

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 of the currently recommended antiretroviral (ARV) regimens for initial therapy consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third active drug. In addition, dolutegravir (DTG)/lamivudine (3TC) is a two-drug, NRTI-limiting regimen that is a recommended option for people with HIV (see [Table 6a](#) in [Initial Combination Antiretroviral Regimens for People With HIV](#)) and would be preferred over others in situations where it is desirable to avoid abacavir (ABC), tenofovir alafenamide (TAF), and tenofovir disoproxil fumarate (TDF). Several other NRTI-limiting/sparing two-drug regimens have been evaluated in clinical studies, but are not yet recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) due to insufficient evidence. Note that two-drug regimens **are not currently recommended** during pregnancy and tenofovir-sparing regimens **are not recommended** in people with hepatitis B virus (HBV)/HIV coinfection unless another HBV-active drug (i.e., entecavir) is added. Clinicians should refer to [HBV/HIV Coinfection](#) for guidance on treatment of people 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

- In the GEMINI-1 and GEMINI-2 trials, 1,433 antiretroviral therapy (ART)–naïve participants with baseline HIV RNA <500,000 copies/mL and no evidence of HBV infection were randomized to receive a two-drug regimen of DTG plus 3TC or a three-drug regimen of DTG plus TDF/emtricitabine (FTC). At Week 96, DTG plus 3TC was non-inferior 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% versus 84% of participants maintaining viral load <50 copies/mL, respectively. The proportion of participants with viral load ≥50 copies/mL 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% confidence interval, 0.64–0.95).¹

The Panel's Recommendation

When ABC, TAF, or TDF cannot be used or are not optimal, the Panel recommends DTG/3TC as an initial regimen for people with HIV (AI) who—

- Have a viral load $\leq 500,000$ copies/mL,
- Have a genotype available that demonstrates sensitivity to 3TC,
- Do not have a history of long-acting cabotegravir (CAB-LA) use as pre-exposure prophylaxis, or
- Have CAB-LA exposure but with documented INSTI sensitivity on genotypic resistance testing.

HBV status must be determined, and if HBV/HIV coinfection is present, another HBV-active drug should be added (see [HBV/HIV Coinfection](#)).

Nucleoside-Limiting Regimens With Some Supporting Data but Not Recommended as Initial Therapy

The Panel **does not recommend** the following nucleoside-limiting or nucleoside-sparing regimens for initial therapy due to insufficient clinical trial data.

Darunavir/Ritonavir Plus Lamivudine

- In the ANDES trial, 336 participants were randomized 1:1 to receive open-label, once-daily dual therapy with darunavir/ritonavir (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 23% of participants had HIV RNA >100,000 copies/mL. At Week 48, 91% of the participants in the dual-therapy group and 93% of the participants in the triple-therapy group achieved an HIV RNA <50 copies/mL, demonstrating that dual therapy was non-inferior 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 (87% and 90%, respectively). **The Panel does not recommend this regimen as initial therapy as the results from this study have not yet been published.**

Darunavir/Ritonavir Plus Raltegravir

- In the NEAT/ANRS 143 study, 805 treatment-naive participants were randomized to receive twice-daily raltegravir (RAL) or once-daily TDF/FTC, each with DRV/r (800 mg/100 mg once daily). At Week 96, DRV/r plus RAL was non-inferior to DRV/r plus TDF/FTC based on the primary endpoint, the proportion of people with virologic or clinical failure. Among those with baseline CD4 counts <200 cells/mm³; however, there were more virologic failures in the RAL plus DRV/r arm. A trend towards more failure was also observed among those with pre-treatment HIV RNA $\geq 100,000$ copies/mL.³ High rates of virologic failure in participants with HIV RNA >100,000 copies/mL were also seen in two smaller studies of DRV/r plus RAL.^{4,5} **The Panel does not recommend DRV/r plus RAL as initial ART because of the higher rate of virologic failure in participants with HIV RNA $\geq 100,000$ copies/mL and the higher pill burden of this regimen compared to other Panel-recommended initial ARV regimens.**

Darunavir/Ritonavir Plus Rilpivirine

- In a single-arm, open-label pilot study, 36 ART-naive participants without genotypic evidence of resistance to DRV or rilpivirine (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 **does not recommend** this regimen as initial ART 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.

Long-Acting Injectable Cabotegravir With Rilpivirine

- The long-acting injectable combination of CAB plus RPV (LA CAB/RPV) has not been studied in ART-naive participants. 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. Study participants who achieved virologic suppression were eligible for randomization to receive LA CAB/RPV every month or to continue oral daily ART. The Panel **does not recommend** the LA CAB/RPV as initial therapy for people with HIV because of the lack of data supporting the efficacy of this combination in people who are ART-naive (**AIII**). People desiring to use LA CAB/RPV early in their treatment history should first attain viral suppression on a recommended regimen before transitioning to LA CAB/RPV. See [Optimizing Antiretroviral Therapy in the Setting of Viral Suppression](#) for more discussion.

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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