3TC) only for patients who are HLA-B*5701 negative; caution with pre-treatment HIV RNA <100,000 copies/mL
  - DRV + ABC (FTC or 3TC) only for patients who are HLA-B*5701 negative; caution with pre-treatment HIV RNA <100,000 copies/mL
  - FPV (once or twice daily) + (ABC or TDF)/(FTC or 3TC)
  - LPV/r (once or twice daily) + (ABC or TDF)/(FTC or 3TC)
- INSTI-based regimens:
  - RAL + ABC/3TC

### Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations (World Health Organization (WHO); 2014) 20

<table>
<thead>
<tr>
<th>Adults (including pregnant/breastfeeding women and adults with TB or HBV coinfection), first-line regimens:</th>
</tr>
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<tbody>
<tr>
<td>- TDF + 3TC (or FTC) + EFV</td>
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<tr>
<td>- Alternate: AZT + 3TC + EFV</td>
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<tr>
<td>- Alternate: AZT + 3TC + NVP</td>
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<td>- Alternate: TDF + 3TC (or FTC) + NVP</td>
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<tr>
<th>Adolescents (10 to 19 years) ≥35 kg, first-line regimens:</th>
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<tr>
<td>- TDF + 3TC (or FTC) + EFV</td>
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<tr>
<td>- Alternate: AZT + 3TC + NVP</td>
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<tr>
<td>- Alternate: TDF + 3TC (or FTC) + NVP</td>
</tr>
<tr>
<td>- Alternate: ABC + 3TC + EFV (or NVP)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Children 3 years to less than 10 years and adolescents &lt;35 kg, first-line regimens:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- ABC + 3TC + EFV</td>
</tr>
<tr>
<td>- Alternate: ABC + 3TC + NVP</td>
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<tr>
<td>- Alternate: AZT + 3TC + EFV</td>
</tr>
<tr>
<td>- Alternate: AZT + 3TC + NVP</td>
</tr>
<tr>
<td>- Alternate: TDF + 3TC (or FTC) + EFV</td>
</tr>
<tr>
<td>- Alternate: TDF + 3TC (or FTC) + NVP</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Children &lt; 3 years, first-line regimens:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- ABC (or AZT) + 3TC + LPV/r</td>
</tr>
<tr>
<td>- Alternate: ABC + 3TC + NVP</td>
</tr>
<tr>
<td>- Alternate: AZT + 3TC + NVP</td>
</tr>
</tbody>
</table>

Pharmacology

The HIV protease inhibitors (PIs) are a class of active antiretroviral agents used in combination with other antiretroviral agents in the treatment of HIV/AIDS infections. The protease inhibitors competitively inhibit the action of viral protease enzyme action by binding to HIV protease active sites and inhibiting the cleavage of Gag-Pol polyprotein precursors. This competitive inhibition results in failure of infectious viral protein activation and renders the virus particles immature and noninfectious. Due to differences between viral and human protein polypeptide chains, the protease inhibitors are only active in HIV cells and do not cause protease inhibition in human cells, thereby reducing the risk for adverse effects. Table 6 provides a list of the adverse events associated with each of the HIV protease inhibitor agents. Viral resistance, as a result of alterations in the virus genome, is common with the PI agents and monotherapy is contraindicated. Resistance to one protease inhibitor is often associated with resistance to all protease inhibitors; although, darunavir and lopinavir/ritonavir have demonstrated effectiveness against resistant HIV strains in clinical trials.

The HIV protease inhibitors are similar in structure but pharmacokinetic properties vary between the agents. See Table 5 for a summary of the pharmacokinetic data available for each of the HIV protease inhibitors. In general, the protease inhibitors are metabolized by CYP3A4. The exception is nelfinavir, which is metabolized by CYP2C19 and CYP3A4. Ritonavir has the greatest inhibitory effect on CYP3A4 and may be taken in combination with other PI agents in an effort to decrease metabolism and increase half-life of the agent. In general, PI half-lives range from 1-15 hours. The PI drugs with shorter half-lives (i.e. indinavir, nelfinavir) may require more frequent dosing, up to three times daily, compared to those with longer half-lives (i.e. atazanavir, darunavir; both dosed once daily). Amprenavir (Agenerase®, GlaxoSmithKline) is a protease inhibitor approved for use by the FDA in 1999, for twice-a-day dosing instead of needing to be taken every eight hours. However, the twice daily dosing required 1,200 mg, administered in 8 large 150 mg gel capsules twice daily. Production of amprenavir was eventually discontinued and a prodrug version (fosamprenavir) is now available. All of the protease inhibitors are classified as high alert medications by the Institute for Safe Medication Practices (ISMP) as the risk of causing significant harm is high if the agent is used inappropriately. Tipranavir carries a black box warning for hepatitis, hepatic decompensation, deaths from hepatic failure and fatal cranial hemorrhage. Due to its significant cytochrome inhibitory affect, ritonavir carries a black box warning for drug-drug interactions which may cause life-threatening adverse reactions when coadministered with sedative hypnotics, antiarrhythmics, or ergot alkaloids. Protease inhibitors are also P-glycoprotein efflux pump substrates which may be a source of drug-interactions. Table 6 provides a summary of the most significant drug interactions associated with HIV protease inhibitor use.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Half-life (h)</th>
<th>Bioavailability (%)</th>
<th>Effect of meals on AUC</th>
<th>Protein binding (%)</th>
<th>Renal Excretion of parent drug (%)</th>
<th>Metabolism</th>
<th>Autoinduction of metabolism</th>
<th>Inhibition of CYP3A4</th>
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<tbody>
<tr>
<td>Atazanavir</td>
<td>6.5-7.9</td>
<td>low</td>
<td>↑70% (light meal)</td>
<td>86</td>
<td>7</td>
<td>CYP3A4</td>
<td>No</td>
<td>++</td>
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<tr>
<td>Darunavir</td>
<td>15</td>
<td>82</td>
<td>↑30%</td>
<td>95</td>
<td>8</td>
<td>CYP3A4</td>
<td>NA</td>
<td>+++</td>
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<tr>
<td>Fosamprenavir</td>
<td>7.7</td>
<td>20-80</td>
<td>↔</td>
<td>90</td>
<td>4</td>
<td>CYP3A4</td>
<td>No</td>
<td>++</td>
</tr>
<tr>
<td>Indinavir</td>
<td>1.8</td>
<td>60-65</td>
<td>↓77%</td>
<td>60</td>
<td>9-12</td>
<td>CYP3A4</td>
<td>No</td>
<td>++</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>5-6</td>
<td>low</td>
<td>↑27% (Moderate fat)</td>
<td>98-99</td>
<td>&lt;3</td>
<td>CYP3A4</td>
<td>Yes</td>
<td>+++</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>3.5-5</td>
<td>20-80 (food and formulation dependent)</td>
<td>↑100-200%</td>
<td>&gt;98</td>
<td>1-2</td>
<td>CYP2C19 &gt; CYP3A4</td>
<td>Yes</td>
<td>++</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>3-5</td>
<td>&gt;60</td>
<td>↑13% (capsule)</td>
<td>98-99</td>
<td>3.5</td>
<td>CYP3A4 &gt; CYP2D6</td>
<td>Yes</td>
<td>+++</td>
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<tr>
<td>Saquinavir</td>
<td>1-2</td>
<td>13</td>
<td>↑570% (high fat)</td>
<td>98</td>
<td>&lt;3</td>
<td>CYP3A4</td>
<td>No</td>
<td>+</td>
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<tr>
<td>Tipranavir</td>
<td>4.8-6.0</td>
<td>NA</td>
<td>↔</td>
<td>99.9</td>
<td>0.5</td>
<td>CYP3A4</td>
<td>Yes</td>
<td>+++</td>
</tr>
</tbody>
</table>

Key: NA = not available
Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database (1950 – 2015), the Cochrane Library and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE, evaluating efficacy of the HIV protease inhibitors are included. Trials evaluating the agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens are excluded. The following reports were excluded (note: some were excluded for more than 1 reason, see table in appendix for additional exclusions):28,33-49

- Individual clinical trials which evaluated endpoints other than reduction of HIV symptoms, such as: pharmacologic characteristics33,50-82, safety83-90, adherence91-96, resistance53,97-99, metabolic effects100 or cost analysis101.
- Individual trials comparing the SGLT2 inhibitors in dose-finding studies or in healthy volunteers54,102-110.
- Individual clinical trials evaluating formulations not currently available in the US111 or clinical trials without access to the full article.112,113

Clinical Efficacy

One meta-analysis and 20 comparative clinical trials comparing the efficacy of the HIV protease inhibitors were identified for evaluation. The meta-analysis identified trials evaluating the efficacy of two protease inhibitors, tipranavir and darunavir, in patients with HIV who had previously received antiretroviral therapy. In total, 14 trials were identified for analysis. According to the study, both tipranavir and darunavir-based antiretroviral regimens are similarly effective in reducing viral load in patients who were ART experienced. The authors concluded that second generation non-peptidic HIV protease inhibitors, tipranavir and darunavir, demonstrate improved resistance profiles in treatment-experienced patients.

