Protease Inhibitor–Based Regimens

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Table 8d. Characteristics of Protease Inhibitor Options as Initial Antiretroviral Therapy in Certain Clinical Scenarios

Characteristic	DRV
Dosing Frequency	Once daily for persons with no prior PI experience.
PK Boosting	DRV should only be used with a PK booster (i.e., RTV or COBI).
Fixed-Dose Formulation	• DRV/c • DRV/c/TAF/FTC
Available as a Single-Drug Tablet	Yes
Adverse Effects	• Skin rash • Increase in serum transaminase • Hyperlipidemia • Diarrhea, nausea
CYP3A4 Drug–Drug Interactions	CYP34A substrate, inhibitor
Other Significant Drug Interactions	N/A

Key: COBI = cobicistat; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; 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), atazanavir/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 people who are ART-naive, and a high barrier to resistance. Because LPV/r, fosamprenavir/ritonavir (FPV/r), ATV (with or without a PK enhancer), and saquinavir/ritonavir (SQV/r) have disadvantages—such as greater pill burden, lower efficacy, or increased toxicity—only boosted DRV in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) is recommended as initial therapy in certain clinical situations (see Table 6b in Initial Combination Antiretroviral Regimens for People With HIV).

Because transmitted PI resistance is uncommon, boosted DRV-based regimens are 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, a boosted DRV-based regimen can be used for rapid antiretroviral therapy (ART) initiation, in the setting of acute HIV infection, and as the preferred option while awaiting resistance test results for people with a history of long-acting cabotegravir (CAB-LA) use as pre-exposure prophylaxis (PrEP). 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 regimens with a first-generation integrase strand transfer inhibitor (INSTI) (e.g., raltegravir or elvitegravir).[1] Because of their high barrier to resistance, PI-based regimens may be useful for people at risk for intermittent therapy because of poor adherence.

DRV requires PK boosting with either RTV or COBI to inhibit the cytochrome P3A4 (CYP3A4) isoenzyme, which may lead to significant drug–drug interactions (see Drug–Drug Interactions). The specific characteristics of DRV are listed in Appendix B, Table 5.

Darunavir/Ritonavir

Efficacy in Clinical Trials

Darunavir/ritonavir (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 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 tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) or abacavir (ABC)/lamivudine (3TC)—in 488 participants who were ART-naive. The rate of virologic suppression at Week 96 was significantly higher 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.[2]
- The AIDS Clinical Trial Group (ACTG) study A5257 (ARDENT), a large, randomized, open-label trial, compared atazanavir/ritonavir (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.[3]
- The DRIVE-FORWARD study compared DRV/r to doravirine (DOR), both administered with two investigator-selected NRTIs, in 769 ART-naive 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.[4] At Week 96, DOR was superior to DRV/r in terms of virologic suppression (73% vs. 66%).[4] 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).

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.[3] 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 ($P = 0.023$).[5]

- 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.[4]

Other Factors and Considerations

- DRV/r is administered once daily with food in people who are ART-naive.
- 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 Drug–Drug Interactions).
- Unlike DRV/c, DRV/r may be used in pregnancy.

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 (tenofovir alafenamide [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)** (see Table 6a). DRV/r plus (TAF or TDF) plus (FTC or 3TC) **(BI)** and DRV/r plus ABC/3TC **(BII)** are also part of *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios* (see Table 6b and Table 7).

Darunavir/Cobicistat

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.[6] 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.[7]
- The DIAMOND study 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-1 RNA <50 copies/mL by the FDA snapshot analysis. 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.[8]

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, and should be avoided if possible.[9] 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

- The Panel recommends DRV/c plus (TAF or TDF) plus (FTC or 3TC) **(BI)** and DRV/c plus ABC/3TC **(BII)** as part of *Other 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 people who have a history of CAB-LA use as PrEP, INSTI genotype resistance testing should be performed before starting ART. If ART is to be started before genotypic testing results are available, DRV/c with (TAF or TDF) plus (FTC or 3TC) can be started **(AIII).**

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

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