

Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Therapy

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The following sections provide detailed information on antiretroviral (ARV) drugs that the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends for initial therapy for most people with HIV and for initial therapy in certain clinical scenarios (see [Recommended Initial Regimens for Most People With HIV](#) and [Initial Antiretroviral Regimens for Certain Clinical Scenarios](#) in the [Initial Combination Antiretroviral Regimens for People With HIV](#) section), including ARV drug characteristics, adverse effects, clinical trial results, and Panel recommendations on their use.

Table 8a. Characteristics of Nucleoside Reverse Transcriptase Inhibitor Options for People Without Prior Antiretroviral Treatment

Note: Listed in order of the Panel's recommendations in Tables 6a and 6b.

Characteristics	TAF/FTC	TDF/FTC	TDF/3TC	3TC or FTC	ABC/3TC
Dosing Frequency	Once daily	Once daily	Once daily	Once daily	Once daily
Available Coformulations for People Without Prior ARV Treatment	TAF 25 mg/FTC BIC/TAF 25 mg/FTC DRV/c/TAF 10 mg/FTC RPV/TAF 25 mg/FTC	TDF/FTC	TDF/3TC DOR/TDF/3TC	DTG/3TC	ABC/3TC DTG/ABC/3TC
Adverse Effects	TAF <ul style="list-style-type: none"> Renal insufficiency, proximal renal tubulopathy (less frequent than with TDF) Decrease in BMD (less than with TDF) 	TDF <ul style="list-style-type: none"> Renal insufficiency, proximal renal tubulopathy Decrease in BMD Renal and bone toxicity are exacerbated by pharmacologic boosters. 	TDF <ul style="list-style-type: none"> Renal insufficiency, proximal renal tubulopathy Decrease in BMD Renal and bone toxicity are exacerbated by pharmacologic boosters. 	3TC or FTC <ul style="list-style-type: none"> No notable adverse effects 	ABC <ul style="list-style-type: none"> HSR to ABC is associated with the presence of HLA-B*5701 allele.^a Evidence increasingly supports a relationship between ABC and major CV events.

Table 8a. Characteristics of Nucleoside Reverse Transcriptase Inhibitor Options for People Without Prior Antiretroviral Treatment

Characteristics	TAF/FTC	TDF/FTC	TDF/3TC	3TC or FTC	ABC/3TC
Other Considerations	<ul style="list-style-type: none"> Also used for HBV treatment. Discontinuation may precipitate HBV flare. See Appendix B for dosing recommendations in people with renal insufficiency. Some studies reported less weight gain and lower LDL, HDL, TC, and triglycerides with TDF than with TAF. TDF should be avoided, if possible, in people with renal disease (CrCl <60 mL/min) and/or osteopenia/osteoporosis. For people with progressively declining renal function, consider avoiding TDF and TAF. 			<ul style="list-style-type: none"> 3TC or FTC or ABC/3TC should not be used as treatment for HBV without adding a potent anti-HBV therapy, such as tenofovir or entecavir. Consider alternative ARV medications in place of ABC in people with higher underlying ASCVD risk or known ASCVD (All). 	

^a Perform HLA-B*5701 testing before initiating ABC; if result is positive, do not start ABC and add ABC to patient's allergy list. See the [HLA-B*5701 Screening](#) section for more information.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; **ASCVD = atherosclerotic cardiovascular disease**; BIC = bictegravir; BMD = bone mineral density; CrCl = creatinine clearance; CV = cardiovascular; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; FTC = emtricitabine; HBV = hepatitis B virus; HDL = high-density lipoprotein; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; LDL = low-density lipoprotein; NRTI = nucleoside reverse transcriptase inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate

Summary

Ten nucleos(t)ide reverse transcriptase inhibitors (NRTIs) have been approved by the U.S. Food and Drug Administration (FDA). Zidovudine (ZDV) was the first ARV drug approved in 1987. Several older NRTIs are no longer available (didanosine [ddI], stavudine [d4T], and zalcitabine [ddC]) or are rarely used (ZDV) in clinical practice in the United States because of high rates of serious toxicities, including mitochondrial toxicity that may lead to myopathy, hepatic steatosis, lactic acidosis, or lipoatrophy; ZDV may cause bone marrow suppression, whereas peripheral neuropathy is commonly seen with ddC, ddI or d4T use. Therefore, these agents are no longer recommended by the Panel for adults or adolescents. The incidence of these complications is substantially lower with the NRTIs that are currently recommended as initial antiretroviral therapy (ART), which include abacavir (ABC), emtricitabine (FTC), lamivudine (3TC), tenofovir alafenamide (TAF), and tenofovir disoproxil fumarate (TDF).^{1,2} A new NRTI, islatravir, was approved by the FDA to use in combination with doravirine (DOR) as a switch regimen for people with viral suppression (see [Optimizing Antiretroviral Therapy in the Setting of Viral Suppression](#)).

