

Integrase Strand Transfer Inhibitor–Based Regimens

(Last updated June 3, 2021; last reviewed June 3, 2021)

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

Characteristics	BIC	DTG	EVG	RAL
Dosing Frequency	Once daily	Once Daily: <ul style="list-style-type: none"> In ART-naive or INSTI-naive persons Twice Daily: <ul style="list-style-type: none"> If used with certain CYP3A4 and UGT1A1 inducers; or 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, or 1,200 mg (two 600-mg tablets) once daily
STR Available for ART-Naive 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 a Single-Drug Tablet	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.			
Other Key Potential Drug Interaction Mechanism	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; 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 Virologic Suppression](#) section.

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.

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

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 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

- Preliminary 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 results from the same study have shown that the prevalence of NTDs in infants who were exposed to DTG at the time of conception is substantially lower than initial estimates at 0.19% (95%

confidence interval [CI] 0.09, 0.40),²¹ and the prevalence difference in NTDs between those with HIV who did or did not receive DTG at conception was 0.09% (95% CI –0.03, 0.30). Based on these newer data, the Panel now considers DTG a recommended option for persons of childbearing potential. 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. See section on [dolutegravir](#) in the [Perinatal Guidelines](#) for more detail.

- Data are insufficient to determine whether use of BIC around the time of conception and during pregnancy is safe. BIC, therefore, is not recommended during pregnancy at this time.
- 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. Thus far, based on data collected from [Antiretroviral Pregnancy Registry](#), the manufacturer, and in a cohort study from the United States and other countries, no case of NTD has 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 women of childbearing potential.

Clinicians should refer to the [Perinatal Guidelines](#) for detailed recommendations on ART 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 a 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 ≥5% included diarrhea, nausea, and headache.
- As discussed in the Summary section, 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-naive 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 3A4 (CYP3A4) substrate and a uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) 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 typically are observed 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-naive patients, DTG plus two NRTIs demonstrated high efficacy in achieving HIV suppression. DTG is given once daily, with or without food.

Preliminary data from a birth outcomes surveillance study in Botswana raised concern of an increased risk of NTDs (0.9%) in infants born to women who were receiving DTG at the time of conception.^{19, 20} Folate fortification of grains in the geographic area of this study was not mandatory, and the frequency of folate prescribed before conception was low (0.1%–0.2%) among the study participants.²⁸ Updated results from the same study have shown that the prevalence of NTDs in infants who were exposed to DTG at the time of conception is substantially lower than initial estimates at 0.19% (95% CI 0.09, 0.40).²¹ The prevalence difference in NTDs between those with HIV who did or did not receive DTG at conception was 0.09% (95% CI 0.03, 0.30), and between DTG at conception and women without HIV was 0.12% (95% CI 0.01, 0.32). This difference in NTD prevalence (0.19% in those on DTG-containing regimens at conception versus 0.11% in those on non-DTG-containing regimens at conception) was not statistically significant and the Panel considers the risk of NTD associated with DTG to be very low. Based on these newer data, the Panel now considers DTG a recommended option for people of childbearing potential. Before initiating a DTG-based regimen, clinicians should discuss the risks and benefits of using DTG with people of child-bearing potential to allow them to make an informed decision.

Efficacy in Clinical Trials

- The efficacy of DTG in ART-naive 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.

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 the discussion in the BIC section above).^{14, 25, 29, 30}
- 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.³¹

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.³² At Week 144, DTG plus ABC/3TC remained superior to EFV/TDF/FTC.³³
- The ADVANCE trial, an open-label, non-inferiority 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 versus 78% in DTG/TDF/FTC versus 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, 34}

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.³⁵ The difference in efficacy between the DTG and DRV/r regimens was more pronounced in patients with pretreatment HIV RNA levels >100,000 copies/mL. At Week 96, DTG remained superior to DRV/r.³⁶
- 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 ATV/r group ($P = 0.005$) achieved HIV RNA viral loads <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.³⁷

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).³⁸ 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 failures 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 loads ≥50 was similar between treatment groups at 3% in both 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]).³⁸

- Two other small, non-randomized single-arm studies showed similar rates of viral suppression with DTG plus 3TC.^{39, 40}

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, some studies have shown greater weight gain among people initiating INSTI-based regimens, including regimens with DTG.^{6, 7, 41, 42} 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
- 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 including RAL, EFV, DRV, and ATV,⁴³ with neuropsychiatric events rarely leading to DTG discontinuation. More limited data are available for BIC because of its more recent licensure.

