

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

Updated: September 24, 2026

Reviewed: September 24, 2026

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 most people with HIV (see [Recommended Initial Regimens for Most People With HIV](#) 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 DTG/3TC is the only two-drug regimen currently recommended (as an Alternative option) during pregnancy (see the [Perinatal Guidelines](#) for more information).

In addition, tenofovir-sparing regimens **are not recommended** in people with chronic hepatitis B virus (HBV)/HIV unless another **potent, high-barrier** HBV-active drug (i.e., entecavir) is added. Clinicians should refer to [HBV/HIV Coinfection](#) for guidance on the 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 T lymphocyte (CD4) cell 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 non-inferiority to DTG plus TDF/FTC with 82% versus 84% of participants maintaining viral load <50 copies/mL, respectively. The proportion of participants with a 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
- In the DOLCE study, 230 treatment-naïve participants with CD4 counts ≤200 cells/mm³ were randomized 2:1 to DTG/3TC or DTG plus TDF/(3TC or FTC).² At baseline, the median CD4 count was 109 cells/mm³ and median viral load 180,000 copies/mL, with 23% having

≥500,000 copies/mL. DTG/3TC demonstrated non-inferiority to the three-drug arm, with no emergent resistance to INSTIs or NRTIs in either group. Although the GEMINI-1 and GEMINI-2 studies excluded those with a screening viral load >500,000 copies/mL, this study supports the use of the two-drug regimen in this population.

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)**, except for individuals—

- With HBV coinfection, unless a potent high-barrier HBV-active drug (i.e., entecavir) is added (see [HBV/HIV Coinfection](#)).
- With unknown HBV serostatus.
- Without results for genotypic resistance testing for reverse transcriptase.
- Who have a history of long-acting cabotegravir (CAB-LA) use as pre-exposure prophylaxis without documented INSTI sensitivity on genotypic resistance testing.
- For whom rapid ART initiation is planned.

Boosted Darunavir Plus Lamivudine or Emtricitabine

- 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.³ This study was conducted in Argentina and used 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 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.³ 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's Recommendation

For the unique situation in which tenofovir and ABC must be avoided and DTG/3TC is not an option, the Panel recommends DRV/r plus 3TC **(BI)** or FTC **(BII)**, or darunavir/cobicistat plus 3TC **(BI)** or FTC **(BII)** (see [Initial Antiretroviral Regimens for Certain Clinical Scenarios](#)), **except** for individuals—

- With HBV coinfection, unless a potent high-barrier HBV-active drug (i.e., entecavir) is added (see [HBV/HIV Coinfection](#)).
- With unknown HBV serostatus.
- Without results from genotypic resistance testing for reverse transcriptase.
- For whom rapid ART initiation is planned.

Regimens With Some Supporting Data but Not Recommended as Initial Therapy

The Panel **does not recommend** the following NRTI-sparing regimens for initial therapy because of insufficient clinical trial data.

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. However, more virologic failures occurred in the RAL plus DRV/r arm among those with baseline CD4 counts <200 cells/mm³. A trend toward more failure was also observed among those with pre-treatment HIV RNA ≥100,000 copies/mL.⁴ 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.^{5,6} 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 ≥100,000 copies/mL and the higher pill burden with this regimen than with 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 darunavir or rilpivirine (RPV) received DRV/r plus RPV for 48 weeks. Half the participants (18 of 36) had baseline HIV viral loads >100,000 copies/mL. Viral suppression (HIV RNA <50 copies/mL) was achieved in 97% of participants (35 of 36) by Week 36, increasing to 100% by Week 48.⁷ 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 2b trial LATTE-2,^{8,9} ART-naive participants were first treated with 20 weeks of DTG/ABC/3TC or oral cabotegravir plus 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** 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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