TAF/FTC, TDF/3TC, and TDF/FTC are NRTI combinations that are part of [Recommended Initial Regimens for Most People With HIV](#). In addition, 3TC may be used as a single NRTI with dolutegravir (DTG), except in individuals in whom ART is to be started before the results of HIV genotypic resistance tests are available and when Hepatitis B status is unknown. DTG/3TC is **not recommended** for people with hepatitis B virus (HBV), **unless entecavir** is added. [Recommended Initial Regimens for Most People With HIV](#) and [Initial Antiretroviral Regimens for Certain Clinical Scenarios](#) provide recommendations and ratings for the individual regimens. These recommendations are based on the virologic potency and durability, short- and long-term toxicity, and dosing convenience of these drugs.

TDF has been associated with bone and kidney toxicities, especially when used with a pharmacologic booster.³ TAF is less likely to cause kidney and bone toxicities than TDF, whereas TDF is associated with lower lipid levels than TAF. Both TAF and TDF are recommended options in pregnancy because of reassuring data from a multinational trial in pregnant women with HIV⁴ and data from the [Antiretroviral Pregnancy Registry](#) that show no evidence of teratogenicity. Please refer to the [Perinatal Guidelines](#) for more information on the use of ARVs during pregnancy.

ABC/3TC, including DTG/ABC/3TC, is no longer recommended as initial therapy in most people with HIV but may be considered in circumstances in which tenofovir (TFV)–containing regimens or DTG/3TC cannot be used. Before starting any regimen with ABC, screening for the HLA-B*5701 allele is necessary because there is a strong link with a potentially life-threatening hypersensitivity reaction in people who test positive for this allele. In addition, **increasing** data continue to support an association between ABC and an increased risk for serious cardiovascular events.⁵⁻⁸

Along with safety and efficacy, cost and access are among the factors to consider when choosing among available options. ABC/3TC, TDF/3TC, TDF/FTC, **FTC**, and 3TC are available as generic formulations.

Clinical Trials Comparing Nucleoside Reverse Transcriptase Inhibitors

Tenofovir Alafenamide Compared to Tenofovir Disoproxil Fumarate

Safety and HIV Efficacy

Two randomized double-blind Phase 3 clinical trials compared the safety and efficacy of elvitegravir/cobicistat (EVG/c)/TDF/FTC and EVG/c/TAF/FTC in 1,733 ART-naïve adults with estimated glomerular filtration rate (eGFR) ≥ 50 mL/min.

- TAF/FTC was virologically non-inferior to TDF/FTC at Week 48 (92% vs. 90% of participants had plasma HIV RNA < 50 copies/mL, respectively),⁹ but TAF/FTC was superior to TDF/FTC at Week 144 (84.2% vs. 80% of participants with plasma HIV RNA < 50 copies/mL), largely driven by a higher rate of treatment discontinuation in the TDF arm.¹⁰
- Participants in the TAF arm had significantly smaller reductions in bone mineral density (BMD) at the spine and hip than those in the TDF arm through 144 weeks.¹⁰ Those receiving TAF also had less pronounced changes in eGFR and renal biomarkers and fewer clinically significant renal events through Week 96.¹¹ Conversely, levels of fasting low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides increased more in the TAF group than in the TDF group at Week 96, with no change in total cholesterol to HDL ratio.¹²

Two randomized studies have compared the safety and efficacy of TAF/FTC to TDF/FTC, with each combination administered with boosted darunavir (DRV) in ART-naïve participants:

- A Phase 2 study of coformulated darunavir/cobicistat (DRV/c) plus TAF/FTC versus DRV/c plus TDF/FTC in treatment-naïve participants demonstrated similar virologic suppression rates in both arms (75% vs. 74%).¹³ In the TAF arm, fewer participants developed proteinuria. Changes in BMD were also less pronounced among participants in the TAF group.
- The AMBER study randomized ART-naïve participants to receive either coformulated DRV/c/TAF/FTC or DRV/c plus TDF/FTC. At Week 48, HIV RNA < 50 copies/mL was achieved in 91% of participants in the DRV/c/TAF/FTC arm versus 88% in the DRV/c plus TDF/FTC arm. Participants in the TAF/FTC arm showed less decline in hip and spine BMD and eGFR than participants in the TDF/FTC arm.¹⁴