Other Factors and Considerations

- 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.⁴⁴⁻⁴⁶ 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

- On the basis of 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

people 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-naive 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.⁴⁷
 - EVG/c/TDF/FTC also was found to be noninferior to ATV/r plus TDF/FTC.⁴⁸
 - 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 because of a lower rate of treatment discontinuation.⁴⁹
- The efficacy of EVG/c/TAF/FTC in ART-naive participants has been evaluated in two randomized, double-blind controlled trials in adults with estimated glomerular filtration rate (eGFR) ≥ 50 mL/min.^{50,51}
 - 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.⁵²

Adverse Effects

- The most common adverse events reported with EVG/c/TDF/FTC were diarrhea, nausea, upper respiratory infection, and headache.^{47, 48}
- The most common adverse events reported with EVG/c/TAF/FTC were nausea, diarrhea, headache, and fatigue.⁵³
- Neuropsychiatric adverse events have been reported in people receiving INSTIs (see the discussion under DTG).

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 pharmacokinetic (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](#)).⁵⁴
- Administration of EVG simultaneously with polyvalent cation-containing antacids or supplements lowers EVG plasma concentrations (see [Table 24d](#)). Separate EVG/c/TDF/FTC or EVG/c/TAF/FTC and polyvalent antacid administration 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 CrCl without reducing glomerular function.⁵⁵ 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.⁵⁶
- EVG/c/TDF/FTC **is not recommended** for patients with pretreatment estimated CrCl <70 mL/min.⁵⁶
- 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.⁵⁷

- At the time of virologic failure, INSTI-associated mutations were detected in some EVG/c/TDF/FTC-treated patients whose therapy failed.^{47,48} These mutations conferred cross-resistance to RAL, with most patients retaining susceptibility to DTG.
- EVG/c is **not recommended** during pregnancy because of low drug exposure when taken during the second and third trimesters.⁵⁸

The Panel's Recommendation

- On the basis of 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.⁵⁹ RAL was superior to EFV at 4 and 5 years,^{60,61} 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.**⁶²
 - 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.³¹
 - 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 (BMD) decreased to a greater extent in participants in the PI/r arms than in participants in the RAL arm.⁶³

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 versus 80.1% in the twice-daily arm). The responses were similar regardless of baseline HIV RNA or CD4 count.⁶⁴

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.⁶⁵
- RAL use has been associated with creatine kinase elevations. Myositis and rhabdomyolysis have been reported.
- Rare cases of severe skin reactions and systemic HSRs in patients who received RAL have been reported during post-marketing surveillance.⁶⁶
- Neuropsychiatric adverse events (e.g., insomnia, headache, depression, and suicidal ideation) have been reported in people receiving INSTIs (see the discussion under DTG).^{43,67}

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-naïve 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 manufacturer, and in a cohort study from the United States and other countries, no cases of NTD 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 people of childbearing potential.**

The Panel's Recommendations

- On the basis of 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 = 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

1. Kheloufi F, Allemand J, Mokhtari S, Default A. Psychiatric disorders after starting dolutegravir: report of four cases. *AIDS*. 2015;29(13):1723-1725. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26372287>.
2. Harris M, Larsen G, Montaner JS. Exacerbation of depression associated with starting raltegravir: a report of four cases. *AIDS*. 2008;22(14):1890-1892. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18753871>.
3. Penafiel J, de Lazzari E, Padilla M, et al. Tolerability of integrase inhibitors in a real-life setting. *J Antimicrob Chemother*. 2017;72(6):1752-1759. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28333231>.