Of the 20 clinical trials identified for evaluation, 14 evaluated the efficacy of the PI agents in treatment-naïve patients and 6 evaluated the efficacy of the agents in treatment-experienced patients. Each of the HIV protease inhibitors was studied in at least one comparative clinical trial. Saquinavir was studied in 8 of the identified clinical trials, while tipranavir was studied in only one of the trials. For a complete summary of the included clinical trials, see the Evidence Tables in the appendix.

Treatment-Naïve Patients

Atazanavir was compared to darunavir in two clinical trials. Lennox et al (2014)115 evaluated the efficacy of the agents in treatment naïve adult patients in 57 sites across the US and Puerto Rico. A total of 1,809 patients were randomized to receive
tenofovir and emtricitabine in combination with atazanavir/ritonavir, darunavir/ritonavir or raltegravir. At 96 weeks, all treatment groups achieved high and similar rates of virologic success. No differences in efficacy were reported between the protease inhibitor treatment groups. Adverse event rates were similar between treatment groups. However, adverse event-related discontinuation rate was higher in the atazanavir treatment group compared to the darunavir treatment group, likely due to the higher rate of hyperbilirubinemia reported in the atazanavir group. Aberg et al (2012)\textsuperscript{116} evaluated the efficacy of atazanavir and darunavir in treatment-naïve adult patients in centers across the US. Sixty-five patients were randomized to receive tenofovir and emtricitabine in combination with atazanavir/ritonavir or darunavir/ritonavir for up to 48 weeks. At the end of the study period, virologic response was similar for the atazanavir (71%) and darunavir (76.5%) treatment groups. Again, overall adverse event rates were similar between treatment groups; however, hyperbilirubinemia was reported more frequently in the atazanavir treatment group.

Atazanavir was also compared to lopinavir in one clinical trial and fosamprenavir in one clinical trial. Molina et al (2008)\textsuperscript{117} evaluated the efficacy of atazanavir and lopinavir in treatment-naïve patients in 134 sites across the world. A total of 883 patients were randomized to receive tenofovir and emtricitabine in combination with atazanavir/ritonavir or lopinavir/ritonavir with a follow-up of 48-96 weeks. At 48-weeks, atazanavir (78% and lopinavir (76%) demonstrated similar rates of virologic response. At 96 weeks, the atazanavir treatment group (74%) demonstrated higher rates of virologic response compared to the lopinavir treatment group (68%, p < 0.05). Smith et al (2008)\textsuperscript{118} evaluated the efficacy of atazanavir and fosamprenavir in 106 treatment-naïve adult patients in a 48-week study. At the end of the study period, the proportion of patients with HIV-RNA < 50 copies/mL was similar across the atazanavir (83%) and fosamprenavir (75%) treatment groups. The most frequently reported adverse events reported varied between the agents with diarrhea and nausea being reported more frequently in the fosamprenavir treatment group and hyperbilirubinemia, fatigue and jaundice are reported more frequently in the atazanavir treatment group.

Darunavir and lopinavir were compared in one long-term clinical trial. A total of 689 treatment-naïve patients were randomized to receive tenofovir and emtricitabine in combination with darunavir/ritonavir or lopinavir/ritonavir with a follow-up time of 192 weeks. The darunavir treatment group demonstrated higher rates of virologic response at 96 weeks and 192 weeks (p < 0.05). Incidence of adverse events was similar across treatment groups (darunavir- 23%, lopinavir- 34%) and the most frequently reported events were diarrhea, nausea and rash. Treatment-related discontinuation rate occurred more frequently in the lopinavir group (p = 0.005), in part due to recommendation to discontinue lopinavir in pregnancy.

Fosamprenavir was compared to saquinavir in one comparative clinical trial and to nelfinavir in one comparative clinical trial. Landman et al (2009)\textsuperscript{119} conducted a small trial evaluating the efficacy of fosamprenavir and saquinavir in treatment-naïve patients. A total of 61 patients were randomized to receive fosamprenavir/atazanavir/ritonavir or saquinavir/atazanavir/ritonavir for up to 16 weeks. At the end of the study period, rate of
early virologic response (< 50 copies/mL) was similar between the fosamprenavir (40%) and saquinavir (42%) treatment groups. Gastrointestinal adverse events were reported more frequently in the fosamprenavir treatment group (30% vs. 16%, p = NS) and hyperbilirubinemia was reported more frequently in the saquinavir treatment group (23% vs. 10%, p = NS). Gathe et al. (2002) evaluated the safety and efficacy of fosamprenavir and nelfinavir in 649 treatment-naive patients. Patients were randomized to receive abacavir and lamivudine in combination with fosamprenavir/ritonavir or nelfinavir for up to 48 weeks. Magnitude and durability of virologic response was similar between treatment groups. No differences in total adverse event rates were reported between treatment groups; although, diarrhea occurred more frequently in the nelfinavir treatment group (p < 0.05).

Nelfinavir was also evaluated in one clinical trial compared to saquinavir and one clinical trial compared to ritonavir. Kirk et al. (2003) evaluated the efficacy nelfinavir and saquinavir in 233 treatment-naive patients in Denmark. Patients were randomized to receive two NRTIs in combination with saquinavir/ritonavir or nelfinavir/nevirapine for up to 48 weeks. At the end of the study period, the proportion of patients with HIV-RNA < 20 copies/mL was greater in the nelfinavir/nevirapine treatment group (69%) compared to the saquinavir/ritonavir treatment group (56%, p = 0.037). No differences in overall adverse event rate were reported between treatment groups and gastrointestinal effects were the most frequently reported events throughout the study. Of note, skin reactions were reported more frequent in the nelfinavir/nevirapine treatment arm (p < 0.05). Gulick et al. (2000) evaluated the efficacy of nelfinavir and ritonavir in NNRTI treatment-naive patients. A total of 277 patients were randomized to receive delavirdine and/or adefovir in combination with ritonavir/saquinavir or nelfinavir/saquinavir for 16 weeks. No differences in efficacy or safety were reported between treatment groups.

Indinavir, ritonavir and saquinavir were evaluated in two clinical trials. Kirk et al. (2001) evaluated the efficacy of the agents in patients aged > 16 years with HIV. A total of 2708 patients taking indinavir, ritonavir or saquinavir in addition to at least 3 additional antiretroviral agents as part of a complete combination ART were evaluated. With a median follow-up period of 30 months, the proportion of patients who experienced clinical progression at 12 months was similar between the ritonavir (11.9%) and saquinavir (11.9%) treatment groups. The proportion of patients who experienced clinical progression at 12 months was lower in the indinavir treatment group (9.2%) when compared to the saquinavir treatment group (11.9%, p = 0.043). Katzenstein et al. (1999) evaluated the efficacy of the agents in 318 adult patients with 0-13 days of prior use of a PI. Patients were randomized to receive indinavir, ritonavir or saquinavir/ritonavir with a follow-up of up to 72 weeks. At the end of the study period, no statistically significant differences in treatment success rate were reported between the indinavir (52%), ritonavir (41%) and saquinavir/ritonavir (58%) treatment groups. However, patients in the saquinavir/ritonavir treatment group (58%) demonstrated a higher rate of HIV-RNA <20 copies/mL count when compared to ritonavir alone (41%, p < 0.05).
Indinavir was compared to saquinavir in two additional clinical trials. Dragsted et al (2003)\textsuperscript{125} evaluated the efficacy of the agents in treatment-naïve adult patients in 28 sites around the world. A total of 306 patients were randomized to receive 2 NRTIs or NNRTIs in combination with indinavir/ritonavir or saquinavir/ritonavir. At 48 weeks, no significant differences in virologic failure rates (~25%) were reported between indinavir and saquinavir treatment groups. However, adverse event-related discontinuation rate was higher in the indinavir treatment group compared to the saquinavir treatment group, reportedly due to the higher rate of renal, skin/hair and gastrointestinal adverse events reported in the indinavir treatment group. Cohen-Stuart et al (1999)\textsuperscript{126} evaluated the efficacy of the agents in 70 treatment-naïve patients with a diagnosis of HIV and demonstration of HIV-related symptoms. Patients were randomized to receive zidovudine and lamivudine in combination with indinavir or saquinavir for up to 24 weeks. No differences in decreased HIV-RNA counts were reported between treatment groups. Increased CD4+ cell counts occurred more frequently in the saquinavir treatment group compared to the indinavir treatment group (p = 0.01). Overall adverse event rate and discontinuation rate were similar across treatment groups.

