

Integrase Strand Transfer Inhibitor–Based Regimens

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Table 8b. Characteristics of Integrase Strand Transfer Inhibitors That Are Recommended for Antiretroviral Therapy–Naïve Patients

| | BIC | DTG | EVG | RAL |
|---|--|--|--|---|
| Dosing Frequency | Once daily | <p>Once Daily</p> <ul style="list-style-type: none"> In ART-naïve or INSTI-naïve persons <p>Twice Daily</p> <ul style="list-style-type: none"> If used with certain CYP3A4 and UGT1A1 inducers; <i>or</i> In INSTI-experienced persons with certain INSTI drug resistance mutations | Once daily; requires boosting with COBI | <ul style="list-style-type: none"> 400 mg twice daily, <i>or</i> 1,200 mg (two 600-mg tablets) once daily |
| STR Available for ART-Naïve Patients | BIC/TAF/FTC | <ul style="list-style-type: none"> DTG/ABC/3TC DTG/3TC | <ul style="list-style-type: none"> EVG/c/TAF/FTC EVG/c/TDF/FTC | No |
| Available as an STR | No | Yes | No | Yes, but requires two tablets per dose |
| Virologic Efficacy Against EVG- or RAL-Resistant HIV | <i>In vitro</i> data indicate activity, but clinical trial data are not available. | Yes, for some isolates; effective with DTG 50 mg twice-daily dose | No | No |
| Adverse Effects | Weight gain, nausea, diarrhea, headache, insomnia; depression and suicidality are rare, occurring primarily in patients with preexisting psychiatric conditions. | | | |
| | ↑ CPK 4% | Hypersensitivity, hepatotoxicity, ↑ CPK, myositis | ↑ TG, ↑ LDL | ↑ CPK, myopathy, hypersensitivity, SJS/TEN |
| CYP3A4 Drug–Drug Interactions | CYP3A4 substrate | CYP3A4 substrate (minor) | EVG is a CYP3A4 substrate; COBI is a CYP3A4 inhibitor | No |
| Chelation with Polyvalent Cation Supplements and Antacids | Oral absorption of all INSTIs may be reduced by polyvalent cations. See Table 24d for recommendations regarding dosing separation of INSTIs and these drugs. | | | |

Table 8b. Characteristics of Integrase Strand Transfer Inhibitors That Are Recommended for Antiretroviral Therapy–Naive Patients

| | BIC | DTG | EVG | RAL |
|---|--|----------------------------------|--|------------------|
| Other Key Potential Drug Interaction Mechanisms | P-gp substrate, UGT1A1 substrate, OCT2 and MATE1 inhibitor | P-gp substrate, UGT1A1 substrate | EVG is a UGT1A1 substrate; COBI is a P-gp inhibitor. | UGT1A1 substrate |

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; BIC = bictegravir; COBI = cobicistat; CPK = creatine phosphokinase; CYP = cytochrome P; DTG = dolutegravir; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LDL = low density lipoprotein; MATE = multidrug and toxic compound extrusion; OCT2 = organic cation transporter 2; P-gp = p-glycoprotein; RAL = raltegravir; SJS/TEN = Stevens Johnson Syndrome/toxic epidermal necrolysis; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglyceride; UGT = uridine diphosphate glucuronosyltransferase+

Summary

Four integrase strand transfer inhibitors (INSTIs)—bictegravir (BIC), dolutegravir (DTG), elvitegravir (EVG), and raltegravir (RAL)—are approved for use in antiretroviral therapy (ART)-naive patients with HIV. Cabotegravir (CAB) is a new INSTI that is approved to be used with rilpivirine (RPV) as part of a long-acting injectable complete antiretroviral (ARV) regimen to replace a stable oral regimen in patients with viral suppression. The role of this combination is discussed in the [Optimizing Antiretroviral Therapy in the Setting of Viral Suppression](#) section. **Long-acting injectable cabotegravir (CAB-LA) is also approved for pre-exposure prophylaxis (PrEP).**

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends one of the following INSTI-based regimens for most people with HIV:

- BIC/tenofovir alafenamide (TAF)/emtricitabine (FTC) (**AI**)
- DTG/abacavir (ABC)/lamivudine (3TC) (if HLA-B*5701 negative and without chronic hepatitis B [HBV] virus coinfection) (**AI**)
- DTG plus (TAF or tenofovir disoproxil fumarate [TDF]) with (FTC or 3TC) (**AI**)
- DTG/3TC (**AI**), except for those with HIV RNA >500,000 copies/mL, with HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

For a person who had exposure to CAB-LA as PrEP, an INSTI-containing regimen should not be initiated unless an INSTI genotypic resistance-test result is available and shows no INSTI-resistance mutations (AIII**). In these cases, boosted darunavir (DRV) plus (TAF or TDF) plus (FTC or 3TC) should be used, pending INSTI resistance results if treatment is initiated before genotypic test results are available (**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

EVG and RAL have a lower barrier to resistance than BIC and DTG. Because of their high barrier to resistance, DTG plus two nucleoside reverse transcriptase inhibitors (NRTIs) or BIC/TAF/FTC may

be considered for patients who must start ART before resistance test results are available. RAL is not available in a single-tablet regimen (STR) formulation, and RAL-containing regimens have a higher pill burden than BIC- and DTG-containing regimens. EVG-based regimens require pharmacokinetic (PK) boosting with cobicistat (COBI), which results in a greater potential for interaction with concomitant medications. Both EVG- and RAL-based regimens are considered *Recommended Initial Regimens in Certain Clinical Situations*.

All INSTIs are generally well tolerated, although there are reports of insomnia in some patients. Depression and suicidal ideation, primarily in patients with a history of psychiatric illnesses, have been reported rarely in patients receiving INSTI-based regimens.¹⁻⁴

Among ARV-naive individuals, initiation of INSTI-containing regimens has been associated with greater weight gain than non-nucleoside reverse transcriptase inhibitor (NNRTI)- or boosted protease inhibitor (PI)-regimens.⁵⁻¹⁰ In randomized trials of ARV-naive individuals, the mean increase in weight from baseline associated with BIC and DTG was similar and greater than with elvitegravir/cobicistat (EVG/c) or with efavirenz (EFV).^{7,11-13} Greater weight gain also has been observed after initiation of TAF^{6,7,14} or with a switch from TDF to TAF,¹⁵ especially in conjunction with INSTIs. Although ARV-associated weight gain appears to disproportionately affect women and Black and Hispanic people,^{5-7,16} predictors and mechanisms for the weight gain are still unclear. Further questions that need to be clarified include regional distribution of the weight gain,¹⁷ whether it is associated with significant cardio-metabolic risk,¹⁸ and whether it is reversible upon discontinuation of the offending agent.

INSTIs in Persons of Childbearing Potential

- Earlier data from a birth outcomes surveillance study in Botswana raised concern of an increased risk of neural tube defects (NTDs) (0.9%) in infants born to women who were receiving DTG at the time of conception.^{19,20} Updated data from the same study showed that the prevalence of NTDs in infants born to women on DTG at the time of conception is not significantly different from those on non-DTG regimens at the time of conception.²¹ Based on these data, the Panel considers DTG an option for persons of childbearing potential. Clinicians should discuss the risks and benefits of using DTG with persons of childbearing potential to allow them to make an informed decision. See the [Dolutegravir](#) section in the Perinatal Guidelines for more detail.
- BIC is **not currently recommended** during pregnancy due to insufficient data on safety and efficacy.
- EVG/c should not be initiated in people who are pregnant or planning to become pregnant because of inadequate drug concentrations in the second and third trimesters. Refer to the [Perinatal Guidelines](#) for further guidance.
- Data on RAL use around the time of conception are limited. Based on data collected from the [Antiretroviral Pregnancy Registry](#), the drug manufacturer, and a cohort study from the United States and other countries, no cases of NTDs have been reported.²²⁻²⁴ Among those who received RAL during pregnancy, the rate of fetal malformations is within the expected range for pregnancy outcomes in the United States.²²⁻²⁴ RAL remains an option for an INSTI-based regimen in persons of childbearing potential.

Clinicians should refer to the [Perinatal Guidelines](#) for detailed recommendations on ARV regimens in treatment-naïve patients, including on the use of INSTI-based regimens during conception and throughout pregnancy.

Integrase Strand Transfer Inhibitors Recommended as Part of an Initial Regimen for Most People with HIV

Bictegravir (BIC)

BIC is an INSTI that is approved by the U.S. Food and Drug Administration for initial therapy in adults with HIV as a component of an STR, once-daily regimen with TAF and FTC.