One analysis evaluated data from 14 randomized trials that compared the virologic efficacy, frequency of renal events, and bone density changes associated with the use of TDF and TAF when either drug was taken with or without pharmacokinetic (PK) boosters (ritonavir [RTV] or cobicistat [COBI]). No significant differences appeared between unboosted regimens with TDF and TAF in terms of virologic efficacy. When used with PK boosters, TAF resulted in a clinically small but statistically significant greater virologic efficacy than TDF (94% vs. 92%; $P = 0.0004$). No difference was seen in bone-related toxicities and clinical or laboratory adverse events between TAF and TDF, regardless of whether used with a boosting agent. The rate of discontinuation due to renal adverse events was higher for those on boosted regimens containing TDF compared with those containing TAF, with a small but statistically significant difference ($P = 0.03$).¹⁵

Although conducted in people without HIV for pre-exposure prophylaxis (PrEP), the DISCOVER trial, with 5,387 treated participants, was the largest trial to directly compare the adverse effects of TAF/FTC with those of TDF/FTC.¹⁶ The following findings were observed after 48 weeks of follow-up:

- Adverse events did not significantly vary between the two groups, including Grade 3 and 4 events, serious adverse events, discontinuations due to adverse events, and overall.
- Changes in renal biomarkers and BMD significantly favored the TAF arm over TDF. One case of proximal tubular disease occurred in the TDF arm.
- LDL, HDL, and total cholesterol were significantly lower in the TDF arm than in the TAF arm, with no significant difference in the total cholesterol to HDL ratio.
- Participants in the TAF arm gained an average of 1.1 kg, whereas those in the TDF arm had a mean loss of 0.1 kg.

Efficacy in People With HIV and HBV

To assess the ability of TAF to maintain HIV and HBV suppression, 72 people with HIV/HBV who had HIV RNA <50 copies/mL and HBV DNA <9 log₁₀ IU/mL on a stable regimen were switched to EVG/c/TAF/FTC.¹⁷ In this study, 96% of participants were on a TDF/FTC-containing regimen before the switch. Key results of the study showed the following:

- Among those who switched to EVG/c/TAF/FTC, HIV suppression was maintained in 91.7% of participants at Week 48, and 91.7% of participants had HBV DNA <29 IU/mL.
- Markers of proximal tubular proteinuria and biomarkers of bone turnover decreased in those who switched to EVG/c/TAF/FTC.¹⁷

Lamivudine Compared to Tenofovir Disoproxil Fumarate/Emtricitabine

A single-tablet regimen (STR) of DTG/3TC has now been approved as an initial ARV regimen. Please refer to the [Integrase Strand Transfer Inhibitor-Based Regimens](#) section for a full discussion.

- GEMINI-1 and GEMINI-2 were identically designed randomized, double-blind clinical trials that found DTG plus 3TC to be noninferior to DTG plus TDF/FTC in ART-naïve adults with HIV RNA <500,000 copies/mL and eGFR ≥50 mL/min.^{18,19}
- The DOLCE study randomized 230 treatment-naïve individuals with CD4 T lymphocyte (CD4) cell count ≤200 cells/mm³ 2:1 to receive DTG/3TC or DTG plus TDF/3TC or TDF/FTC.²⁰ At baseline, the median CD4 count was 109 cells/mm³ and viral load 180,000 copies/mL, with 23% having >500,000 copies/mL. The study demonstrated noninferiority between arms and no emergent resistance to integrase strand transfer inhibitors (INSTIs) or NRTIs in either group. Among participants with a pre-treatment viral load >500,000 copies/mL, there was no significant difference in virologic response between the DTG/3TC and triple therapy arms. 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.