Treatment-Experienced Patients

Antoniou et al (2010)\textsuperscript{127} evaluated the efficacy of combination therapy tipranavir/ritonavir or darunavir/ritonavir in 85 patients with multi-drug resistant HIV infection. No differences in virologic response or sustained virologic suppression were reported between treatment groups. In addition, no differences in safety were reported between the agents. Johnson et al (2005)\textsuperscript{128} evaluated the efficacy of atazanavir, ritonavir, saquinavir and lopinavir in treatment-experienced patients aged 16-18 years in Europe and North/South America. A total of 358 patients were randomized to receive tenofovir and one additional NRTI in combination with atazanavir/ritonavir, atazanavir/saquinavir or lopinavir/ritonavir for up to 96 weeks. No differences in magnitude/durability of viral load reduction or in rate of adverse events were reported between treatment groups.

Haas et al (2003)\textsuperscript{129} evaluated the efficacy of atazanavir and ritonavir in the treatment of HIV in 85 patients who had demonstrated a response to a prior ART regimen. Patients were randomized to receive two NRTIs in combination with atazanavir/saquinavir or ritonavir/saquinavir. At 48 weeks, no significant differences in virologic response were reported between atazanavir treatment groups (29-41%) and the ritonavir treatment group (35%). No differences in adverse event-related discontinuation rate were reported between treatment groups (9-30%). However, increases in cholesterol were significantly more frequent in the ritonavir treatment group (p < 0.05). Roca et al (2000)\textsuperscript{130} evaluated the efficacy of indinavir and nelfinavir in patients with active HIV infection who received ART previously. A total of 112 patients were randomized to receive stavudine and lamivudine in combination with indinavir or nelfinavir for up to 9 months. No differences in CD4 cell count or HIV-RNA count were reported between treatment groups. Frequency of treatment-related adverse events was similar between treatment groups; although, adverse event-related discontinuation rate was higher in the indinavir treatment group (60%) compared to the nelfinavir treatment group (38%, p < 0.05)
Chavanet et al (2001)\textsuperscript{131} evaluated the efficacy of nelfinavir and ritonavir in treatment-experienced adult patients with previous PI exposure $> 6$ months. A total of 31 patients were randomized to receive NRTI therapy in combination with ritonavir/saquinavir or nelfinavir/saquinavir for 3 months. No differences in viral load stabilization or decrease were reported between treatment groups. Para et al (2000)\textsuperscript{132} conducted a similar trial comparing indinavir to saquinavir in 89 adult patients who have received previous ART. Patients were randomized to receive a complete ARV therapeutic regimen in combination with indinavir or saquinavir for up to 24 weeks. According to the data, indinavir was associated with higher rates of viral load decreases (49\%) when compared to the saquinavir treatment group (4-8\%, $p < 0.001$). This data suggests indinavir may be more effective in treatment-experienced patients.

Some trials comparing dual therapy to monotherapy are available. In general, these trials demonstrated similar or increased rates of efficacy with dual PI therapy compared to mono-PI therapy. This suggests that twice-daily indinavir-ritonavir and, to a lesser extent, amprenavir-ritonavir may be effective for many patients with viruses resistant to protease inhibitors.\textsuperscript{53} Quadruple therapy, including SQV-SGC and NFV, gave a more durable response than triple therapy with either single protease inhibitor. Quadruple therapy might particularly benefit NRTI-experienced patients and those with high baseline viral loads.\textsuperscript{29} The overall efficacy of ritonavir-boosted protease inhibitor monotherapy is inferior to HAART.\textsuperscript{32}

\textit{Special Populations}

Some data is available for the evaluation of the HIV protease inhibitors in the treatment of HIV in the pediatric population. Rusconi et al (2012)\textsuperscript{133} reported “dual-boosted protease inhibitor therapy was virologically and immunologically effective and it could be considered as a possible alternative to a rescue regimen in children and adolescents.” However, hypercholesterolemia and hypertriglyceridemia need close follow-up in this patient population.\textsuperscript{133} Rodriguez-French et al (2004)\textsuperscript{134} reported similar rates of safety and efficacy for fosamprenavir and nelfinavir in treatment-naïve pediatric patients with HIV infection. Of note, diarrhea occurred more frequently in the nelfinavir treatment group and rash occurred more frequently in the fosamprenavir treatment group. In addition, there are a number of observational and noncomparative trials which evaluate the protease inhibitors in the pediatric population. Overall, the protease inhibitors demonstrate safety and efficacy in pediatric patients but may require additional monitoring.
Safety

The HIV protease inhibitors are preferred agents in antiretroviral combination therapy regimens as they are associated with potent anti-HIV activity and have relatively favorable resistance patterns. However, the protease inhibitor agents are also associated with both short- and long-term toxicities, which may limit use. Table 6 provides a list of the adverse events reported with protease inhibitor use. The most common adverse events reported with protease inhibitor therapy vary between the agents and include gastrointestinal irritation, skin reactions and metabolic disturbances. The metabolic disturbances may include hyperlipidemia, lipodystrophy and impaired glucose tolerance. Some of the protease inhibitors are also indicated in the development of hyperbilirubinemia. Clinicians should monitor patients receiving protease inhibitors carefully for adverse events, especially those involving altered lipid and glucose metabolism. In addition, adverse events may occur more frequently in pediatric patients and older adults (age > 50 years) and careful monitoring of bone, kidney, metabolic, cardiovascular and liver health of older patients receiving ART is recommended. The HIV protease inhibitors also have pharmacokinetic interactions due to cytochrome P450 metabolism. For example, the agents have a significant interaction with oral contraceptives and additional or alternative contraceptive methods are recommended in women of childbearing age to prevent unintended pregnancy. Some of the antiretroviral therapies may also be associated with teratogenic effects and careful selection of combination therapies in pregnant women is warranted.

**Atazanavir**: Adverse effects reported with atazanavir therapy include diarrhea and nausea, which may disappear after the first few weeks of therapy. The most common laboratory abnormality associated with atazanavir therapy includes unconjugated hyperbilirubinemia, although this is not associated with hepatotoxicity. Approximately 40% of subjects receiving 400 mg atazanavir once daily in initial clinical trials developed a significant increase in total bilirubin, although only 5% developed jaundice. Postmarketing reports include hepatic adverse reactions of cholecytitis, cholelithiasis, cholestasis, and other hepatic function abnormalities because atazanavir is metabolized by CYP3A4, concomitant administration of agents that induce this enzyme (e.g., rifampin) is contraindicated.

**Darunavir**: Adverse effects most frequently reported with darunavir therapy are gastrointestinal (GI) irritation. Darunavir is associated with increases in plasma triglycerides and cholesterol and, like fosamprenavir, contains a sulfa moiety, and rash has been reported in up to 10% of recipients. Darunavir therapy has also been associated with episodes of hepatotoxicity and is metabolized by CYP3A4. Concomitant administration of agents that induce CYP3A4 (e.g., rifampin) is contraindicated. The drug interaction profile of darunavir/ritonavir is dominated by those expected with ritonavir.