Efficacy in Clinical Trials

- The efficacy of BIC in ART-naïve adults has been evaluated in two large Phase 3, randomized double-blind, clinical trials that compared BIC to DTG administered in combination with two NRTIs. The primary efficacy endpoint was the proportion of participants with plasma HIV RNA <50 copies/mL at Week 48.
 - The GS-US-380-1490 trial randomized participants 1:1 to receive either BIC/TAF/FTC or DTG with coformulated TAF/FTC. Both regimens were given once daily. At Week 96, 84% of participants in the BIC arm and 86% of those in the DTG arm achieved HIV RNA <50 copies/mL.¹⁴
 - The GS-US-380-1489 trial randomized participants 1:1 to receive BIC/TAF/FTC or coformulated DTG/ABC/3TC once daily. At Week 96, 88% of participants in the BIC/TAF/FTC arm and 90% of those in the DTG/ABC/3TC arm achieved HIV RNA <50 copies/mL.²⁵
 - Week 144 follow-up from both trials demonstrated noninferiority of the BIC/TAF/FTC regimen to both DTG-containing regimens, with high levels of virologic suppression and no treatment-emergent resistance. Weight gain was seen across all treatment groups in both studies, with no differences in median changes from baseline in weight at Week 144 for either study. Median weight gain was 4.1 kg in the BIC/TAF/FTC group and 3.5 kg in the DTG/ABC/3TC group in GS-US-1489. In GS-US-1490, median weight gain was 4.4 kg in the BIC/TAF/FTC group and 5.0 kg in the DTG/TAF/FTC group.¹¹

Adverse Effects

- BIC is generally well tolerated. In clinical trials, the most commonly reported adverse reactions of any grade with an incidence $\geq 5\%$ included diarrhea, nausea, and headache.
- As discussed in the Summary section above, some studies have shown greater weight gain among people initiating INSTI-based regimens, particularly Black women. In a pooled analysis of eight randomized controlled trials in ART-naïve individuals, the weight gain at 96 weeks with BIC- and DTG-based regimens was similar (approximately 3.5 kg).⁷
- Serious neuropsychiatric adverse events were uncommon (<1%) in clinical trials, and mainly occurred in the setting of preexisting depression or other psychiatric illness or prior suicide attempt.²⁶

Other Factors and Considerations

- BIC is a cytochrome P450 (CYP) 3A4 substrate and a uridine diphosphate glucuronosyltransferase (UGT) 1A1 substrate, and its metabolism may be affected by concomitant use of CYP3A4 and UGT1A1 inducers or inhibitors. Rifampin or other rifamycins may decrease BIC or TAF concentrations, which may result in a loss of therapeutic effect. For patients who require rifamycins, BIC/FTC/TAF should not be used. Use of certain anticonvulsants and St. John's wort also should be avoided.²⁶
- BIC is an inhibitor of the drug transporters OCT2 and MATE1, which may lead to increased concentrations of drugs that are substrates of these transporters. For this reason, dofetilide is **contraindicated** with BIC/TAF/FTC.
- BIC is not a CYP3A4 inducer or inhibitor; thus, unlike EVG/c, BIC is unlikely to affect the metabolism of medications that are CYP3A4 substrates.
- Like other INSTIs, oral absorption of BIC may be reduced when BIC is coadministered with polyvalent cations (e.g., aluminum-, magnesium-, or calcium-containing antacids, or calcium or iron supplements). See Drug–Drug Interaction [Table 24d](#) for details on dosing BIC with polyvalent cations.
- BIC decreases tubular secretion of creatinine without affecting glomerular function. Increases in serum creatinine are observed typically within the first 4 weeks of BIC therapy (with a median increase of 0.10 mg/dL after 48 weeks). This increase is comparable to that seen with other drugs that have a similar effect on creatinine secretion, including DTG, RPV, and COBI.
- Treatment-emergent mutations that confer BIC resistance have not yet been reported in people receiving BIC for initial therapy. BIC has not been studied in people with prior INSTI failure or INSTI-related resistance mutations and, therefore, should not be used in these individuals until more data are available.
- Data are insufficient to determine whether use of BIC around the time of conception and during pregnancy is safe.