4. Hoffmann C, Welz T, Sabranski M, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. *HIV Med.* 2017;18(1):56-63. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27860104>.
5. Bernardino JJ, Mocroft A, Wallet C, et al. Body composition and adipokines changes after initial treatment with darunavir-ritonavir plus either raltegravir or tenofovir disoproxil fumarate-emtricitabine: A substudy of the NEAT001/ANRS143 randomised trial. *PLoS One.* 2019;14(1):e0209911. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30689664>.
6. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. *N Engl J Med.* 2019;381(9):803-815. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31339677>.
7. Sax PE, Erlandson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. *Clin Infect Dis.* 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31606734>.
8. Bourgi K, Jenkins CA, Rebeiro PF, et al. Weight gain among treatment-naive persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. *J Int AIDS Soc.* 2020;23(4):e25484. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32294337>.
9. Bourgi K, Rebeiro PF, Turner M, et al. Greater weight gain in treatment-naive persons starting dolutegravir-based antiretroviral therapy. *Clin Infect Dis.* 2020;70(7):1267-1274. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31100116>.
10. Bedimo R, Li X, Adams-Huet B, et al. Differential BMI changes following PI- and InSTI-based ART initiation by sex and race. Presented at: Conference on Retroviruses and Opportunistic Infections; 2019. Seattle, WA.
11. Orkin C, DeJesus E, Sax PE, et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials. *Lancet HIV.* 2020;7(6):e389-e400. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32504574>.
12. Calmy A, Tovar Sanchez T, Kouanfack C, et al. Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open label, phase 3 non-inferiority trial in Cameroon. *Lancet HIV.* 2020;7(10):e677-e687. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33010241>.
13. Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. *Lancet HIV.* 2020;7(10):e666-e676. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33010240>.
14. Stellbrink HJ, Arribas JR, Stephens JL, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: Week 96 results from a randomised, double-blind, multicentre,

- phase 3, non-inferiority trial. *Lancet HIV*. 2019;6(6):e364-e372. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31068272>.
15. Gomez M, Seybold U, Roeder J, Harter G, Bogner JR. A retrospective analysis of weight changes in HIV-positive patients switching from a tenofovir disoproxil fumarate (TDF)- to a tenofovir alafenamide fumarate (TAF)-containing treatment regimen in one German university hospital in 2015-2017. *Infection*. 2019;47(1):95-102. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30269210>.
 16. Bedimo R, Adams-Huet B, Taylor BS, Lake J, Luque A. Integrase inhibitor-based HAART is associated with greater BMI gains in blacks, hispanics and women. Presented at: IDWeek; 2018. San Francisco, CA. Available at: <https://idsa.confex.com/idsa/2018/webprogram/Paper71208.html>.
 17. Bhagwat P, Ofotokun I, McComsey GA, et al. Changes in waist circumference in HIV-infected individuals initiating a raltegravir or protease inhibitor regimen: effects of sex and race. *Open Forum Infect Dis*. 2018;5(11):ofy201. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30465010>.
 18. Schafer JJ, Sassa KN, O'Connor JR, Shimada A, Keith SW, DeSimone JA. Changes in body mass index and atherosclerotic disease risk score after switching from tenofovir disoproxil fumarate to tenofovir alafenamide. *Open Forum Infect Dis*. 2019;6(10):ofz414. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31660372>.
 19. Zash R, Holmes L, Makhema J, et al. Surveillance for neural tube defects following antiretroviral exposure from conception. Presented at: 22nd International AIDS Conference (AIDS 2018); 2018. Amsterdam. Available at: https://www.natap.org/2018/IAC/IAC_52.htm.
 20. Zash R, Makhema J, Shapiro RL. Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception. *N Engl J Med*. 2018;379(10):979-981. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30037297>.
 21. Zash R, Holmes L, Diseko M, et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo study, Botswana. Presented at: AIDS 2020 - 23rd International AIDS Conference; 2020. Virtual. Available at: https://www.natap.org/2020/IAC/IAC_112.htm.
 22. Shamsuddin H, Raudenbush C, Sciba B, et al. Pregnancy outcome following raltegravir exposure. Presented at: ID Week; 2019. Washington, DC. Available at: <https://www.eventscribe.com/2019/IDWeek/fsPopup.asp?Mode=presInfo&PresentationID=582846>.
 23. Gantner P, Sylla B, Morand-Joubert L, et al. "Real life" use of raltegravir during pregnancy in France: the Coferal-IMEA048 cohort study. *PLoS One*. 2019;14(4):e0216010. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31017957>.
 24. Rasi V, Cortina-Borja M, Peters H, Sconza R, Thorne C. Brief report: surveillance of congenital anomalies after exposure to raltegravir or elvitegravir during pregnancy in the United Kingdom and Ireland, 2008-2018. *J Acquir Immune Defic Syndr*. 2019;80(3):264-268. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30531300>.
 25. Wohl DA, Yazdanpanah Y, Baumgarten A, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-