Abacavir/Lamivudine Compared to Tenofovir Disoproxil Fumarate/Emtricitabine

Several randomized controlled trials in ART-naïve participants compared ABC/3TC to TDF/FTC, each administered in combination with a third ARV drug (see the [Integrase Strand Transfer Inhibitor-Based Regimen](#) section).²¹⁻²⁴

- The ACTG 5202 study, a randomized controlled trial in >1,800 participants, evaluated the efficacy and safety of ABC/3TC and TDF/FTC when each combination was used with either efavirenz (EFV) or atazanavir/ritonavir (ATV/r). In people with baseline HIV RNA $\geq 100,000$ copies/mL, the time to virologic failure was significantly shorter with ABC/3TC than with TDF/FTC, regardless of whether the third active drug was EFV or ATV/r. In addition, the time to first adverse event was also shorter in the ABC/3TC groups.²¹
- In the HEAT study, 688 participants received ABC/3TC or TDF/FTC with once-daily lopinavir/ritonavir. Virologic efficacy was similar in the two study arms, including in a subgroup of participants with HIV RNA $\geq 100,000$ copies/mL.²³
- The ASSERT study compared open-label ABC/3TC with TDF/FTC in 385 HLA-B*5701-negative people with HIV who were ART-naïve; all participants also received EFV. The primary study endpoint was renal safety of the regimens. Although eGFR did not differ significantly between the regimens, biomarkers associated with tubular dysfunction (retinol-binding protein and beta-2 microglobulin) increased significantly in the TDF/FTC arm compared with the ABC/3TC arm (+50% vs. +24% and no change vs. -47%, respectively). At Week 48, the proportion of participants with HIV RNA <50 copies/mL was lower among ABC/3TC-treated participants (59%) than among TDF/FTC-treated participants (71%).²²

Nucleoside Reverse Transcriptase Inhibitor Options for Initial Therapy

Tenofovir Alafenamide/Emtricitabine

TAF, an oral prodrug of TFV, is hydrolyzed to TFV in plasma and then converted to TFV-diphosphate (TFV-DP) intracellularly, where it exerts its activity as an NRTI. Unlike TDF, which readily converts to TFV in plasma after oral absorption, TAF remains relatively stable in plasma, resulting in lower plasma and higher intracellular TFV concentrations. After oral administration, TAF 25 mg resulted in plasma TFV concentrations that were 90% lower than those seen with TDF 300 mg. Intracellular TFV-DP concentrations, however, were substantially higher with TAF.

Adverse Effects

Renal and Bone Effects

- In randomized controlled trials that compared TAF and TDF in people without prior ARV treatment experience or those with viral suppression, TAF had more favorable effects on renal biomarkers and BMD than TDF.
- For people with progressively declining renal function, consider avoiding TAF. TAF should be avoided for creatinine clearance (CrCl) <30 mL/min (unless on hemodialysis).

Lipid Effects

- In randomized controlled trials in ART-naïve participants, in switch studies, and in a large study of PrEP, levels of LDL and HDL cholesterol and triglycerides were lower in participants who received TDF than those who received TAF. However, total cholesterol to HDL ratios did not differ between participants receiving TAF and those receiving TDF. The clinical significance of this finding is not clear.^{9,12,25}

Weight Gain

- Initiation of TAF in previously untreated individuals and in people without HIV has been associated with greater weight gain than initiation of TDF²⁶⁻²⁸ and ABC.²⁷ In ADVANCE, an open-label trial conducted in South Africa that compared EFV/TDF/FTC versus DTG plus TDF/FTC versus DTG plus TAF/FTC in ART-naïve participants, a greater increase in body weight was reported with initiation of TAF than with TDF.²⁶ See the [Weight Gain in People With Treated HIV](#) section for more information.

Other Factors and Considerations

- TAF/FTC is available in fixed-dose combinations (FDCs) with bictegravir (BIC), DRV/c, EVG/c, and rilpivirine (RPV), allowing the regimens to be administered as a single pill taken once daily.
- TAF-containing regimens are approved for people with eGFR ≥ 30 mL/min. Renal function, urine glucose, and urine protein should be assessed before initiating treatment with TAF, and these assessments should be repeated periodically during treatment. EVG/c/FTC/TAF was safe and effective in a single-arm switch study that was conducted in people on hemodialysis.²⁹ Based on the results from this study, TAF/FTC can be used without dosage adjustment in people with HIV who require hemodialysis.
- Both TAF and FTC are active against HBV. In people with HIV/HBV, TAF/FTC may be used as the NRTI pair in an ARV regimen because these drugs have activity against both viruses (see [Hepatitis B Virus/HIV Coinfection](#)).¹⁷
- Discontinuation of TAF can precipitate an HBV flare if no other potent, high barrier-to-resistance HBV-active drug (i.e., entecavir) is in the regimen.
- TAF is recommended as a *Preferred* drug in pregnancy because of reassuring data from a multinational trial of pregnant women and data from the [Antiretroviral Pregnancy Registry](#) that show no evidence of teratogenicity.⁴ See the [Perinatal Guidelines](#) for more information on ARV use during pregnancy.

