

Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal

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Most currently recommended antiretroviral (ARV) regimens consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third active drug. In some clinical situations, it is preferable to avoid abacavir (ABC), tenofovir alafenamide (TAF), and tenofovir disoproxil fumarate (TDF), such as in patients who are HLA-B*5701 positive or at high risk of cardiovascular disease and with significant renal impairment. In this situation, dolutegravir/lamivudine (DTG/3TC), which is recommended for most people with HIV, is the preferred option. In addition, several other NRTI-limiting two-drug regimens have been evaluated in clinical studies. Of note, two-drug regimens **should not be used** in people with hepatitis B virus (HBV)/HIV coinfection or during pregnancy. Clinicians should refer to [HBV/HIV Coinfection](#) for guidance on treatment of patients with HBV infection when TAF or TDF cannot be used as part of the ARV regimen.

Strategies Supported by Evidence from Clinical Trials

Dolutegravir/Lamivudine (DTG/3TC)

- In the GEMINI-1 and GEMINI-2 trials, 1,433 antiretroviral therapy (ART)-naive participants with baseline HIV RNA <500,000 copies/mL and no evidence of HBV infection were randomized to receive DTG plus 3TC or DTG plus TDF/emtricitabine (FTC). At week 96, DTG plus 3TC was noninferior to DTG plus TDF/FTC based on the proportion of participants with viral loads <50 copies/mL (86% in DTG plus 3TC group and 89.5% in DTG plus TDF/FTC group).¹ Virologic nonresponse was uncommon, occurring in 3.1% of participants who received DTG plus 3TC and 2% of participants who received DTG plus TDF/FTC. No instances of treatment-emergent NRTI or integrase strand transfer inhibitor (INSTI) resistance occurred in either treatment group. Among participants who started the study with CD4 counts <200 cells/mm³, the proportion of participants with HIV RNA <50 copies/mL at week 96 was lower in the DTG plus 3TC group than in the DTG plus TDF/FTC group; however, the difference was not related to a higher rate of virologic failures in the two-drug group. At week 144, DTG plus 3TC maintained noninferiority to DTG plus TDF/FTC with 82% vs 84% of participants maintaining viral load <50 copies/mL, respectively. The proportion of participants with viral loads ≥50 was similar between both treatment groups at 3%. There was a lower risk of drug-related adverse events with DTG plus 3TC versus DTG plus TDF/FTC (19.6% vs 25.0%; relative risk ratio, 0.78; 95% CI: 0.64 to 0.95).¹
- Clinicians should refer to the [INSTI section](#) for a review of the recent data on DTG use during conception and risk of neural tube defects in infants. Before initiating a DTG-based regimen, clinicians should discuss the risks and benefits of using DTG with persons of childbearing potential, to allow them to make an informed decision.

The Panel's Recommendation:

- The Panel recommends DTG/3TC as an initial regimen for most people with HIV (**AI**); as such, this is the preferred regimen when use of ABC, TAF, or TDF is not optimal. DTG/3TC **is not recommended**:
 - for individuals with HIV RNA >500,000 copies/mL,
 - for patients with HBV/HIV coinfection, or
 - when antiretroviral therapy (ART) is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

Darunavir/Ritonavir plus Lamivudine (DRV/r plus 3TC)

- In the ANDES trial, 145 participants were randomized 1:1 to receive open-label, once-daily dual therapy with DRV/r plus 3TC or triple therapy with DRV/r plus TDF/3TC. This study was conducted in Argentina, and the researchers used an FDC of DRV/r 800 mg/100 mg that is available in that country. The median baseline HIV RNA was 4.5 log₁₀ copies, and 24% of participants had HIV RNA >100,000 copies/mL. At week 48, 93% of the participants in the dual-therapy group and 94% of the participants in the triple-therapy group achieved an HIV RNA <50 copies/mL; dual therapy was noninferior to triple therapy.² The rates of virologic suppression among study participants who had pre-therapy HIV RNA levels >100,000 copies/mL were similar in the dual- and triple-therapy groups (91% and 92%, respectively).

The Panel's Recommendation:

- On the basis of results from a small study with a relatively short follow-up period, DRV/r plus 3TC can be considered for use in people who cannot take ABC, TAF, or TDF (**CI**). Although the ANDES trial supports the use of DRV/r plus 3TC, it is a small trial of NRTI-limiting regimens, and larger studies are warranted.

Darunavir/Ritonavir plus Raltegravir (DRV/r plus RAL)

- In the NEAT/ANRS 143 study, 805 treatment-naive participants were randomized to receive twice-daily RAL or once-daily TDF/FTC, each with DRV/r (800 mg/100 mg once daily). At week 96, DRV/r plus RAL was noninferior to DRV/r plus TDF/FTC based on the primary endpoint of proportion of patients with virologic or clinical failure. Among those with baseline CD4 counts <200 cells/mm³, however, there were more virologic failures in the RAL + DRV/r arm; a trend towards more failure was also observed among those with pretreatment HIV RNA ≥100,000 copies/mL.³ High rates of virologic failure in patients with HIV RNA >100,000 copies/mL were also seen in two smaller studies of DRV/r plus RAL.^{4,5}

The Panel's Recommendation:

- On the basis of these study results, the Panel recommends that DRV/r plus RAL be considered for use only in patients with HIV RNA <100,000 copies/mL and CD4 counts >200 cells/mm³, and only in those patients who cannot take ABC, TAF, or TDF (**CI**).

A Nucleoside-Limiting Regimen with Insufficient Supporting Data

Darunavir/Ritonavir plus Rilpivirine (DRV/r plus RPV)

- In a single-arm, open-label, pilot study, 36 ART-naive participants without genotypic evidence of resistance to DRV or RPV received DRV/r plus RPV for 48 weeks. Half of the participants (18 of 36) had baseline HIV viral loads >100,000 copies/mL. By week 36, 97% of participants (35 of 36) achieved HIV RNA <50 copies/mL, and by week 48, all achieved viral suppression (HIV RNA <50 copies/mL).⁶

The Panel's Recommendation:

- At this time, the Panel **does not recommend** DRV/r plus RPV given the small sample size of the study described above and the lack of comparative data evaluating DRV/r plus RPV as initial therapy for people with HIV.

Cabotegravir with Rilpivirine (CAB plus RPV)

The combination of cabotegravir (CAB) and RPV has not been studied in ART-naive patients. In the Phase 3 trial FLAIR and Phase IIb trial LATTE-2,^{7,8} ART-naive participants were first treated with 20 weeks of DTG/ABC/3TC or oral CAB + ABC/3TC, respectively, and, if they achieved virologic suppression, were eligible for randomization to receive long acting injectable CAB plus RPV every month or to continue oral

daily ART. Neither CAB nor RPV is active against hepatitis B, therefore should not be used in persons with hepatitis B infection without the addition of treatment for hepatitis B. There are insufficient data for this regimen in pregnancy or around the time of conception.

The Panel's Recommendation:

- The Panel **does not recommend** CAB/RPV as initial therapy for people with HIV because of the lack of data supporting the efficacy of this combination in ART-naive patients. Patients desiring to use injectable CAB plus RPV early in their treatment history should first attain viral suppression on a recommended regimen, then transition to a month of oral CAB and RPV with maintenance of suppression before transitioning to injectable CAB plus RPV. See [Optimizing Regimens](#) section for discussion.

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

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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