- feriority trial. *Lancet HIV*. 2019;6(6):e355-e363. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31068270>.
26. BIKTARVY [package insert]. Gilead. 2021. Available at: https://www.accessdata.fda.gov/drug-satfda_docs/label/2021/210251s0101bl.pdf.
 27. Zash R, Holmes L, Diseko M, et al. Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. *N Engl J Med*. 2019;381(9):827-840. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31329379>.
 28. Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet*. 2017;390(10107):2073-2082. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/28867499>.
 29. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet*. 2017;390(10107):2063-2072. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/28867497>.
 30. Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis*. 2013;13(11):927-935. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24074642>.
 31. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med*. 2013;369(19):1807-1818. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24195548>.
 32. Walmsley S, Baumgarten A, Berenguer J, et al. Brief report: dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. *J Acquir Immune Defic Syndr*. 2015;70(5):515-519. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26262777>.
 33. NAMSAL ANRS Study Group, Kouanfack C, Mpoudi-Etame M, et al. Dolutegravir-based or low-dose efavirenz-based regimen for the treatment of HIV-1. *N Engl J Med*. 2019;381(9):816-826. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31339676>.
 34. Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet*. 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24698485>.
 35. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir is superior to once-daily darunavir/ritonavir in treatment-naive HIV-1-positive individuals: 96 week results from FLAMINGO. *J Int AIDS Soc*. 2014;17(4 Suppl 3):19490. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25393999>.
 36. Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a

- randomised, open-label, non-inferiority, phase 3b study. *Lancet HIV*. 2017. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28729158>.
37. Cahn P, Madero JS, Arribas JR, et al. Durable efficacy of dolutegravir plus lamivudine in Antiretroviral treatment-naive adults with HIV-1 infection: 96-week results from the GEMINI-1 and GEMINI-2 randomized clinical trials. *J Acquir Immune Defic Syndr*. 2020;83(3):310-318. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31834000>.
 38. Cahn P, Rolon MJ, Figueroa MI, Gun A, Patterson P, Sued O. Dolutegravir-lamivudine as initial therapy in HIV-1 infected, ARV-naive patients, 48-week results of the PADDLE (Pilot Antiretroviral Design with Dolutegravir LamivudinE) study. *J Int AIDS Soc*. 2017;20(1):1-7. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28537061>.
 39. Nyaku AN, Zheng L, Gulick RM, et al. Dolutegravir plus lamivudine for initial treatment of HIV-1-infected participants with HIV-1 RNA <500 000 copies/mL: week 48 outcomes from ACTG 5353. *J Antimicrob Chemother*. 2019;74(5):1376-1380. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30668695>.
 40. Bourgi K, Rebeiro PF, Turner M, et al. Greater weight gain in treatment naive persons starting dolutegravir-based antiretroviral therapy. *Clin Infect Dis*. 2019;70(7). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31100116>.
 41. Bourgi K, Jenkins C, Rebeiro PF, et al. Greater weight gain among treatment-naive persons starting integrase inhibitors. Presented at: Conference on Retroviruses and Opportunistic Infections; 2019. Seattle, Washington. Available at: <https://www.croiconference.org/sessions/greater-weight-gain-among-treatment-naive-persons-starting-integrase-inhibitors>.
 42. Fettiplace A, Stainsby C, Winston A, et al. Psychiatric symptoms in patients receiving dolutegravir. *J Acquir Immune Defic Syndr*. 2017;74(4):423-431. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27984559>.
 43. Fulcher JA, Du Y, Zhang TH, Sun R, Landovitz RJ. Emergence of integrase resistance mutations during initial therapy containing dolutegravir. *Clin Infect Dis*. 2018;67(5):791-794. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29933437>.
 44. Pena MJ, Chueca N, D'Avolio A, Zarzalejos JM, Garcia F. Virological failure in HIV to triple therapy with dolutegravir-based firstline treatment: rare but possible. *Open Forum Infect Dis*. 2019;6(1):ofy332. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30631792>.
 45. Lubke N, Jensen B, Huttig F, et al. Failure of dolutegravir first-line ART with selection of virus carrying R263K and G118R. *N Engl J Med*. 2019;381(9):887-889. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31461601>.
 46. Wohl DA, Cohen C, Gallant JE, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *J Acquir Immune Defic Syndr*. 2014;65(3):e118-120. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24256630>.
 47. Clumeck N, Molina JM, Henry K, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results.