The Panel's Recommendation

- On the basis of clinical trial safety and efficacy data, and its availability as a component of various FDCs, the Panel considers TAF/FTC a recommended NRTI combination for initial ART in most people with HIV when prescribed with BIC or DTG **(AI)**, and as part of [Initial Antiretroviral Regimens for Certain Clinical Scenarios](#) when given with RPV **(BII)**, DOR **(BIII)**, RTV-boosted DRV (DRV/r **(BI)**), or DRV/c **(BI)**.

Tenofovir Disoproxil Fumarate/Emtricitabine and Tenofovir Disoproxil Fumarate/Lamivudine

TDF, with either 3TC or FTC, has been studied in combination with DOR, EFV, RPV, several boosted protease inhibitors (PIs), EVG/c, raltegravir, and DTG in randomized clinical trials.³⁰⁻³⁷

Adverse Effects

Renal Effects

- New-onset or worsening renal impairment has been associated with TDF use.^{38,39} Risk factors may include advanced HIV disease, longer treatment history, low body weight (especially in women),⁴⁰ and preexisting renal impairment.⁴¹ Adverse effects on renal biomarkers, such as proteinuria, especially tubular proteinuria, were more frequent with TDF than with TAF.⁴²
- Adverse renal outcomes are more likely when TDF/FTC is coadministered with PK boosters (RTV or COBI). A meta-analysis of randomized trials found that discontinuation due to renal adverse events is more frequent in people who take TDF/FTC than TAF/FTC with PK boosters.¹⁵

Bone Effects

- Although initiation of all NRTI-containing regimens has been associated with a decrease in BMD, the loss of BMD is greater with TDF-containing regimens. For example, in two randomized studies that compared TDF/FTC with ABC/3TC, participants who received TDF/FTC experienced a significantly greater decline in BMD than ABC/3TC-treated participants.^{43,44} BMD generally stabilizes following an early decline after ART initiation. Loss of BMD is also greater with TDF than with TAF.
- Cases of osteomalacia associated with proximal renal tubulopathy have been reported with the use of TDF.⁴⁵ Adverse bone outcomes have been found to be more likely when TDF/FTC is coadministered with PK boosters. However, a meta-analysis found no difference in bone-related toxicities between TAF and TDF, regardless of boosting.¹⁵

Other Factors and Considerations

- TDF/3TC is available as a coformulated generic drug.
- TDF/3TC is available in an FDC with DOR 100 mg.
- Renal function, urine glucose, and urine protein should be assessed before initiating treatment with TDF and periodically during treatment (see [Laboratory Testing for Initial Assessment and Monitoring of People With HIV](#)). In people who have preexisting renal insufficiency (CrCl <60 mL/min),⁴⁶ use of TDF should be avoided, **if possible**. If TDF is used, a dose adjustment is required if the person's CrCl falls below 50 mL/min (see [Appendix B](#) for dose recommendations).
- TDF, FTC, and 3TC are active against HBV. In people with HBV/HIV, TDF/FTC or TDF/3TC may be used as the NRTI pair of the ARV regimen because these drugs have activity against both viruses (see [Hepatitis B Virus/HIV Coinfection](#)).
- **Discontinuation of TDF can precipitate an HBV flare if no other potent, high barrier-to-resistance HBV-active drug (i.e., entecavir) is in the regimen.**

The Panel's Recommendations

- On the basis of clinical trial safety and efficacy data, long-term experience in clinical practice, and the combination's availability as a component of FDC drugs, the Panel considers TDF/FTC and TDF/3TC—
 - As recommended NRTI combinations for initial ART in most people with HIV when combined with DTG **(AI)**,

- o As recommended NRTI combinations for initial ART when combined with DRV/c or DRV/r for people who have a history of long-acting injectable cabotegravir (CAB-LA) use as PrEP, pending the results of genotypic resistance testing (AIII),
- o As part of [Initial Antiretroviral Regimens for Certain Clinical Scenarios](#).
- TDF should be avoided, if possible, in people with renal disease (CrCl <60 mL/min) and/or osteopenia/osteoporosis.
- When TDF is used, especially in conjunction with a PK booster, clinicians should monitor for renal and bone safety during therapy. Boosters should be avoided when possible in people taking TDF.

