

Protease Inhibitor–Based Regimens

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Table 8d. Characteristics of Protease Inhibitor Options That Are Recommended as Initial Therapy for People with HIV

Characteristic	ATV	DRV
Dosing Frequency	Once daily	<ul style="list-style-type: none"> Once daily for PI-naïve patients Twice daily for PI-experienced patients with certain PI mutations
PK Boosting	PK boosting with RTV or COBI generally is recommended. Unboosted ATV also is FDA-approved for ART-naïve patients.	DRV only should be used with a PK booster (i.e., RTV or COBI).
Fixed-Dose Formulation	ATV/c	<ul style="list-style-type: none"> DRV/c DRV/c/TAF/FTC
Available as a Single-Drug Tablet	Yes	Yes
Adverse Effects	<ul style="list-style-type: none"> Jaundice Indirect hyperbilirubinemia Cholelithiasis Nephrolithiasis PR prolongation 	<ul style="list-style-type: none"> Skin rash Increase in serum transaminases Hyperlipidemia A higher cardiovascular risk was reported in participants taking DRV-based regimens than in those taking ATV-based regimens in an observational cohort study.
CYP3A4 Drug-Drug Interactions	CYP3A4 substrate, inhibitor	CYP3A4 substrate, inhibitor
Other Significant Drug Interactions	ATV absorption is reduced when ATV is given with acid-lowering therapies. See Table 24a for ATV dosing recommendations when the drug is coadministered with acid-lowering agents.	N/A

Key: ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; COBI = cobicistat; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; FDA = Food and Drug Administration; FTC = emtricitabine; N/A = not applicable; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide

Summary

The U.S. Food and Drug Administration (FDA)-approved protease inhibitors (PIs) include atazanavir (ATV), ATV/cobicistat (ATV/c), darunavir (DRV), darunavir/cobicistat (DRV/c), fosamprenavir (FPV), indinavir (IDV), lopinavir/ritonavir (LPV/r), nelfinavir (NFV), ritonavir (RTV), saquinavir (SQV), and tipranavir (TPV). PI-based regimens using pharmacokinetic (PK) enhancement with

either cobicistat (COBI) or RTV (also called PK boosting) increase concentration and prolong the half-lives of the PI. These regimens have demonstrated virologic potency, durability in treatment-naive patients, and a high barrier to resistance. Because LPV/r, FPV/r, unboosted ATV, and SQV/r have disadvantages, such as greater pill burden, lower efficacy, or increased toxicity, only boosted DRV and ATV in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) are recommended as initial therapy in certain clinical situations.

Because transmitted PI resistance is uncommon, boosted ATV or DRV-based regimens are recommended for rapid antiretroviral therapy (ART) initiation or in the setting of acute HIV infection, before resistance test results are available. As few or no PI mutations are detected when a patient's first PI-based regimen fails, which is not the case with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens and some integrase strand transfer inhibitor (INSTI)-based regimens,¹ PI-based regimens may be useful for patients at risk for intermittent therapy because of poor adherence.

All recommended PIs require PK boosting with either RTV or COBI to inhibit the CYP3A4 isoenzyme, which may lead to significant drug-drug interactions (see [Drug–Drug Interactions](#)). Each PI has specific characteristics related to its virologic potency, adverse effects profile, and PK properties. The characteristics of the two recommended PIs are listed in [Appendix B, Table 9](#) and [Appendix B, Table 5](#). Several metabolic abnormalities, including dyslipidemia and insulin resistance, have been associated with PI use. The currently available PIs differ in their propensity to cause these metabolic complications, which also depends on the dose of RTV used as a PK-enhancing agent. Large observational cohort studies found an association between some PIs (i.e., DRV/r, FPV, IDV, and LPV/r) and an increased risk of cardiovascular events; this risk was not seen with ATV.²⁻⁵ Another observational cohort study of predominantly male participants found a lower rate of cardiovascular events in those receiving ATV-containing regimens than in those receiving other regimens.⁶

Darunavir/Ritonavir (DRV/r)

Efficacy in Clinical Trials

- The ARTEMIS study compared DRV/r (800 mg/100 mg once daily) with LPV/r (800 mg/200 mg once daily or 400 mg/100 mg twice daily), both administered in combination with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), in a randomized, open-label, noninferiority trial. DRV/r was noninferior to LPV/r at Week 48⁷ and superior at Week 192.⁸
- The FLAMINGO study compared DRV/r with dolutegravir (DTG), each administered in combination with two NRTIs, in 488 participants who were ART-naive. The rate of virologic suppression at Week 96 was significantly greater among those who received DTG than in those who received DRV/r. The higher rate of virologic failure observed in the DRV/r group was related primarily to the number of failures among those with a viral load >100,000 copies/mL and secondarily to more drug discontinuations in the DRV/r group.⁹
- ACTG A5257 (ARDENT), a large, randomized, open-label trial compared ATV/r to DRV/r or raltegravir (RAL) over 96 weeks, each given with TDF/FTC. The trial showed similar virologic efficacy for DRV/r, ATV/r, and RAL, but more participants in the ATV/r group discontinued randomized treatment because of adverse events.¹⁰