The Panel's Recommendation

- Based on clinical trial data, the Panel categorizes the combination of BIC/TAF/FTC administered once daily as a *Recommended Initial Regimen for Most People with HIV (AI)*.
- BIC should not be used during pregnancy because of insufficient safety data.

Dolutegravir (DTG)

DTG is an INSTI with a higher barrier to resistance than EVG or RAL. In ART-naïve patients, DTG plus two NRTIs demonstrated high efficacy in achieving HIV suppression. DTG is given once daily, with or without food.

Efficacy in Clinical Trials

- The efficacy of DTG in ART-naïve patients has been evaluated in several fully powered randomized controlled clinical trials. In these trials, DTG-based regimens were noninferior or superior to a comparator INSTI-, NNRTI-, or PI-based regimen. The primary efficacy endpoint

in these clinical trials was the proportion of participants with plasma HIV RNA <50 copies/mL.^{12,27,28}

DTG plus Two NRTIs versus Other INSTIs plus Two NRTIs:

- DTG-based regimens (with TAF/FTC or ABC/3TC) have been compared to BIC/TAF/FTC in two randomized controlled trials. These regimens have shown virologic efficacy that is similar to BIC/TAF/FTC (see discussion in the BIC section above).^{14,25,27,29}
- The SPRING-2 trial compared DTG 50 mg once daily to RAL 400 mg twice daily. Each drug was administered in combination with an investigator-selected, two-NRTI combination (ABC/3TC or TDF/FTC) to 822 participants. At Week 96, DTG was noninferior to RAL.³⁰

DTG plus Two NRTIs versus EFV plus Two NRTIs:

- The SINGLE trial compared DTG 50 mg once daily plus ABC/3TC to EFV/TDF/FTC in 833 participants. At Week 48, DTG plus ABC/3TC was superior to EFV/TDF/FTC, primarily because the study treatment discontinuation rate was higher in the EFV arm than in the DTG arm.³¹ At Week 144, DTG plus ABC/3TC remained superior to EFV/TDF/FTC.³²
- The ADVANCE trial, an open-label, noninferiority trial conducted in South Africa, compared DTG with either TDF/FTC or TAF/FTC to EFV/TDF/FTC. At Week 96, the DTG-based regimens were noninferior to the EFV regimen based on the proportion of participants with HIV RNA levels <50 copies/mL (79% in DTG/TAF/FTC vs. 78% in DTG/TDF/FTC vs. 74% in EFV/TDF/FTC arms). More participants discontinued the trial regimen in the EFV group than in the DTG group. Mean weight gain was 7.1 kg in the DTG/TAF/FTC group, 4.3 kg in the DTG/TDF/FTC group, and 2.3 kg in the EFV/TDF/FTC) and was greater among women than men.¹³
- The NAMSAL ANRS 12313 study, an open-label, multicenter randomized noninferiority trial conducted in Cameroon, compared DTG to EFV 400 mg, both combined with TDF/3TC. At Week 96, DTG was noninferior to EFV 400 mg, with HIV RNA <50 copies/mL in 74% and 72% of participants in the DTG and EFV arms, respectively. Virologic suppression was reached more rapidly in the DTG group, and no DTG resistance mutations were acquired through Week 96. Median weight gain was 5.0 kg in the DTG group versus 3.0 kg in the EFV group.^{12,33}

DTG plus Two NRTIs versus Ritonavir-boosted Protease Inhibitor (PI/r) plus Two NRTIs:

- The FLAMINGO study, a randomized open-label clinical trial, compared DTG 50 mg once daily to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily, each administered in combination with investigator-selected ABC/3TC or TDF/FTC. At Week 48, DTG was superior to DRV/r, with 90% and 83% of participants achieving HIV RNA <50 copies/mL, respectively. The rate of participants who discontinued their assigned regimen was higher in the DRV/r arm.³⁴ The difference in efficacy between the DTG and DRV/r regimens was more pronounced in patients with pre-treatment HIV RNA levels >100,000 copies/mL. At Week 96, DTG remained superior to DRV/r.³⁵
- The ARIA trial, an open-label, Phase 3b randomized controlled trial, compared the efficacy and safety of DTG/ABC/3TC to atazanavir/ritonavir (ATV/r) plus TDF/FTC in ART-naive, nonpregnant women. At Week 48, 82% of participants in the DTG group and 71% in the ATV/r

group ($P = 0.005$) achieved HIV RNA <50 copies/mL. The difference was driven by a lower rate of virologic nonresponse and fewer withdrawals due to adverse events in the DTG group.²⁸