**Fosamprenavir**: Adverse effects most frequently reported with fosamprenavir therapy include GI irritation (diarrhea, nausea, vomiting), hyperglycemia, fatigue, paresthesias and headache. Fosamprenavir therapy is associated with rash and severe rash has been reported in up to 8% of patients. The onset of skin rash is usually within 2 weeks of beginning therapy. Fosamprenavir
does not have effects on plasma lipid profiles and is not generally associated with drug-interactions.

**Indinavir:** “A unique and common adverse effect of indinavir is crystalluria and nephrolithiasis. This stems from the poor solubility of the drug, which is lower at pH 7.4 than at pH 3.5. Precipitation of indinavir and its metabolites in urine can cause renal colic, and nephrolithiasis occurs in ~3% of patients.” Patients receiving indinavir treatment should drink plenty fluids to prevent renal complications. Similar to atazanavir, indinavir causes asymptomatic hyperbilirubinemia which is not generally associated with serious long-term sequelae. Long-term administration of indinavir is associated with the HIV lipodystrophy syndrome, fat accumulation and hyperglycemia. Dermatologic complications have been reported with indinavir therapy and may include loss, dry skin, dry/cracked lips and ingrown toenails.

**Lopinavir:** GI adverse effects reported with lopinavir therapy are generally mild compared to other PI agents and may include loose stools, diarrhea, nausea and vomiting. The most common laboratory abnormalities associated with lopinavir therapy include elevated total cholesterol and triglycerides. Lopinavir metabolism is highly dependent on CYP3A4 and concomitant administration of agents that induce CYP3A4 (i.e. rifampin, St. John's wort) should be avoided. The liquid formulation of lopinavir contains 42% ethanol and should not be administered with disulfiram or metronidazole.

**Nelfinavir:** Nelfinavir is generally well tolerated. The most important side effect of nelfinavir is diarrhea, which resolves in most patients within the first 4 weeks of therapy. “Up to 20% of patients report chronic occasional diarrhea lasting >3 months, although <2% of patients discontinue the drug because of diarrhea. Nelfinavir augments intestinal calcium-dependent chloride channel secretory responses in vitro, and electrolyte analysis of stool is most consistent with a secretory diarrhea.” Nelfinavir may also be associated with glucose intolerance, elevated cholesterol levels and elevated triglycerides. Because nelfinavir is metabolized by CYPs 2C19 and 3A4, concomitant administration of agents that induce these enzymes may be contraindicated.

**Ritonavir:** Adverse effects most frequently reported with ritonavir therapy are gastrointestinal (GI) irritation, including nausea, vomiting, diarrhea, anorexia, abdominal pain and taste perversion. Peripheral paresthesias have been reported with ritonavir therapy but generally disappear within a few weeks of initiating therapy. Long-term ritonavir therapy may cause dose-dependent elevations in serum cholesterol. “Ritonavir is one of the most potent known inhibitors of CYP3A4, markedly increasing the plasma concentrations and prolonging the elimination of many drugs. Ritonavir should be used with caution in combination with any CYP3A4 substrate and should not be combined with drugs that have a narrow therapeutic index such as midazolam, triazolam, fentanyl, and ergot derivatives.”

**Saquinavir:** Adverse effects reported with saquinavir therapy are generally mild and short lived and most are gastrointestinal in nature (nausea, vomiting, diarrhea, and abdominal discomfort). Long-term use of saquinavir may be associated with lipodystrophy. “Saquinavir clearance is increased with CYP3A4 induction; thus, co-administration of inducers of CYP3A4 such as
rifampin, phenytoin, or carbamazepine lowers saquinavir concentrations and should be avoided.”^{21}

**Tipranavir:** Tipranavir is associated with rare but serious adverse events, including fatal hepatotoxicity. “Through 48 weeks of treatment, grade 3 or 4 elevation of hepatic transaminases occurred in 20% of treatment-naive and 10% of treatment-experienced patients. Tipranavir use has been associated with rare intracranial hemorrhage (including fatalities) and bleeding episodes in patients with hemophilia. The drug has anticoagulant properties in vitro and in animal models, and these effects are potentiated by vitamin E.”^{21,22} Elevation in lipids and triglycerides are frequently reported with tipranavir use and transient rash may occur as tipranavir contains a sulfa moiety.^{2,3}
<table>
<thead>
<tr>
<th>Product</th>
<th>Frequency</th>
<th>Cardiovascular</th>
<th>Central Nervous System</th>
<th>Endocrine &amp; Metabolic</th>
<th>Gastrointestinal</th>
<th>Hepatic</th>
<th>Neuromuscular/Skeletal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir (REYATAZ®)</td>
<td>&gt;10%</td>
<td></td>
<td></td>
<td>↑ amylase ↑ serum cholesterol</td>
<td>nausea</td>
<td>jaundice ↑ serum bilirubin</td>
<td>↑ CPK</td>
<td>cough fever skin rash</td>
</tr>
<tr>
<td></td>
<td>2-10%</td>
<td>AV block (first or second degree) peripheral edema P-R interval prolongation</td>
<td>depression dizziness headache insomnia neuropathy peripheral</td>
<td>hyperglycemia hypoglycemia lipodystrophy ↑ serum triglycerides</td>
<td>abdominal pain diarrhea vomiting ↑ serum lipase</td>
<td>↑ serum ALT ↑ serum AST</td>
<td>limb pain myalgia neutropenia ↓ hemoglobin nasal congestion oropharyngeal pain rhinorrea thrombocytopenia wheezing</td>
<td></td>
</tr>
<tr>
<td>Atazanavir and Cobicistat (EVOTAZ®)</td>
<td>&gt;10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>abnormal bilirubin levels jaundice</td>
<td>scleral icterus</td>
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<tr>
<td></td>
<td>1-10%</td>
<td>AV block (first or second degree) cardiac conduction disturbances P-R interval prolongation</td>
<td>abnormal dreams depression fatigue headache insomnia</td>
<td>↑ cholesterol cushingoid appearance Fanconi’s syndrome glycosuria ↑ GGT buffalo hump ↑ serum triglycerides truncal obesity</td>
<td>diarrhea nausea ↑ serum amylase ↑ serum lipase upper abdominal pain vomiting</td>
<td>hepatotoxicity (pts w/hepatitis) ↑ serum ALT ↑ serum AST</td>
<td>amyotrophy ↑ CPK lipoatrophy rhabdomyolysis acute renal failure breast hypertrophy ↓ creatinine clearance hematuria hemorrhage immune reconstitution syndrome nephrolithiasis renal insufficiency ↑ serum creatinine skin rash Stevens-Johnson syndrome</td>
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<tr>
<td>Darunavir (PREZISTA®)</td>
<td>&gt;10%</td>
<td></td>
<td>hypercholesterolemia hyperglycemia ↑ LDL cholesterol</td>
<td>diarrhea nausea vomiting</td>
<td></td>
<td></td>
<td>skin rash</td>
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<tr>
<td></td>
<td>2-10%</td>
<td>fatigue headache</td>
<td>↑ amylase diabetes mellitus lipodystrophy ↑ serum triglycerides</td>
<td>abdominal distention abdominal pain anorexia decreased appetite dyspepsia ↑ serum lipase</td>
<td>↑ serum ALT ↑ serum AST</td>
<td>weakness</td>
<td>increased bleeding (pts w/hemophilia) pruritus</td>
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<tr>
<td>Darunavir and Cobicistat (PREXCOBIX®)</td>
<td>1-10%</td>
<td></td>
<td>headache</td>
<td>abdominal pain diarrhea flatulence nausea vomiting</td>
<td></td>
<td>↑ liver enzymes</td>
<td>drug-induced hypersensitivity immune reconstitution syndrome</td>
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<td>Medication</td>
<td>&gt;10%</td>
<td>1-10%</td>
<td>2-10%</td>
<td>&gt;2-10%</td>
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<tr>
<td><strong>Fosamprenavir</strong>&lt;br&gt;(LEXIVA®)</td>
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<td>hyperglycemia</td>
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<td>↑ serum lipase</td>
<td>↑ serum amylase</td>
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<td>vomiting</td>
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<td>dizziness drowsiness</td>
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<td>anorexia</td>
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<td></td>
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<td>fatigue headache</td>
<td>hyperglycemia</td>
<td>↑ appetite</td>
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<tr>
<td><strong>Lopinavir and Ritonavir</strong>&lt;br&gt;(KALETRA®)</td>
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<td>vasodilation</td>
<td>↑ GGT</td>
<td>↑ serum ALT</td>
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<td>↑ serum ALT</td>
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<td></td>
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<td>paresthesia</td>
<td>hypertriglyceridemia</td>
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<td>weight loss</td>
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<tr>
<td><strong>Ritonavir</strong>&lt;br&gt;(NORVIR®)</td>
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<td>flushing</td>
<td>↑ GGT</td>
<td>↑ serum ALT</td>
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<td>↑ serum transaminases</td>
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</tbody>
</table>