- The DRIVE-FORWARD study compared DRV/r to doravine (DOR), both administered with two investigator-selected NRTIs, in 769 ART-naive participants. At 48 weeks, DOR was found to be noninferior to DRV/r, with 80% of participants who received DOR and 84% of participants who received DRV/r achieving HIV RNA levels <50 copies/mL.¹¹ At Week 96, DOR was superior to DRV/r in terms of virologic suppression (73% vs. 66%).¹¹ Rates of virologic failure were low and similar in the DOR and DRV/r groups (9% vs. 11%). Treatment-emergent resistance to any study drug occurred in 2 of 383 (1%) participants in the DOR group and 1 of 383 (<1%) participants in the DRV/r group.

Adverse Effects

- Patients taking DRV/r may develop a skin rash, which is usually mild-to-moderate in severity and self-limited. Treatment discontinuation is necessary on rare occasions when severe rash with fever or elevated transaminases occur.
- ACTG A5257 showed similar lipid changes in participants in the ATV/r and DRV/r arms. Bone mineral density (BMD) decreased to a greater extent in participants in the ATV/r and DRV/r arms than in participants in the RAL arm.¹⁰ The likelihood of developing metabolic syndrome was equivalent among the three arms, although a larger increase in waist circumference was observed at 96 weeks in participants assigned to the RAL arm than in those assigned to the DRV/r arm ($P \leq 0.02$).¹²
- An observational cohort study suggested that DRV/r is associated with increased rates of cardiovascular disease when compared to ATV/r.⁵

Other Factors and Considerations

- DRV/r is administered once daily with food in treatment-naive patients.
- DRV has a sulfonamide moiety and should be used with caution in patients with severe sulfonamide allergies. In clinical trials, the incidence and severity of rash were similar in participants with and without a history of sulfonamide allergy. Most patients with sulfonamide allergy can tolerate DRV.
- DRV/r is a potent CYP3A4 inhibitor, which may lead to significant interactions with other medications metabolized through this same pathway (see [Drug–Drug Interactions](#)).

The Panel’s Recommendations

- On the basis of efficacy and safety data from clinical trials and clinical experience, the Panel classifies DRV/r with tenofovir alafenamide (TAF) or TDF with FTC or lamivudine (3TC) (**AI**), or with abacavir (ABC)/3TC (**BII**) as *Recommended Initial Regimens in Certain Clinical Situations*.

Darunavir/Cobicistat (DRV/c)

Efficacy in Clinical Trials

- The AMBER trial enrolled 725 ART-naive participants in a Phase 3 randomized controlled trial that compared the single-tablet regimen (STR) DRV/c/TAF/FTC with DRV/c plus TDF/FTC. At 48 weeks, similar virologic suppression rates among participants were achieved in both arms of

the study (91% and 88% had HIV RNA <50 copies/mL, respectively). No treatment-emergent mutations associated with DRV or TAF/TDF resistance were observed in either group.¹³ At 96 weeks, 85% of participants on the STR maintained HIV RNA levels <50 copies/mL.¹⁴

- The DIAMOND study evaluated DRV/c/TAF/FTC as an STR in 109 patients in a rapid-initiation model of care. At Week 48, 97 (89%) participants completed the study and 92 (84%) achieved HIV-1 RNA <50 copies/mL by the FDA snapshot analysis. No protocol-defined virologic failures occurred, and incidences of adverse events and adverse drug reactions (33%) were low. No study drug-related serious adverse events occurred, and only one (<1%) participant discontinued because of a study drug-related adverse event.¹⁵

Adverse Effects

- The most common drug-related adverse events were diarrhea, nausea, fatigue, flatulence, rash, and headache.

Other Factors and Considerations

- DRV/c 800 mg/150 mg is available as a coformulated boosted PI or as an STR with TAF/FTC 10 mg/200 mg.
- Both DRV and COBI exposures are reduced markedly during second and third trimesters of pregnancy, and should be avoided if possible.¹⁶ However, if pregnant women with viral suppression while on DRV/c elect to continue on the drug, frequent viral load monitoring is recommended.

The Panel's Recommendations

- The Panel recommends DRV/c plus TAF/FTC or TDF/FTC (**AI**) and DRV/c plus ABC/3TC (**BII**) as *Recommended Initial Regimens in Certain Clinical Situations*.
- DRV/c plus TDF/FTC is **not recommended** for patients with creatinine clearance (CrCl) <70 mL/min, whereas DRV/c plus TAF/FTC is **not recommended** for patients with CrCl <30 mL/min.