- J Acquir Immune Defic Syndr.* 2014;65(3):e121-124. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24346640>.
48. Squires K, Kityo C, Hodder S, et al. Integrase inhibitor versus protease inhibitor based regimen for HIV-1 infected women (WAVES): a randomised, controlled, double-blind, phase 3 study. *Lancet HIV.* 2016;3(9):e410-e420. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27562742>.
 49. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet.* 2015;385(9987):2606-2615. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25890673>.
 50. Wohl D, Oka S, Clumeck N, et al. Brief report: a randomized, double-blind comparison of tenofovir alafenamide versus tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine for initial HIV-1 treatment: week 96 results. *J Acquir Immune Defic Syndr.* 2016;72(1):58-64. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26829661>.
 51. Arribas JR, Thompson M, Sax PE, et al. Brief report: randomized, double-blind comparison of tenofovir alafenamide (TAF) vs tenofovir disoproxil fumarate (TDF), each coformulated with elvitegravir, cobicistat, and emtricitabine (E/C/F) for initial HIV-1 treatment: week 144 results. *J Acquir Immune Defic Syndr.* 2017;75(2):211-218. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28282300>.
 52. Genvoya package insert [package insert]. Gilead. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/207561s025lbl.pdf.
 53. Mathias AA, West S, Hui J, Kearney BP. Dose-response of ritonavir on hepatic CYP3A activity and elvitegravir oral exposure. *Clin Pharmacol Ther.* 2009;85(1):64-70. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18815591>.
 54. German P, Liu HC, Szwarcberg J, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. *J Acquir Immune Defic Syndr.* 2012;61(1):32-40. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22732469>.
 55. Stribild package insert. Gilead. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203100s035lbl.pdf.
 56. Eron JJ, Jr., Lelievre JD, Kalayjian R, et al. Safety of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in HIV-1-infected adults with end-stage renal disease on chronic haemodialysis: an open-label, single-arm, multicentre, phase 3b trial. *Lancet HIV.* 2018;S2352-3018(18):30296-30290. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30555051>.
 57. Momper JD, Best BM, Wang J, et al. Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV. *AIDS.* 2018;32(17):2507-2516. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30134297>.
 58. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet.* 2009;374(9692):796-806. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19647866>.

59. DeJesus E, Rockstroh JK, Lennox JL, et al. Efficacy of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: week-192 overall and subgroup analyses from STARTMRK. *HIV Clin Trials*. 2012;13(4):228-232. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22849964>.
60. Rockstroh JK, DeJesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. *J Acquir Immune Defic Syndr*. 2013;63(1):77-85. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23412015>.
61. Raffi F, Rachlis A, Stellbrink HJ, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. *Lancet*. 2013;381(9868):735-743. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23306000>.
62. Lennox JL, Landovitz RJ, Ribaldo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann Intern Med*. 2014;161(7):461-471. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25285539>.
63. Cahn P, Sax PE, Squires K, et al. Raltegravir 1200 mg once daily vs 400 mg twice daily, with emtricitabine and tenofovir disoproxil fumarate, for previously untreated HIV-1 Infection: Week 96 results from ONCEMRK, a randomized, double-blind, noninferiority Trial. *J Acquir Immune Defic Syndr*. 2018;78(5):589-598. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29771789>.
64. Bhagwat P, Ofotokun I, McComsey GA, et al. Predictors of severe weight/body mass index gain following antiretroviral initiation. Presented at: Conference on Retroviruses and Opportunistic Infections; 2017. Seattle, Washington. Available at: <https://www.croiconference.org/sessions/predictors-severe-weightbody-mass-index-gain-following-antiretroviral-initiation>.
65. Isentress package insert. Merck Sharp & Dohme Corp. 2017. Available at: http://www.merck.com/product/usa/pi_circulars/i/isentress/isentress_pi.pdf.
66. Gray J, Young B. Acute onset insomnia associated with the initiation of raltegravir: a report of two cases and literature review. *AIDS Patient Care STDS*. 2009;23(9):689-690. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19663717>.