## Common Side Effects

- **Fosamprenavir (LEXIVA®)**
  - Hypertriglyceridemia
  - Diarrhea
  - Rash

- **Indinavir (CRIXIVAN®)**
  - Abdominal pain
  - Nausea
  - Hyperbilirubinemia
  - Nephrolithiasis

- **Lopinavir and Ritonavir (KALETRA®)**
  - Vasodilation
  - Anxiety
  - Fatigue
  - Headache
  - Insomnia

- **Nelfinavir (VIRACEPT®)**
  - Diarrhea

- **Ritonavir (NORVIR®)**
  - Flushing
  - Dizziness
  - Fatigue
  - Paresthesia

## Additional Side Effects

- **Fosamprenavir (LEXIVA®)**
  - Hyperglycemia
  - ↑ serum lipase
  - Vomiting

- **Indinavir (CRIXIVAN®)**
  - Fat redistribution
  - Hypercholesterolemia
  - Hyperuricemia

- **Lopinavir and Ritonavir (KALETRA®)**
  - ↑ GGT
  - ↑ serum ALT

- **Nelfinavir (VIRACEPT®)**
  - ↑ serum ALT

- **Ritonavir (NORVIR®)**
  - ↑ CPK
  - Musculoskeletal pain
  - Weakness

## Other Side Effects

- **Nelfinavir (VIRACEPT®)**
  - ↓ lymphocytes
  - ↓ neutrophils

- **Ritonavir (NORVIR®)**
  - Oropharyngeal pain
  - Pruritus
  - Skin rash

## Additional Information

- **Skin Rash**
  - Rash
  - Alanine transaminase
  - Aspartate transaminase
  - Lipid abnormalities
  - Pruritus
<table>
<thead>
<tr>
<th>Drug (Brand)</th>
<th>&gt;10%</th>
<th>1-10%</th>
<th>&gt;10%</th>
<th>2-10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir (INVIRASE®)</td>
<td>depression drowsiness headache insomnia malaise peripheral neuropathy</td>
<td>↑ serum amylase taste perversion throat irritation</td>
<td>nausea</td>
<td>↑ serum amylase ↑ serum ALT ↑ serum AST ↑ bilirubin hepatic decompensation (pts w/hepatitis) ↑ serum AL↑ serum AST back pain ↑ CPK paresthesia weakness bronchitis ↑ creatinine kinase dry lips/skin eczema influenza pneumonia pruritus rash sinusitis verruca</td>
</tr>
<tr>
<td>Tipranavir (APTIVUS®)</td>
<td>↑ serum amylase ↑ amylase diarrhea weight loss</td>
<td>↑ serum ALT ↑ serum AST ↑ CPK ↑ GGT myalgia anemia bleeding ↑ bleeding time cough dyspnea epistaxis fever intracranial hemorrhage neutropenia ↓ WBC</td>
<td>↑ transaminases ↑ CPK skin rash</td>
<td>↑ serum amylase ↑ amylase diarrhea nausea vomiting weight loss</td>
</tr>
</tbody>
</table>
Summary

HIV, the virus that causes acquired immune deficiency syndrome (AIDS), is a worldwide health challenge and is the world's leading cause of death from infection. The virus causes a chronic infection with a gradual onset of clinical symptoms starting with general malaise and illness, progressing to the development of opportunistic diseases and ultimately death. All patients with HIV should receive Antiretroviral Therapy (ART) to reduce the risk of disease progression and to prevent transmission. The goal of HIV therapy is to decrease viral load, increase CD4+ T cell count and prevent opportunistic infections. The biggest challenge with HIV/AIDS treatment is the development of resistance to drug therapy. Before initiation of ART, genotypic drug-resistance testing is recommended to help guide therapy decisions. In addition, all patients should receive education outlining the benefits and risks of therapy and the importance of adherence before initiation of therapy.

The HIV protease inhibitors are recommended for use in the treatment of HIV/AIDS as part of a comprehensive combination therapy regimen. Clinical evidence suggests, when used in combination regimens, the protease inhibitors all demonstrate efficacy in the treatment of HIV-1. In general, standard combination therapy consists of two nucleoside reverse transcriptase inhibitors (NRTI) combined with a third antiretroviral agent from one of the other direct-acting antiviral drug classes, such as a protease inhibitor. The US Department of Health and Human Services recommends darunavir/ritonavir in combination with tenofavir and lamivudine or emtricitabine as their preferred PI-based regimen. There are a number of additional protease inhibitor-based therapies, as well as integrase inhibitor-based and NNRTI-based regimens, outlined in the guideline documents and therapy should be guided by both current guideline recommendations and genotype testing in addition to individual patient characteristics (medical history, concurrent medication therapies, etc.).

The protease inhibitors are associated with short- and long-term toxicities, which may limit use. The most common adverse events reported with protease inhibitor therapy vary between the agents and may include gastrointestinal irritation, skin reactions and metabolic disturbances. The metabolic disturbances reported with PI use include hyperlipidemia, lipodystrophy and impaired glucose tolerance. Clinicians should monitor patients receiving protease inhibitors carefully for adverse events, especially pediatric patients, older adults and those at risk for altered lipid and glucose metabolism.
References


118. Smith KY, Weinberg WG, Dejesus E, et al. Fosamprenavir or atazanavir once daily boosted with ritonavir 100 mg, plus tenofovir/emtricitabine, for the initial treatment of HIV infection: 48-week results of ALERT. *AIDS research and therapy.* 2008;5:5.


Clotet B. Strategies for overcoming resistance in HIV-1 infected patients receiving HAART. *AIDS reviews.* Jul-Sep 2004;6(3):123-130.


## Evidence Table 1. Systematic Reviews Evaluating the HIV Protease Inhibitors

<table>
<thead>
<tr>
<th>Reference/Study Design</th>
<th>N</th>
<th>Patient Population</th>
<th>Treatment Interventions</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
</table>
| Berhan et al, 2013114  | 6,301 | ART experienced patients with plasma viral load above 1,000 copies HIV RNA/ml          | The treatments evaluated were:                                                           | Outcome 1: Viral load reduction by ≥1 log_{10} copies HIV-RNA/ml from baseline  
  - TPV/r 500/200 mg or DRV/r 600/100 mg twice daily based regimen  
    o Outcome 1 N = 3,163  
    o Outcome 2 N = 2,189  
    o Outcome 3 N = 2,861  
  - Investigator selected boosted comparator PIs (CPIs)  
    o Outcome 1 N = 3,138  
    o Outcome 2 N = 2,156  
    o Outcome 3 N = 2,821  
  Conducted: No date range mentioned in the methodology | Not assessed in the meta-analysis. |