Atazanavir/Ritonavir (ATV/r) or Atazanavir/Cobicistat (ATV/c)

Efficacy in Clinical Trials

ATV/r plus Two NRTIs versus LPV/r plus Two NRTIs

- The CASTLE study compared once-daily ATV/r (300 mg/100 mg) with twice-daily LPV/r (400 mg/100 mg), each administered in combination with TDF/FTC. In this open-label, noninferiority study, the two regimens showed similar virologic and CD4 responses at 96 weeks.¹⁷

ATV/r plus Two NRTIs versus EFV plus Two NRTIs

- The ACTG A5202 study compared open-label ATV/r and efavirenz (EFV), each given in combination with placebo-controlled TDF/FTC or ABC/3TC. Efficacy was similar in the ATV/r and EFV groups.¹⁸ In a separate analysis, women assigned to receive ATV/r were found to have a

higher risk of virologic failure than women assigned to receive EFV or men assigned to receive ATV/r.¹⁹

ATV/r plus Two NRTIs versus INSTI plus Two NRTIs

- In a study that compared ATV/r plus TDF/FTC to elvitegravir/cobicistat (EVG/c)/TDF/FTC, virologic suppression rates through 144 weeks were similar among participants in the two groups.²⁰ A Phase 3 clinical trial of 575 women evaluated EVG/c plus FTC/TDF versus ATV/r plus FTC/TDF.²¹ At Week 48, the virologic suppression rate in the EVG/c arm was superior to that in the ATV/r arm. Nineteen women in the PI arm and five women in the INSTI arm discontinued therapy because of an adverse event.
- In a Phase 3 trial, 499 ART-naive women were randomized to receive either ATV/r plus TDF/FTC or DTG/ABC/3TC. At 48 weeks, the rate of virologic suppression (HIV RNA <50 copies/mL) in the DTG arm was noninferior to that in the ATV/r arm, and fewer drug-related adverse events occurred in the DTG arm.²²

ATV/r plus Two NRTIs versus DRV/r plus Two NRTIs versus RAL plus Two NRTIs

- ACTG A5257 (ARDENT) was a large, randomized, open-label trial that compared ATV/r to DRV/r or RAL over 96 weeks, each given with TDF/FTC. The trial showed similar virologic efficacy for DRV/r, ATV/r, and RAL, but more participants in the ATV/r group discontinued randomized treatment because of adverse events, mostly elevated indirect bilirubin/jaundice, or gastrointestinal toxicities. Lipid changes in participants in the ATV/r and DRV/r arms were similar. BMD decreased to a greater extent in participants in the ATV/r and DRV/r arms than in participants in the RAL arm.¹⁰

ATV/c versus ATV/r plus Two NRTIs

- In the Gilead Study 114, all patients received TDF/FTC and ATV and were randomized to receive either RTV or COBI as PK enhancers. Both RTV and COBI were given as a separate tablet with matching placebos.²³ Through 144 weeks, the percentage of patients who achieved virologic suppression was similar in both study arms. The percentages of adverse events that caused patients to discontinue treatment and changes in serum creatinine and indirect bilirubin levels also were comparable.²⁴

Adverse Effects

- The main adverse effect associated with ATV/c or ATV/r is reversible indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. The risk for treatment-limiting indirect hyperbilirubinemia is greatest for patients who carry two UGT1A1 decreased-function alleles.²⁵
- Nephrolithiasis,²⁶⁻²⁸ nephrotoxicity,²⁹ and cholelithiasis³⁰ also have been reported in patients who received ATV.
- Both ATV/c and ATV/r can cause gastrointestinal side effects, including diarrhea.

Other Factors and Considerations

- ATV/c and ATV/r are dosed once daily with food.

- ATV requires acidic gastric pH for dissolution. As a result, concomitant use of drugs that raise gastric pH (e.g., antacids, H₂ antagonists, and particularly proton pump inhibitors) may impair absorption of ATV. [Table 24a](#) provides recommendations for use of ATV/c or ATV/r with these agents.
- ATV/c and ATV/r are potent CYP3A4 inhibitors and may have significant interactions with other medications that are metabolized through this same pathway (see [Drug–Drug Interactions](#)).
- Large observational cohort studies found an association between some PIs (DRV/r, FPV, IDV, and LPV/r) and an increased risk of cardiovascular events; this risk was not seen with ATV.²⁻⁵ Another observational study of a cohort of predominantly male participants found a lower rate of cardiovascular events in participants receiving ATV-containing regimens than in participants receiving other regimens.⁶

The Panel’s Recommendations

- Based on clinical trial safety and efficacy data, the Panel classifies ATV/r and ATV/c plus (TAF or TDF) with (FTC or 3TC) (**BI**) as *Recommended Initial Regimens in Certain Clinical Situations*.
- ATV/c plus TDF/FTC **is not recommended** for patients with CrCl <70 mL/min, and ATV/c plus TAF/FTC **is not recommended** for patients with CrCl <30 mL/min.
- COBI should be avoided in pregnancy, because levels of COBI and its boosted drugs are lower in the second and third trimesters. However, if pregnant women with suppressed virus on ATV/c elect to continue the drug, frequent viral load monitoring is recommended.

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