

Protease Inhibitor–Based Regimens

Updated: September 24, 2026

Reviewed: September 24, 2026

Table 8d. Characteristics of Protease Inhibitor Options as Initial Antiretroviral Therapy

Characteristic	DRV
Dosing Frequency	Once daily
PK Boosting	DRV should only be used with a PK booster (i.e., RTV or COBI).
Fixed-Dose Formulation	<ul style="list-style-type: none"> • DRV/c • DRV/c/TAF/FTC
Available as a Single-Drug Tablet	Yes
Adverse Effects	<ul style="list-style-type: none"> • Skin rash • Increase in serum transaminase • Hyperlipidemia • Diarrhea, nausea
CYP3A4 Drug–Drug Interactions	CYP3A4 substrate, inhibitor
Other Significant Drug Interactions	N/A

Key: COBI = cobicistat; CYP = cytochrome P450; DRV = darunavir; DRV/c = darunavir/cobicistat; FTC = emtricitabine; N/A = not applicable; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide

Summary

Ten protease inhibitors (PIs) have been approved by the U.S. Food and Drug Administration. Currently used PI-based regimens use pharmacokinetic (PK) enhancement (also called PK boosting) with either cobicistat (COBI) or ritonavir (RTV) to increase concentrations and prolong the half-lives of the PI. These regimens have demonstrated virologic potency, durability in people who are antiretroviral therapy (ART)–naïve, and a high barrier to resistance. Because the older PIs, such as lopinavir and atazanavir (ATV), have disadvantages—such as greater pill burden, lower efficacy, or increased toxicity—they are no longer recommended. Boosted darunavir (DRV), when combined with one or two nucleoside reverse transcriptase inhibitors (NRTIs), is the only PI recommended for initial therapy (see [Recommended Initial Regimens for Most People With HIV](#) and [Initial Antiretroviral Regimens for Certain Clinical Scenarios](#)).

Because transmitted PI resistance is uncommon, a boosted DRV–based regimen (with two NRTIs) is preferred over a non-nucleoside reverse transcriptase inhibitor (NNRTI)–based regimen as an option for treatment initiation before resistance test results are available. In addition, similar to a second-generation INSTI, a boosted DRV–based regimen can be used for rapid ART initiation and is the preferred option while awaiting resistance test results for people with a history of long-acting cabotegravir (CAB-LA) use for pre-exposure prophylaxis (PrEP). Similar to what is seen with second-generation INSTIs, few or no resistance mutations are detected when a patient's first regimen fails, which is not the case with NNRTI-based regimens and regimens with a first-

generation INSTI (e.g., raltegravir [RAL] or elvitegravir).¹ Because of their high barrier to resistance, PI-based regimens may be useful for people at risk for poor adherence.

DRV requires PK boosting with either RTV (DRV/r) or COBI (DRV/c) to inhibit the cytochrome P450 (CYP) 3A4 isoenzyme, which may lead to significant drug–drug interactions (see [the Liverpool HIV Drug Interaction Checker](#)). The specific characteristics of DRV are listed in [Appendix A, Table 5](#).

Darunavir/Cobicistat

Efficacy in Clinical Trials

- The AMBER trial enrolled 725 ART-naïve participants in a Phase 3 randomized controlled trial that compared the single-tablet regimen (STR) DRV/c/tenofovir alafenamide (TAF)/emtricitabine (FTC) with DRV/c plus tenofovir disoproxil fumarate (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.² At 96 weeks, 85% of participants on the STR maintained HIV RNA levels <50 copies/mL compared to 84% in the DRV/c plus TDF/FTC arm.³
- In the open-label, multicenter LAPTOP trial, 447 adults with advanced HIV disease were randomized to receive either bictegravir (BIC)/TAF/FTC or DRV/c/TAF/FTC. The primary composite outcome was the time to first occurrence of specified virological or clinical event. At 48 weeks, the primary composite outcome was observed in 22% of participants in the BIC/TAF/FTC group versus 32% in the DRV/c/TAF/FTC group, demonstrating noninferiority of BIC/TAF/FTC. At Week 48, 69% and 61% of participants achieved HIV RNA <50 copies/mL in the BIC/TAF/FTC and DRV/c/TAF/FTC groups, respectively. Compared with the DRV/c/TAF/FTC group, participants in the BIC/TAF/FTC group were more likely to achieve HIV RNA <50 copies/mL at Week 4 (16% vs. 1%), Week 8 (35% vs. 7%), and Week 12 (46% vs. 17%).⁴
- The DIAMOND study was a single-arm trial that evaluated DRV/c/TAF/FTC as an STR in 109 participants in a rapid-initiation model of care. At Week 48, 97 (89%) participants completed the study and 92 (84%) achieved HIV RNA <50 copies/mL. No protocol-defined virologic failures occurred, and incidences of adverse events at least possibly related to study drugs (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.⁵

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 the second and third trimesters of pregnancy; therefore, DRV/c **is not recommended** as part of initial therapy in pregnancy.⁶ However, if pregnant women with viral suppression while on DRV/c elect to continue on the drug, frequent viral load monitoring is recommended. For further information, please refer to the [Perinatal Guidelines](#).