Key: ART = antiretroviral therapy, TPV = tipranavir; DRV = darunavir; r = ritonavir; PI = protease inhibitor; OR = odds ratio; 95% CI = 95% confidence interval; ATV = atazanavir
<table>
<thead>
<tr>
<th>Reference/Study Design</th>
<th>N</th>
<th>Patient Selection</th>
<th>Treatment Interventions</th>
<th>Results</th>
<th>Safety</th>
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<tbody>
<tr>
<td><strong>Treatment naïve patients</strong></td>
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</table>
| Lennox et al, 2014\(^{115}\) | 1,809 | Treatment naïve patients aged ≥18 years with HIV1-RNA > 1,000 copies/mL and no resistance to NRTI or PIs | The following three in combination with tenofovir 300mg and emtricitabine 200mg daily:  
- ATV/r 300/100 mg daily  
  o N = 605  
- RAL 400 mg twice daily  
  o N = 603  
- DRV/r 800/100 mg daily  
  o N = 601 | Primary Endpoint: Incidence of virologic failure by 96 weeks with a margin of equivalence defined as -10% to 10%:  
- ATV/r vs RAL  
  o 3.4% (97.5% CI -0.7–7.4%)  
- DRV/r vs RAL  
  o 5.6% (97.5% CI 1.3–9.9%)  
- ATV/r vs DRV/r  
  o -2.2% (97.5% CI -6.7–2.3%) | Adverse event discontinuation rate:  
- ATV/r v. RAL: 12.7% (97.5% CI 9.4%-16.1%)  
- ATV/r v. DRV/r: 9.2% (97.5% CI 5.5%-12.9%)  
Most common adverse events cited for discontinuation  
- ATV/r: hyperbilirubinemia  
- DRV/r: Diarrhea, nausea, and vomiting  
- RAL: headache |
| Setting: 57 sites in the US and Puerto Rico |  | Follow-up: at least 96 weeks | Conducted: May ’09 – June ’11 | | |
| **Aberg et al, 2012\(^{116}\)** | 65 | Treatment naïve patients aged ≥18 years with HIV1-RNA ≥ 1,000 copies/mL and not resistant to DRV, ATV, TDF, and FTC | The following two in combination with tenofovir 300mg and emtricitabine 200mg daily:  
- ATV/r 300/100 mg daily  
  o N = 31  
- DRV/r 800/100 mg daily  
  o N = 34 | Primary Endpoint: To evaluate the change in triglyceride levels from baseline to week 12  
Efficacy data for both arms was provided (although no statistical analyses were carried out to accompany them). At week 48, the following percentage of patients achieved virologic response:  
- ATV/r = 71.0%  
- DRV/r = 76.5% | Rates of adverse events were comparable between the two arms. The only exception was grade 2-4 hyperbilirubinemia, which was observed more in the ATV/r arm. |
<table>
<thead>
<tr>
<th>Reference/Study Design</th>
<th>N</th>
<th>Patient Selection</th>
<th>Treatment Interventions</th>
<th>Results</th>
<th>Safety</th>
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<tbody>
<tr>
<td>Landman et al, 2009<strong>119</strong> prospective open-label randomized pilot trial</td>
<td>61</td>
<td>Treatment-naive patients</td>
<td>Fosamprenavir/atazanavir/ritonavir (n = 30) Saquinavir/atazanavir/ritonavir (n = 31)</td>
<td>Primary endpoint: early virologic success, defined as plasma viral load &lt;50 copies/mL at week 16  - Fosamprenavir/atazanavir/ritonavir: 12/30 (40%)  - Saquinavir/atazanavir/ritonavir: 13/31 patients (42%) “Ritonavir-boosted dual protease inhibitor regimens targeting only one step of viral replication were insufficient to rapidly suppress plasma HIV RNA to &lt;50 copies/mL in antiretroviral-naive patients with high viral load at baseline.”</td>
<td>Gastrointestinal adverse events:  - Fosamprenavir/atazanavir/ritonavir: 30%  - Saquinavir/atazanavir/ritonavir: 16% Hyperbilirubinemia:  - Fosamprenavir/atazanavir/ritonavir: 10%  - Saquinavir/atazanavir/ritonavir: 23%</td>
</tr>
<tr>
<td>Reference/Study Design</td>
<td>N</td>
<td>Patient Selection</td>
<td>Treatment Interventions</td>
<td>Results</td>
<td>Safety</td>
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</table>
| Ortiz et al, 2008\(^{138}\) & Mills et al, 2009\(^{139}\) & Orkin et al, 2012 | 689 | Treatment naive patients aged ≥18 years with HIV1-RNA ≥ 5,000 copies/mL | The following two arms in combination with tenofovir 300mg and emtricitabine 200mg daily:  
- DRV/r 800/100 mg daily (n = 343)  
- LPV/r 800/200 mg total daily dose (1-2 times daily; n = 346) | **Primary Endpoint:** Non-inferiority with respect to the proportion of patients who achieved virologic response (HAV1-RNA < 50 copies/mL)  
**Week 48**  
- DRV/r = 84%  
- LPV/r = 78%  
  - Difference DRV/r vs LPV/r = 5.6\(^{\text{95% CI}}\) -0.1–11%  
  - Considered non-inferior  
**Week 96**  
- DRV/r = 79%  
- LPV/r = 71%  
- Difference DRV/r vs LPV/r = 8.4%  
  - 95% CI 1.9–14.8%, P < 0.001  
  - Considered non-inferior  
**Secondary Endpoint:** Durability and statistical superiority of virologic response over 96 and 192 weeks of DRV/r to LPV/r  
**Week 96**  
- Difference DRV/r vs LPV/r = 8.3%  
  - 95% CI 1.8–14.7%, P = 0.012  
  - Superiority of DRV/r shown  
**Week 192**  
- DRV/r = 68.8%  
- LPV/r = 57.2%  
- Difference DRV/r vs LPV/r = 11.6%  
  - 95% CI 4.4–18.8%  
  - Superiority of DRV/r shown | **Week 48:** Permanent discontinuation due to adverse events (including pregnancies):  
- DRV/r = 3%  
- LPV/r = 7%  
**Week 96:** Discontinuation of treatment due to adverse events:  
- DRV/r = 4%  
- LPV/r = 9%  
Incidence of grade 2-4 adverse events:  
- DRV/r = 23%  
- LPV/r = 34%  
**Week 192:** Permanent discontinuation due to adverse events (including pregnancies):  
- DRV/r = 7.6%  
- LPV/r = 14.5%  
  - P = 0.005  
Most common adverse events: diarrhea, nausea, and rash. |
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<tr>
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<th>Safety</th>
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</thead>
<tbody>
<tr>
<td>Molina et al, 2008 \cite{117} &amp; Molina et al, 2010 Open-label, multi-center, randomized non-inferiority trial</td>
<td>883</td>
<td>Treatment naïve patients aged ≥18 years with HIV1-RNA ≥ 5,000 copies/mL</td>
<td>The following two in combination with tenofovir 300mg and emtricitabine 200mg daily: - ATV/r 300/100 mg daily ( N = 440 ) - LPV/r 400/100 mg twice daily ( N = 443 )</td>
<td><strong>Primary Endpoint:</strong> Non-inferiority with respect to the proportion of patients who achieved virologic response (HIV1-RNA &lt; 50 copies/mL) at week 48 - ATV/r = 78% - LPV/r = 76% ( 95% \text{CI} -3.8–7.1%; ) non-inferior</td>
<td><strong>Week 48:</strong> Serious adverse events occurred in the following percentage of patients: - ATV/r = 12% - LPV/r = 10% <strong>Week 96:</strong> Serious adverse events occurred in the following percentage of patients: - ATV/r = 14% - LPV/r = 11% Most common adverse events were diarrhea and nausea.</td>
</tr>
<tr>
<td>Smith et al, 2008 \cite{118} Multi-center, open-label, randomized trial</td>
<td>106</td>
<td>Treatment naïve patients aged ≥18 years</td>
<td>The following two in combination with tenofovir 300mg and emtricitabine 200mg daily: - ATV/r 300/100 mg daily ( N = 53 ) - FPV/r 1400/100 mg daily ( N = 53 )</td>
<td><strong>Primary Endpoint:</strong> Comparison of the proportion of patients with HIV1-RNA &lt; 50 copies/mL at week 48 - ATV/r = 83% - FPV/r = 75%, ( p = \text{NS} )</td>
<td>Diarrhea and nausea were reported more frequently in the FPV/r arm compared to the ATV/r arm. Hyperbilirubinemia, fatigue, and jaundice were reported more frequently in the ATV/r arm compared to the FPV/r arm.</td>
</tr>
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</table>