DTG/3TC:

- In the GEMINI-1 and GEMINI-2 trials, 1,433 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/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).³⁶ 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 INSTI resistance occurred in either treatment group. Among participants who started the study with CD4 counts <200 cells/mm³, the rate of those 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 failure in the two-drug group. Overall mean change in weight from baseline was 3.1 kg in the DTG plus 3TC group and 2.1 kg in the DTG plus TDF/FTC 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 3% in both treatment groups. A lower risk of drug-related adverse events was found with DTG plus 3TC versus DTG plus TDF/FTC (20% vs. 27%; relative risk, 0.76 [95% CI, 0.63–0.92]).³⁶
- Two other small, nonrandomized single-arm studies showed similar rates of viral suppression with DTG plus 3TC.^{37,38}

Adverse Effects

- DTG is generally well tolerated. The most reported adverse reactions of moderate-to-severe intensity were insomnia and headache.
- As discussed in the Summary section above, some studies have shown greater weight gain among people initiating INSTI-based regimens, including regimens with DTG.^{6,7,39,40} In a pooled analysis of eight randomized controlled trials in ART-naive individuals, the weight gain at 96 weeks with BIC- and DTG-based regimens was similar (approximately 3.5 kg).⁷
- Neuropsychiatric adverse events (e.g., sleep disturbances, depression, anxiety, suicidal ideation) associated with the initiation of DTG and other INSTIs have been reported.^{1,2} However, analyses of data from large randomized controlled trials and a health care database demonstrated similar rates of neuropsychiatric adverse events between DTG-based regimens and regimens that included RAL, EFV, DRV, and ATV.⁴¹ Neuropsychiatric events rarely led to DTG discontinuation. Data on BIC are more limited because of its recent licensure.

Other Factors and Consideration

- DTG, like BIC, decreases tubular secretion of creatinine without affecting glomerular function, with increases in serum creatinine observed within the first 4 weeks of treatment.
- DTG has fewer drug interactions than EVG/c. See [Table 24d](#) for specific drug–drug interactions that require dosage adjustment.

- DTG absorption, like absorption for other INSTIs, may be reduced when the ARV is coadministered with polyvalent cations (see [Table 24d](#)). DTG should be taken at least 2 hours before or 6 hours after cation-containing antacids or laxatives are taken. Alternatively, DTG and supplements containing calcium or iron can be taken simultaneously with food.
- Treatment-emergent mutations that confer DTG resistance have been rarely reported in patients receiving DTG as part of a three-drug regimen for initial therapy.⁴²⁻⁴⁴ The incidence of resistance with DTG is much lower than with EVG or RAL, which suggests that DTG, like BIC, has a higher barrier to resistance than EVG or RAL.

The Panel's Recommendations

- Based on clinical trial data, the Panel categorizes DTG in combination with ABC/3TC (**AI**), TAF/FTC (**AI**), or TDF/(FTC or 3TC) (**AI**) as a *Recommended Initial Regimen for Most People with HIV*.
- The Panel also recommends the use of DTG/3TC (**AI**) as a *Recommended Initial Regimen for Most People with HIV*, except for those with HIV RNA >500,000 copies/mL, with HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or of HBV testing are available.
- 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.

Integrase Strand Transfer Inhibitors Recommended as Part of an Initial Regimen in Certain Clinical Situations

Elvitegravir (EVG)

EVG is available as a component of two STRs: EVG/c/TDF/FTC and EVG/c/TAF/FTC. COBI is a specific, potent CYP3A inhibitor that has no activity against HIV. It acts as a PK enhancer of EVG, which allows once-daily dosing of the combination but increases the likelihood of significant drug interactions.