Emtricitabine Versus Lamivudine

FTC and 3TC generally are used interchangeably in combination with other ARVs, based on the results of randomized clinical trials and a meta-analysis of 12 trials that compared virologic efficacy and safety.^{47,48}

- In the ATHENA cohort, virologic efficacy of TDF/FTC was compared to TDF/3TC when either was combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI)—EFV or nevirapine⁴⁹—or with a boosted PI.⁵⁰ No difference was reported in the rates of virologic failure in people who were taking TDF/FTC and people who were taking TDF/3TC when these drug combinations were used with a boosted PI. TDF/3TC was associated with higher rates of virologic failure than TDF/FTC in the NNRTI analysis; however, participants in the NNRTI cohort who were taking 3TC generally had higher viral load and lower CD4 count and were more likely to be using injection drugs at the start of the study than those taking FTC.

Adverse Effects

- Both FTC and 3TC have been well tolerated with no significant treatment-limiting adverse effects.
- In early clinical trials, FTC was infrequently associated with mild hyperpigmentation of palms and soles.

Other Factors and Considerations

- FTC and 3TC are generic in the United States and coformulated with other drugs (see Table 8a above).
- o Both 3TC and FTC have activity against HBV but are insufficient for HBV treatment when used alone due to the emergence of resistance. People with HBV should also receive another potent HBV drug such as TAF, TDF, or entecavir.
- Discontinuation of FTC or 3TC can precipitate a flare in HBV if no other HBV-active drugs (i.e., TAF, TDF, or entecavir) are in the regimen.
- See [Appendix B](#) for dosing recommendations in people with renal impairment.
- No significant drug interactions have been identified with FTC. Sorbitol-containing drugs can decrease 3TC concentration, and coadministration should be avoided.
- Both FTC and 3TC select for the M184V mutation when viral suppression is suboptimal.

The Panel's Recommendation

- FTC and 3TC are considered interchangeable in combination with other ARV drugs.

Lamivudine or Emtricitabine as a Single Nucleoside Reverse Transcriptase Inhibitor

- o Based on the GEMINI-1 and GEMINI-2 studies,¹⁹ which found DTG plus 3TC to be noninferior to DTG plus TDF/FTC in ART-naïve people with HIV RNA <500,000 copies/mL, and the DOLCE study,²⁰ which found no significant difference between DTG/3TC and triple therapy in those with HIV RNA >500,000 copies/mL, the single NRTI combination regimen of DTG/3TC can be used regardless of baseline viral load.
- o In the ANDES trial, 336 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.⁵¹ This study was conducted in Argentina using 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/mL, and 23% of participants had HIV RNA >100,000 copies/mL. At Week 48, 91% of participants receiving dual therapy and 93% of those receiving triple therapy achieved an HIV RNA <50 copies/mL, demonstrating noninferiority of the dual therapy regimen.⁵¹ The rates of viral suppression among study participants with baseline HIV RNA >100,000 copies/mL were similar in the dual- and triple-therapy groups (87% and 90%, respectively).

Other Factors and Considerations

- 3TC with DTG is available as an STR.
- 3TC and FTC are active against HBV but are insufficient for HBV treatment when used alone due to the emergence of resistance.
- Discontinuation of 3TC or FTC can precipitate a flare in HBV if no other HBV-active drug (i.e., TAF, TDF, entecavir) is in the regimen.
- 3TC is available in two brand-name formulations (one for HIV and the other for HBV), but the doses are different. The dose for HIV treatment is 3TC 300 mg daily, whereas the dose for HBV is 100 mg daily.
- See [Appendix B](#) for dosing recommendations in people with renal impairment.
- Sorbitol-containing drugs can decrease 3TC concentration, and coadministration should be avoided.

The Panel's Recommendations

The Panel recommends the use of—

- DTG/3TC (**AI**) as a [Recommended Initial Regimen for Most People With HIV](#).
- DRV/r + (3TC [**BI**] or FTC [**BII**]) or DRV/c + (3TC or FTC) (**BII**) as [Initial Antiretroviral Regimens for Certain Clinical Scenarios](#).

These regimens are **not recommended** for individuals—

- With HBV coinfection, unless receiving entecavir.
- With unknown HBV serostatus.
- Without results from genotypic resistance testing for reverse transcriptase.
- For whom rapid ART initiation is planned.