**Setting:** 134 sites in 29 countries, including the US

**Follow-Up:** 96 weeks

**Conducted:** November ‘05 – June ‘06

**Setting:** 16 outpatient sites in the US

**Follow-Up:** 48 weeks

**Conducted:** April ‘05 – September ‘06
<table>
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| Dragsted et al, 2003   | 306| Treatment naïve and experienced patients aged ≥ 18 years | The following two in combination with at least 2 NRTIs and/or NNRTIs (as selected by the treating physician):  
  - IDV/r 800/100 mg twice daily  
  - SQV/r 1000/100 mg twice daily | **Primary Endpoint:** Difference in the rate of virologic failure between both arms (defined based on the patient’s viral load upon inclusion)  
  - IDV/r vs SQV/r = 2.2% (95% CI -2.8–7.2%), p = NS | Grade 3-4 adverse events were experienced by the following percentage of patients in each arm:  
  - IDV/r = 41%  
  - SQV/r = 24%  
  - P = 0.001  
  Patients in the IDV/r arm experienced more renal, dermatological, and gastrointestinal severe adverse effects than those in the SQV/r arm. |
| *Phase 4, open-label, multi-center, randomized trial* |    | *Setting:* 28 sites in 13 countries, including the US |  
  - Follow-Up: 48 weeks Conducted: September ’00 – March ’01 | | |
| Kirk et al, 2003      | 233| PI- and NNRTI-naïve patients about to initiate their first HAART regimen | The following two in combination two NRTIs:  
  - SQV/r 400/400 mg twice daily  
  - NFV/NVP 1250/200 mg twice daily | **Primary Endpoint:** Comparison of the proportion of patients with HIV1-RNA ≤ 20 copies/mL at week 48  
  - SQV/r = 56%  
  - NFV/NVP = 69%  
  - P = 0.037 | The following percentage of patients switched therapy based on adverse events:  
  - SQV/r = 73%  
  - NFV/NVP = 80%  
  - P = 0.99  
  The most limiting adverse event in both groups was gastrointestinal events. Skin reactions and allergy were significantly more common in the NFV/NVP arm. |
<p>| <em>Randomized, controlled, open-label trial</em> | | <em>Setting:</em> Denmark |</p>
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| Fischl et al, 2003[^140] Randomized, open-label study | 517 | Persons with advanced human immunodeficiency virus (HIV) disease and little to no experience with ART | Subjects received lamivudine (150 mg) and zidovudine (300 mg) twice daily along with:  
  • Indinavir (IDV) 800 mg three times daily (n = 168)  
  • efavirenz 600 mg once daily plus indinavir 1000 mg three times daily (EFV/IDV, n = 173)  
  • nelfinavir 1250 mg twice daily plus indinavir 1000 mg twice daily (NFV/IDV, n = 176) | Virologic failure  
  • EFV/IDV < IDV, p = 0.04  
  • NFV/IDV > IDV, p = 0.006 | Adverse event rate  
  • EFV/IDV = NFV/IDV = IDV  
  The most frequent grade 3 or 4 signs or symptoms reported were aches or pains, fatigue, or gastrointestinal complaints (nausea, vomiting, and diarrhea) |
| Gathe et al, 2002[^120] Phase III, open-label, multi-center, randomized, non-inferiority study | 649 | Treatment naïve patients aged ≥18 years with HIV1-RNA ≥ 1,000 copies/mL  
  Setting: 101 centers in North America, Europe, South Africa, and Australia | The following two in combination with abacavir and lamivudine twice daily:  
  • FPV/r 1400/200 mg daily  
    o N = 322  
  • NFV 1250 mg twice daily  
    o N = 327  
  Follow-Up: 48 weeks | Primary Endpoint: Comparison of the magnitude and durability of virologic response over 48 weeks  
  HIV1-RNA < 400 copies/mL  
  • FPV/r = 69%  
  • NFV = 68%  
    o 1% (95% CI -6–8%)  
    o Considered non-inferior  
  HAV1-RNA < 50 copies/mL  
  • FPV/r = 55%  
  • NFV = 53% | Grade 2-4 adverse events were experienced by the following percentage of patients in each arm:  
  • FPV/r = 41%  
  • NFV = 39%  
  Diarrhea was significantly more common in the NFV arm. |
| Kirk et al, 2001[^89] Prospective, observational, multicenter cohort study | 2708 | HIV-infected patients older than 16 years | HAART with ≥ 3 drugs including:  
  • Indinavir (n = 1342)  
  • Ritonavir (n = 556)  
  • Saquinavir (n = 810)  
  Median follow-up: 30 months | Proportion of patients who had experienced clinical progression at 12 months  
  • Indinavir: 9.2%  
  • Ritonavir: 11.9%  
  • Saquinavir: 11.9% | Not reported |