Efficacy in Clinical Trials

- The efficacy of EVG/c/TDF/FTC in ART-naïve participants has been evaluated in two randomized, double-blind, active-controlled trials.
 - At 144 weeks, EVG/c/TDF/FTC was noninferior to fixed-dose EFV/TDF/FTC.⁴⁵
 - EVG/c/TDF/FTC also was found to be noninferior to ATV/r plus TDF/FTC.⁴⁶
 - In a randomized blinded trial that compared EVG/c/TDF/FTC to ATV/r plus TDF/FTC in women with HIV, EVG/c/TDF/FTC had superior efficacy, in part, due to a lower rate of treatment discontinuation.⁴⁷
- The efficacy of EVG/c/TAF/FTC in ART-naïve participants has been evaluated in two randomized, double-blind controlled trials in adults with estimated glomerular filtration rate (eGFR) ≥ 50 mL/min.^{48,49}
 - At 48 and 96 weeks, TAF was noninferior to TDF when both drugs were combined with EVG/c/FTC; at 144 weeks, EVG/c/TAF/FTC was superior to EVG/c/TDF/FTC.⁵⁰

Adverse Effects

- The most common adverse events reported with EVG/c/TDF/FTC were diarrhea, nausea, upper respiratory infection, and headache.^{45,46}
- The most common adverse events reported with EVG/c/TAF/FTC were nausea, diarrhea, headache, and fatigue.²⁶
- Neuropsychiatric adverse events have been reported in people receiving INSTIs (see discussion in the DTG section above).

Other Factors and Considerations

- EVG is metabolized primarily by CYP3A enzymes; as a result, CYP3A inducers or inhibitors may alter EVG concentrations.
- Because COBI is a PK enhancer, it is a CYP3A enzyme inhibitor, which may lead to significant interactions with medications that are metabolized by this enzyme (see [Table 24d](#)).⁵¹
- Administration of EVG simultaneously with polyvalent cation-containing antacids or supplements lowers EVG plasma concentrations (see [Table 24d](#)). Separate administration of EVG/c/TDF/FTC or EVG/c/TAF/FTC and polyvalent antacids by at least 2 hours; administer polyvalent cation-containing supplements at least 2 hours before or 6 hours after EVG.
- COBI inhibits active tubular secretion of creatinine, resulting in increases in serum creatinine and a reduction in estimated creatinine clearance (CrCl) without reducing glomerular function.⁵² Patients with a confirmed increase in serum creatinine >0.4 mg/dL from baseline while taking EVG/c/TDF/FTC should be monitored closely and evaluated for evidence of TDF-related proximal renal tubulopathy.²⁶
- EVG/c/TDF/FTC **is not recommended** for patients with pre-treatment estimated CrCl <70 mL/min.²⁶
- EVG/c/TAF/FTC **is not recommended** for patients with estimated CrCl <30 mL/min unless they are on chronic hemodialysis. An observational study of 55 people with HIV who were on hemodialysis suggested that EVG/c/TAF/FTC given once daily (after hemodialysis on dialysis days) can be used safely in persons with no resistance to any of the ARV drugs in this STR.⁵³
- At the time of virologic failure, INSTI-associated mutations were detected in some EVG/c/TDF/FTC-treated patients whose therapy failed.^{45,46} These mutations conferred cross-resistance to RAL, with most patients retaining susceptibility to DTG.
- EVG/c **is not recommended** during pregnancy due to low drug exposure when taken during the second and third trimesters.⁵⁴

The Panel's Recommendation

- Based on the above considerations, the Panel classifies EVG/c/TAF/FTC and EVG/c/TDF/FTC as *Recommended Initial Regimens in Certain Clinical Situations (BI)*. EVG/c/TAF/FTC should be used only in people with estimated CrCl ≥ 30 mL/min unless they are on chronic hemodialysis. EVG/c/TDF/FTC should be used only in people with estimated CrCl ≥ 70 mL/min.

Raltegravir (RAL)

RAL was the first INSTI approved for use in both ARV-naive and ARV-experienced patients.