The Panel's Recommendations

- For people who have a history of CAB-LA use as PrEP, INSTI genotype resistance testing should be performed before starting an INSTI-based regimen. If ART is to be started before genotypic testing results are available, DRV/c with (TAF or TDF) plus (FTC or lamivudine [3TC]) can be started **(AIII)**.
- The Panel recommends DRV/c plus (TAF or TDF) plus (FTC or 3TC) **(BI)** and DRV/c plus abacavir (ABC)/3TC **(BII)** as part of [Initial Antiretroviral Regimens for Certain Clinical Scenarios](#).
- Per product label recommendation, DRV/c plus TDF/FTC **is not recommended** for people with creatinine clearance (CrCl) <70 mL/min, whereas DRV/c plus TAF/FTC **is not recommended** for people with CrCl <30 mL/min.
- For the unique situation in which tenofovir (TFV) and ABC must be avoided and DTG/3TC is not an option, the Panel recommends DRV/c plus (3TC or FTC) **(BII)** (see [Initial Antiretroviral Regimens for Certain Clinical Scenarios](#)), except for individuals—
 - o With hepatitis B virus (HBV) coinfection, unless receiving entecavir.
 - o With unknown HBV serostatus.
 - o Without results from genotypic resistance testing for reverse transcriptase.
 - o For whom rapid ART initiation is planned.

Darunavir/Ritonavir

Efficacy in Clinical Trials

With Two Nucleoside Reverse Transcriptase Inhibitors

DRV/r has been studied in several large, randomized controlled trials in people with HIV without prior antiretroviral (ARV) experience. These trials compared DRV/r-based regimens (**DRV 800 mg/RTV 100 mg**) to PI-, INSTI-, or NNRTI-based regimens. Summaries of the results from some key trials are listed below.

- The FLAMINGO study compared DRV/r with dolutegravir (DTG), each administered in combination with two NRTIs—either TDF/FTC or ABC/3TC—in 488 participants who were ART-naïve. The rate of viral suppression at Week 96 was significantly higher among those who received DTG than among 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.⁷
- The AIDS Clinical Trial Group (ACTG) study A5257 (ARDENT), a randomized, open-label trial, compared atazanavir/ritonavir (ATV/r) to DRV/r or RAL over 96 weeks, each given with TDF/FTC. **A total of 1,809 treatment-naïve adults were enrolled.** The trial showed similar virologic efficacy for DRV/r, ATV/r, and RAL, but more participants in the ATV/r group discontinued randomized treatment due to adverse events.⁸
- The DRIVE-FORWARD study compared DRV/r to doravirine (DOR), both administered with two investigator-selected NRTIs, in 769 ART-naïve participants. At 48 weeks, DOR was found to be non-inferior to DRV/r, with 80% and 84% of participants achieving HIV RNA levels <50 copies/mL, respectively.⁹ At Week 96, DOR was superior to DRV/r in terms of viral suppression (73% vs. 66%).⁹ 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 was infrequent,

occurring in <1% of participants in both the DOR group (2 of 383) and the DRV/r group (1 of 383).

DRV/r-based regimens have also been assessed in randomized trials as first-line ARV treatment for individuals presenting with advanced HIV, as summarized below.

- In the open label ADVANZ-4 trial, 104 ART-naïve adults with advanced HIV (CD4 T lymphocyte cell counts <100 cells/mm³) were randomized to receive either DTG plus ABC/3TC or DRV/r plus ABC/3TC. Virologic responses were similar at 48 weeks but faster for the DTG arm, with a significantly higher proportion of participants in the DTG arm achieving undetectable viral load at Weeks 4 and 12.¹⁰

With One Nucleoside Reverse Transcriptase Inhibitor

- In the ANDES trial, 336 ART-naïve participants were randomized to receive open-label, once-daily dual therapy with DRV/r plus 3TC or triple therapy with DRV/r plus TDF/3TC.¹¹ This study was conducted in Argentina using a fixed-dose combination of DRV/r 800 mg/100 mg that is available in that country. The median baseline HIV RNA was 4.5 log₁₀ copies/mL, and 23% of participants had HIV RNA >100,000 copies/mL. At Week 48, 91% of participants in the dual-therapy group and 93% of those in the triple-therapy group achieved HIV RNA <50 copies/mL, demonstrating noninferiority with dual therapy.¹¹ The rates of viral suppression among study participants with baseline HIV RNA levels >100,000 copies/mL were similar in the dual- and triple-therapy groups (87% and 90%, respectively).