[^140]: [Fischl et al.](#)  
[^120]: [Gathe et al.](#)  
[^89]: [Kirk et al.](#)
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<tr>
<td>Gulick et al, 2000\textsuperscript{122}</td>
<td>277</td>
<td>NNRTI treatment naïve patients</td>
<td>Delavirdine and/or Adefovir in combination with • SQV/r (n = 139) • SQV/NFV (n = 138) Duration: 16 weeks</td>
<td>Virologic Response ((&lt;500) HIV RNA copies/mL) • SQV/r: 28% • SQV/NFV: 33%, p = NS</td>
<td>Adverse event rate • SQV/r = SQV/NLV, p = 0.07</td>
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<tr>
<td>Katzenstein et al, 1999\textsuperscript{124}</td>
<td>318</td>
<td>Patients $\geq$ 18 years old with documented HIV infection and 0–13 days prior use of PIs</td>
<td>Two NRTIs in combination with: • Indinavir 800 mg three times daily (n = 107) • Ritonavir 600 mg twice daily (n = 107) • Saquinavir/r 400/600 mg twice daily (n = 104) Follow-up: up to 72 weeks</td>
<td>$\leq20$ HIV RNA copies/mL at 72 weeks • Indinavir: 51% • Ritonavir: 41% • Saquinavir/r: 58% • Saquinavir/r &gt; Ritonavir, p &lt; 0.05 Virus loads of $\leq20$ copies/mL at 72 weeks • Indinavir: 63% • Ritonavir: 55% • Saquinavir/r: 77%, p = NS Treatment success rate • Indinavir: 52% • Ritonavir: 41% • Saquinavir/r: 58%, p = NS</td>
<td>Adverse event discontinuation rate: • Indinavir: 27% • Ritonavir: 68% • Saquinavir/r: 33%, p &lt; 0.001 Renal adverse reactions were most common among patients receiving indinavir, whereas gastrointestinal and neurologic adverse reactions were more often experienced by patients receiving ritonavir.</td>
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<td>Cohen Stuart et al, 1999\textsuperscript{126}</td>
<td>70</td>
<td>Patients who were antiretroviral-naïve and who had a CD4 cell count &lt; 500 x 10(6)/l and/or $&gt;10000$ HIV RNA copies/ml plasma and/or HIV-related symptoms</td>
<td>ART with zidovudine 200 mg three times per day plus lamivudine 150 mg twice per day plus either • Indinavir 800 mg three times daily (n = 35) • Saquinavir 1200 mg three times daily (n = 35) Follow-up 24 weeks</td>
<td>Decrease in HIV RNA • Indinavir = Saquinavir Increase in CD4 cell counts • Indinavir &lt; Saquinavir, p = 0.01</td>
<td>Overall adverse event rate: • Indinavir = Saquinavir Discontinuation rate: • Indinavir = Saquinavir</td>
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\textit{Treatment experienced patients}
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<tr>
<td>Antoniou et al, 2010†</td>
<td>85</td>
<td>Patients with multidrug resistant HIV</td>
<td>Tipranavir/ritonavir (TPV/r; n = 38)</td>
<td>Virologic Response (viral load &lt; 50 copies/mL)</td>
<td>Adverse event rate</td>
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<td>Darunavir/ritonavir (DRV/r; n = 47)</td>
<td>- TPV/r: 82%</td>
<td>TPV/r = DRV/r</td>
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<td>- DRV/r: 79%, p = NS</td>
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<td>Sustained virologic suppression (2 or more sequential viral load results below 50 copies/mL)</td>
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<td>- TPV/r: 74%</td>
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<td>- DRV/r: 72%, p = NS</td>
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<td>Safety</td>
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<td>Johnson et al, 2005 &amp;</td>
<td>358</td>
<td>Treatment experienced patients aged ≥16-18 years (legal minimum age as locally required) that had failed ≥ 2 HAART regimens that included one or more NRTI and PI and had previously responded to at least 1 HAART regimen with a 1 log₁₀ copies/mL viral load reduction or a viral load decline to &lt; 400 copies/mL</td>
<td>The following in combination with tenofovir 300mg daily and one NRTI:</td>
<td>Primary Endpoint: Comparison of the magnitude and durability of viral load reduction from baseline based on the timed average difference through week 48 and 96</td>
<td>Grade 2-4 adverse events</td>
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<tr>
<td>Johnson et al, 2006</td>
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<td>Setting: Europe and North and South America</td>
<td>- ATV/r 300/100 mg daily</td>
<td>Week 48</td>
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<td>- ATV/SQV 400/1200 mg daily</td>
<td>- ATV/r vs LPV/r = 0.13 log₁₀ copies/mL (97.5% CI -0.12–0.39); non-inferior</td>
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<td>- LPV/r 400/100 mg twice daily</td>
<td>- ATV/SQV vs LPV/r = 0.33 log₁₀ copies/mL (97.5% CI 0.07–0.60); inferior</td>
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<td>Week 96</td>
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<td>- ATV/r vs LPV/r = 0.14 log₁₀ copies/mL (97.5% CI -0.13–0.41), non-inferior</td>
<td>Secondary Endpoint: Mean change of HIV1-RNA from baseline to week 48 and 96</td>
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<td>Week 48</td>
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<td>- ATV/r = 1.93 log₁₀ copies/mL</td>
<td>- ATV/SQV = 1.55 log₁₀ copies/mL</td>
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<td>- LPV/r = 1.87 log₁₀ copies/mL</td>
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<td>Week 96</td>
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<td></td>
<td>- ATV/r = -2.29 log₁₀ copies/mL</td>
<td>- LPV/r = -2.08 log₁₀ copies/mL</td>
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| **Haas et al, 2003**<sup>129</sup> | 85 | Treatment experienced patients having at least 1000 HIV-1 RNA copies/ml, 100 x 106 CD4 cells/l (75 x 106 cells/l without AIDS diagnosis) and virologic response to a prior regimen | Two NRTIs in combination with:  
- ATV/SQV 400/1200 mg once daily (n = 34)  
- ATV/SQV 600/1200 mg once daily (n = 28)  
- r/SQV 400 mg/400 mg twice daily (n = 23)  
Duration: 48 weeks | **Primary Endpoint:** Assess safety and tolerability  
**Secondary Endpoints:** Mean change in HIV1-RNA, viral load and CD4+ T cell count  
Virologic response (> 1.0 log(10) decrease HIV-1 RNA or HIV-1 RNA < 400 copies/ml):  
- ATV 400 mg = 41%  
- ATV 600 mg = 29%  
- r = 35%; p = NS  
Adverse-event discontinuation rate:  
- ATV 400 mg = 9%  
- ATV 600 mg = 11%  
- r = 30%; p = NS  
Mean change in low-density cholesterol  
- ATV 400 mg = -0.6%  
- ATV 600 mg = -6.7%  
- r = 23.2%; p < 0.05  
Mean change in triglyceride  
- ATV 400 mg = -4.8%  
- ATV 600 mg = -27.1%  
- r = 93%; p < 0.001 |  |
| **Chavanet et al, 2001**<sup>131</sup> | 31 | Patients age > 18 with HIV and previous PI exposure > 6 months, unchanged HAART > 3 months, and viral load > 3 log | NRTIs in combination with:  
- r/SQV 200/600 mg twice daily (n = 16)  
- NFV/SQV 1000/600 mg twice daily (n = 15)  
Duration: 3 months | **Plasma viral load stabilization or decrease >/= 0.5 log**  
- r/SQV: 10  
- NFV/SQV: 8  
Not reported |  |
| **Para et al, 2000**<sup>132</sup> | 89 | Patients age > 18 with HIV-1 infection | ARV therapy including  
- SQV 1200 mg every 8 hours (n = 59)  
- IDV 800 mg every 8 hours (n = 30)  
Follow-up: 24 weeks | **Achieved viral RNA level of <500 copies/mL**  
- SQV: 4.8%  
- IDV: 49%; p < 0.001  
Not reported |  |
<table>
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<tbody>
<tr>
<td>Roca et al, 2000&lt;sup&gt;130&lt;/sup&gt; Randomized, open-label, prospective study.</td>
<td>112</td>
<td>Patients with HIV and CD4 cell count below 500 × 106/l or HIV RNA plasma level &gt; 5000 copies/ml</td>
<td>Art with stavudine 40 mg (30 mg if weight &lt; 60 kg) twice daily and lamivudine 150 mg twice daily with • IDV 800 mg three times daily (n = 56) • NFV 750 mg three times daily (n = 56)</td>
<td>CD4+ Call increase &gt; 100/mL • IDV: 42% • NFV: 35%, p = NS</td>
<td>Frequency of treatment-related side effects • IDV: 54% • NFV: 46%, p = NS Treatment-related discontinuation rate • IDV: 60% • NFV: 38%, p &lt; 0.05</td>
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<td><strong>Pediatric patients</strong></td>
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<td>HIV RNA level below limit of detection • IDV: 46% • NFV: 47%, p = NS</td>
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<td>Rodriguez-French et al, 2004&lt;sup&gt;134&lt;/sup&gt; Multi-center, open-label, randomized study</td>
<td>249</td>
<td>Treatment naïve patients aged ≥13-18 years (legal minimum age as locally required) with HIV1-RNA ≥ 5,000 copies/mL Setting: US, Puerto Rico, Panama, and South Africa</td>
<td>The following two in combination with abacavir 300mg and lamivudine 150mg twice daily: • FPV 1400 mg twice daily o N = 166 • NFV 1250 mg twice daily o N = 83 Follow-Up: 48 weeks Conducted: November ‘00 – July ‘01</td>
<td>Primary Endpoint: Comparison of the efficacy and durability of the antiviral response (HIV1-RNA &lt; 400 copies/mL) at 48 weeks • FPV = 66% • NFV = 51%</td>
<td>Adverse events of at least grade 2 in severity were experienced by the following percentage of patients: • FPV = 30% • NFV = 34% Diarrhea was more common in the NFV arm. Rash was more common in the FPV arm.</td>
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Key: NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; ATV = atazanavir; RAL = raltegravir; DRV = darunavir; r = ritonavir; 97.5% or 95% CI = 97.5% or 95% confidence interval; LPV = lopinavir; TDF = tenofovir; FTC = emtricitabine; FPV = fosamprenavir; SQV = saquinavir; NFV = nelfinavir; HAART = highly active antiretroviral therapy.
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<th>Evidence Table 3. Excluded Clinical Trials</th>
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<tr>
<td><strong>Bench Science Studies (synthesis, delivery systems, drug concentration quant, cell culture/animal studies, T-cell proliferation, etc.)</strong></td>
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<tr>
<td>PubMed ID (Reference)</td>
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<td><strong>PK (ADME) or Kinetics Studies</strong></td>
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31. 19528289 (von Hentig, 2009, Cytochrome P450 3A inhibition by atazanavir and ritonavir, but not demography or drug formulation, influences saquinavir population pharmacokinetics in human immunodeficiency virus type 1-infected adults)
32. 19203907 (Boffito, 2008, Pharmacokinetics, efficacy, and safety of darunavir/ritonavir 800/100 mg once-daily in treatment-naive and -experienced patients)
33. 18769354 (Mathias, 2008, Effect of ritonavir-boosted tipranavir or darunavir on the steady-state pharmacokinetics of elvitegravir)
34. 18536180 (Pawinski, 2008, Pharmacokinetic monitoring of HIV-1 protease inhibitors in the antiretroviral therapy)
35. 18520949 (Busti, 2008, Effects of atazanavir/ritonavir or fosamprenavir/ritonavir on the pharmacokinetics of rosvastatin)
36. 18333863 (Abel, 2008, Effects of CYP3A4 inhibitors on the pharmacokinetics of maraviroc in healthy volunteers)
37. 18154777 (Ootofukun, 2008, Pharmacokinetics of a nindivite‐ritonavir‐fosamprenavir regimen in patients with human immunodeficiency virus)
38. 18043478 (Sekar, 2007, Pharmacokinetic interaction between darunavir and saquinavir in HIV-negative volunteers)
39. 17910618 (Jutjesen, 2007, Pharmacokinetics of two randomized trials evaluating the safety and efficacy of indinavir, saquinavir and lopinavir in combination with low-dose ritonavir: the MaxCmin1 and 2 trials)
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