Efficacy in Clinical Trials

RAL 400 mg Twice Daily plus Two NRTIs versus Comparator Drug plus Two NRTIs:

- The efficacy of RAL at a dose of 400 mg twice daily (with either TDF/FTC or ABC/3TC) as initial therapy was evaluated in two randomized, double-blind, controlled clinical trials and a third open-label randomized trial.
 - STARTMRK compared RAL 400 mg twice daily to EFV 600 mg once daily, each administered in combination with TDF/FTC. RAL was noninferior to EFV at 48 weeks.⁵⁵ RAL was superior to EFV at 4 and 5 years,^{56,57} in part, because of more frequent discontinuations due to adverse events in the EFV group than in the RAL group.
 - The SPRING-2 trial compared DTG 50 mg once daily to RAL 400 mg twice daily, each administered in combination with investigator-selected ABC/3TC or TDF/FTC. At Week 96, DTG was noninferior to RAL. At 48 weeks, no treatment-emergent resistance had occurred in those with virologic failure in the DTG arm, but in the RAL arm, one patient had an INSTI-resistance mutation and four had NRTI-resistance mutations.⁵⁸
 - The SPRING-2 trial also provided nonrandomized data on the efficacy of RAL plus ABC/3TC. In this trial, 164 participants (39 participants with baseline viral loads $\geq 100,000$ copies/mL and 125 participants with baseline viral loads $< 100,000$ copies/mL) received RAL in combination with ABC/3TC. After 96 weeks, no difference in virologic response was evident between the ABC/3TC and TDF/FTC groups when RAL was given as the third drug.³⁰
 - ACTG A5257, a large randomized open-label trial, compared three NNRTI-sparing regimens that contained RAL, ATV/r, or DRV/r, each given with TDF/FTC. At Week 96, all three regimens had similar virologic efficacy, but RAL was superior to both ATV/r and DRV/r for the combined endpoints of virologic efficacy and tolerability. Participants had greater increases in lipid levels in the PI/r arms than in the RAL arm, and bone mineral density decreased to a greater extent in participants in the PI/r arms than in participants in the RAL arm.⁵⁹

RAL 1,200 mg Once Daily plus TDF/FTC versus RAL 400 mg Twice Daily plus TDF/FTC:

- In a Phase 3 randomized, double-blind, active comparator-controlled trial (the ONCEMRK trial), the efficacy of once-daily RAL 1,200 mg (formulated as two 600-mg tablets) was compared to RAL 400 mg twice daily, each administered with TDF/FTC. At 96 weeks, a similar proportion of participants in both groups achieved HIV RNA suppression (81.5% in the once-daily arm vs. 80.1% in the twice-daily arm). The responses were similar regardless of baseline HIV RNA or CD4 count.⁶⁰

Adverse Effects

- RAL, when compared in a randomized trial to DRV/r or ATV/r, all with TDF/FTC, led to a greater mean increase in waist circumference.⁶¹

- RAL use has been associated with creatine kinase elevations. Myositis and rhabdomyolysis have been reported.
- Rare cases of severe skin reactions and systemic hypersensitivity reactions in patients who received RAL have been reported during post-marketing surveillance.⁶²
- Neuropsychiatric adverse events (e.g., insomnia, headache, depression, suicidal ideation) have been reported in people receiving INSTIs (see discussion in the DTG section above).^{41,63}

Other Factors and Considerations

- RAL can be administered as 1,200 mg (two 600-mg tablets) once daily or as 400 mg twice daily with or without food in ART-naive patients. RAL is not available as an STR.
- Coadministration of RAL as either 400 mg twice daily or 1,200 mg once daily with aluminum-containing and/or magnesium-containing antacids **is not recommended**. Calcium carbonate-containing antacids may be coadministered with RAL 400 mg twice daily, but not with RAL 1,200 mg once daily. Polyvalent cation-containing supplements also may reduce absorption of RAL. See [Table 24d](#) for dosing recommendations.
- RAL has a lower barrier to resistance than RTV-boosted PIs, BIC, and DTG.
- Data on RAL use around the time of conception are limited. Thus far, based on data collected from the [Antiretroviral Pregnancy Registry](#), the drug manufacturer, and a cohort study from the United States and other countries, no cases of NTDs have been reported.²²⁻²⁴ Among those who received RAL during pregnancy, the rate of fetal malformations is within the expected range for pregnancy outcomes in the United States.²²⁻²⁴ RAL remains an option for an INSTI-based regimen for persons of childbearing potential.

The Panel's Recommendations

- Based on these clinical trial data, the Panel considers RAL given as 1,200 mg (two 600-mg tablets) once daily or as 400 mg twice daily plus TDF/FTC (**BI**) or TAF/FTC (**BII**) as a *Recommended Initial Regimen in Certain Clinical Situations*.

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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