Adverse Effects

- People with HIV who take 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 occurs with fever or elevated transaminases.
- ACTG A5257 showed similar lipid changes in participants in the ATV/r and DRV/r arms. Bone mineral density decreased to a greater extent in participants in the ATV/r and DRV/r arms compared to participants in the RAL arm.⁸ 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 ($P = 0.023$).¹²
- In the DRIVE-FORWARD study, treatment-related diarrhea was more frequently reported in the DRV/r arm, and greater increases were observed in fasting low-density lipoprotein cholesterol, triglycerides, non-high-density lipoprotein cholesterol, and total cholesterol compared to the DOR arm.⁹

Other Factors and Considerations

- DRV/r is administered once daily with food.
- DRV has a sulfonamide moiety and should be used with caution in people 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 people 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 [the Liverpool HIV Drug Interaction Checker](#)).

- Unlike DRV/c, dose-adjusted DRV/r may be used in pregnancy (see the [Perinatal Guidelines](#) for more information).

The Panel's Recommendations

- Based on efficacy and safety data from clinical trials and clinical experience, the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) classifies DRV/r with (TAF or TDF) plus (FTC or 3TC) as a [Recommended Initial Regimen for Most People With HIV](#) who have a history of CAB-LA use as PrEP, pending the results of INSTI genotype testing **(AIII)**.
- DRV/r plus (TAF or TDF) plus (FTC or 3TC) **(BI)** and DRV/r plus ABC/3TC **(BII)** are also part of [Initial Antiretroviral Regimens for Certain Clinical Scenarios](#) (also see [Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios](#)).
- For the unique situation in which TFV and ABC must be avoided and DTG/3TC is not an option, the Panel recommends DRV/r plus (3TC **[BI]** or FTC **[BII]**) (see [Initial Antiretroviral Regimens for Certain Clinical Scenarios](#)), except for individuals—
 - o With HBV coinfection, unless receiving entecavir.
 - o With unknown HBV serostatus.
 - o Without results from genotypic resistance testing for reverse transcriptase.
 - o For whom rapid ART initiation is planned.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

References

1. Gunthard HF, Calvez V, Paredes R, et al. Human immunodeficiency virus drug resistance: 2018 recommendations of the International Antiviral Society–USA panel. *Clin Infect Dis*. 2019;68(2):177-187. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30052811>.
2. Eron JJ, Orkin C, Gallant J, et al. A week-48 randomized phase-3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naïve HIV-1 patients. *AIDS*. 2018;32(11):1431-1442. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29683855>.
3. Orkin C, Eron JJ, Rockstroh J, et al. Week 96 results of a phase 3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naïve HIV-1 patients. *AIDS*. 2019; Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31833849>.
4. Behrens GMN, Assoumou L, Liegeon G, et al. Integrase versus protease inhibitor therapy in advanced HIV disease (LAPTOP): a multicountry, randomised, open-label, non-inferiority trial. *Lancet Infect Dis*. 2026;26(5):510-521. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/41344354>.
5. Huhn GD, Crofoot G, Ramgopal M, et al. Darunavir/cobicistat/emtricitabine/tenofovir alafenamide in a rapid-initiation model of care for human immunodeficiency virus type 1 infection: primary analysis of the DIAMOND study. *Clin Infect Dis*. 2020;71(12):3110-3117. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31879782>.
6. Crauwels HM, Osiyemi O, Zorrilla C, Bicer C, Brown K. Reduced exposure to darunavir and cobicistat in HIV-1-infected pregnant women receiving a darunavir/cobicistat-based regimen. *HIV Med*. 2019;20(5):337-343. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30873741>.
7. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naïve adults with HIV-1 infection (FLAMINGO): 96-week results from a randomised, open-label, phase 3b study. *Lancet HIV*. 2015;2(4):e127-36. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26424673>.
8. Lennox JL, Landovitz RJ, Ribaud HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naïve volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann Intern Med*. 2014;161(7):461-71. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25285539>.
9. Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naïve adults with HIV-1 (DRIVE-FORWARD): 96-week results of a randomised, double-blind, non-inferiority, phase 3 trial. *Lancet HIV*. 2020;7(1):e16-e26. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31740348>.
10. Miro JM, Torres F, Manzardo C, et al. Immune reconstitution in very advanced HIV patients treated with dolutegravir vs. darunavir-based triple antiretroviral therapy: the ADVANZ-4 randomized clinical trial. *Clin Microbiol Infect*. 2026;32(1):169-176. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/41083105>.
11. Figueroa MI, Sued O, Cecchini D, et al. Dual therapy based on co-formulated darunavir/ritonavir plus lamivudine for initial therapy of HIV infection: the ANDES randomized controlled trial. *Int J Antimicrob Agents*. 2024;64(4):107301. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/39151647>.

12. Ofotokun I, Na LH, Landovitz RJ, et al. Comparison of the metabolic effects of ritonavir-boosted darunavir or atazanavir versus raltegravir, and the impact of ritonavir plasma exposure: ACTG 5257. *Clin Infect Dis*. 2015;60(12):1842-51. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25767256>.