DTG/3TC is **not recommended** in people who have received CAB-LA as PrEP and do not have INSTI genotype resistance testing results available demonstrating DTG sensitivity.

Abacavir/Lamivudine

ABC plus 3TC has been studied in combination with EFV, several PIs, and DTG in people who are ART-naïve.^{24,52-54}

Adverse Effects

Hypersensitivity Reactions

- Clinically suspected hypersensitivity reactions (HSRs) were observed in 5% to 8% of individuals who started ABC in clinical trials conducted before the use of HLA-B*5701 testing. The risk of HSRs is highly associated with the presence of the HLA-B*5701 allele; approximately 50% of people who are HLA-B*5701-positive and are given ABC will have a related HSR.^{55,56} HLA-B*5701 testing should be performed if ABC use is being considered. A person who tests positive for HLA-B*5701 should not be given ABC, and ABC hypersensitivity should be noted on the person's allergy list. People who are HLA-B*5701 negative are far less likely to experience an HSR, but they should be counseled about the symptoms of the reaction. People who discontinue ABC because of a suspected HSR **should never be rechallenged**, regardless of their HLA-B*5701 status.

Cardiovascular Risk

- An association between ABC use and myocardial infarction (MI) was first reported in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. This large, multinational, observational study group found that recent (i.e., within 6 months) or current use of ABC was associated with an increased risk of an MI, particularly in participants with preexisting cardiac risk factors.^{5,6}
- Since the D:A:D report, several studies have evaluated the relationship between ABC therapy and cardiovascular events. Some studies have found an association.⁵⁷⁻⁶⁴ Others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.⁶⁵⁻⁶⁹
- A recent analysis of the REPRIEVE trial, a double-blind, multicenter, placebo-controlled study of pitavastatin versus placebo, examined the effects of both prior and current ABC use on major adverse cardiovascular events (MACE).⁷ Among 7,769 participants, 9.2% had prior exposure to ABC at enrollment (median duration: 3 years), and 12.7% were receiving ABC at study entry (median duration: 1.47 years). In adjusted analyses, both former (adjusted hazard ratio [aHR] 1.62; 95% confidence interval [CI], 1.14–2.30) and current ABC use (aHR 1.41; 95% CI, 1.01–1.96) were associated with an increased hazard of MACE.
- A second REPRIEVE analysis compared ABC- versus TFV-based backbones at trial entry with respect to the risk of first MACE.⁸ Among 6,356 people with HIV, 883 were receiving ABC. Baseline-adjusted estimates suggested a higher hazard of first MACE with ABC compared with TDF (hazard ratio [HR] 1.4; 95% CI, 0.9–2.1) and TAF (HR 1.5; 95% CI, 0.9–2.3).
- No consensus has been reached on the association between ABC use and MI risk or the mechanism for such an association; however, the evidence increasingly supports a relationship between ABC and MACE.

Other Factors and Considerations

- ABC/3TC is available as a coformulated tablet and as a coformulated STR with DTG.
- Generic formulations of ABC and 3TC are available separately and as a coformulated tablet.

- ABC does not cause renal dysfunction and can be used instead of TDF in people with underlying renal dysfunction or in those who are at high risk for renal effects. No dose adjustment is required in people with renal dysfunction.

The Panel's Recommendations

- ABC should be prescribed only for people who are HLA-B*5701 negative.
- Due to the need for HLA-B*5701 testing before use, ongoing concerns about increased risk of cardiovascular events seen in association with ABC (observed in some but not all studies), and the availability of other effective and well-tolerated options, the Panel no longer recommends DTG/ABC/3TC for most individuals initiating ART and now classifies DTG/ABC/3TC as part of [*Initial Antiretroviral Regimens for Certain Clinical Scenarios \(BI\)*](#) (see [*Integrase Strand Transfer Inhibitor–Based Regimens as Initial Antiretroviral Therapy*](#) for discussion regarding the clinical efficacy data for DTG/ABC/3TC).
- ABC/3TC used in combination with DRV/r or DRV/c is also recommended as part of [*Initial Antiretroviral Regimens for Certain Clinical Scenarios \(BII\)*](#).
- Consider alternative ARV medications in place of ABC in people with HIV and higher underlying ASCVD risk or known ASCVD **(AII)**. See [*Cardiovascular Complications in People With HIV*](#) for more information.

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

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