Integrase Strand Transfer Inhibitor–Based Regimens as Initial Antiretroviral Therapy

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Table 8b. Characteristics of Integrase Strand Transfer Inhibitors That Are Recommended as Part of Initial Antiretroviral Therapy

	BIC	DTG
Dosing Frequency	Once daily	**Once Daily** • As initial ART or for people with no INSTI-resistance mutations **Twice Daily** • If used with certain CYP3A4 and UGT1A1 inducers; *or* • In people with certain INSTI drug resistance mutations
STR Available as Initial ART	BIC/TAF/FTC	• DTG/ABC/3TC • DTG/3TC
Available as a Single Drug Tablet	No	Yes
Virologic Efficacy Against EVG- or RAL-Resistant HIV	*In vitro* data indicate activity, but clinical trial data are not available.	Yes, for some isolates; effective with DTG 50 mg twice daily
Adverse Reactions	• ↑ CPK • CNS side effects were rarely reported in clinical trials. • Diarrhea, nausea, and headache may occur in some cases.	• ↑ CPK, myositis • CNS side effects such as insomnia and headache have been reported; depression and suicidality are rare, occurring primarily in people with preexisting conditions. • Hypersensitivity, hepatotoxicity
CYP3A4 Drug–Drug Interactions	CYP3A4 substrate	CYP3A4 substrate (minor)
Chelation With Polyvalent Cation Supplements and Antacids	Oral absorption may be reduced by polyvalent cations. See the Liverpool HIV Drug Interaction Checker for recommendations regarding dosing separations and these drugs.	

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

	BIC	DTG
Other Key Potential Drug Interaction Mechanisms	P-gp substrate, UGT1A1 substrate, OCT2 and MATE1 inhibitor	P-gp substrate, UGT1A1 substrate, OCT2 inhibitor, potential MATE1 inhibitor
Other Factors	Not recommended for initial therapy in those with a history of CAB-LA use as PrEP unless INSTI sensitivity is documented on genotypic resistance testing. Both BIC and DTG decrease tubular secretion of creatinine without affecting glomerular function. This may result in an increase in serum creatinine of approximately 0.1–0.2 mg/dL.	

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; BIC = bictegravir; CAB-LA = long-acting injectable cabotegravir; CNS = central nervous system; CPK = creatine phosphokinase; CYP = cytochrome P450; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; MATE1 = multidrug and toxic compound extrusion 1; OCT2 = organic cation transporter 2; P-gp = p-glycoprotein; PrEP = pre-exposure prophylaxis; RAL = raltegravir; STR = single-tablet regimen; TAF = tenofovir alafenamide; UGT = uridine diphosphate glucuronosyltransferase

Four oral integrase strand transfer inhibitors (INSTIs)—bictegravir (BIC), dolutegravir (DTG), elvitegravir (EVG), and raltegravir (RAL)—are approved for use in people with HIV as initial antiretroviral therapy (ART). Intramuscular cabotegravir (CAB) is approved for use with rilpivirine (RPV) (with or without an oral CAB + RPV lead-in) as part of a long-acting injectable complete antiretroviral (ARV) regimen to replace a stable oral regimen in people with HIV and 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 first-generation INSTIs EVG and RAL have some disadvantages, including a low barrier to resistance. In addition, because EVG must be given with cobicistat (COBI), a pharmacokinetic (PK) booster, it has a high potential for drug–drug interactions, whereas RAL-based regimens have a higher pill burden than other INSTI regimens. Because of these disadvantages, elvitegravir/cobicistat (EVG/c) and RAL are no longer recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) as initial ART. Because the second-generation INSTIs BIC and DTG have high barriers to resistance, BIC/tenofovir alafenamide (TAF)/emtricitabine (FTC), DTG plus (TAF or tenofovir disoproxil fumarate [TDF]) plus (FTC or lamivudine [3TC]), and DTG/3TC are recommended for most people with HIV (see Appendix A, Table 4 for more information on the INSTIs BIC and DTG).

This section of the guidelines will focus on BIC and DTG, the two INSTIs recommended by the Panel as part of Recommended Initial Regimens for Most People With HIV and Initial Antiretroviral Regimens for Certain Clinical Scenarios (also see Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios).

Panel's Recommendations for Integrase Strand Transfer Inhibitor–Based Regimens

The Panel recommends one of the following INSTI-based regimens as initial ART for people with HIV who **do not** have a history of using CAB-LA as PrEP (see *Recommended Initial Regimens for Most People With HIV*):

- BIC/TAF/FTC **(AI)**
- DTG plus (TAF or TDF) with (FTC or 3TC) **(AI)**

- DTG/3TC **(AI),** except for individuals—
  - With hepatitis B virus (HBV) coinfection, unless on entecavir.
  - With unknown HBV serostatus.
  - Without results from genotypic resistance testing for reverse transcriptase.
  - For whom rapid ART initiation is planned.

Several scenarios exist in which an individual or partner may have prior INSTI exposure. For people who previously received 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).** INSTI resistance has been reported in people who acquired HIV following exposure to CAB-LA as PrEP.[1] If treatment is initiated before genotypic test results are available, boosted darunavir (DRV) plus (TAF or TDF) with (FTC or 3TC) should be used, pending INSTI resistance results **(AIII).** See *Recommended Initial Regimens for Most People With HIV* for more details.

For the following groups, an INSTI genotype test should be obtained prior to beginning an INSTI-based regimen, but an INSTI-based regimen can be started before the return of genotype results (see Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios).

- People who potentially acquired HIV from a partner with virologic failure while on an INSTI, because of the low rates of transmitted INSTI resistance in the United States
- People who have never used CAB-LA for PrEP and who acquired HIV despite using INSTI-based post-exposure prophylaxis, because selection of INSTI-resistant virus is likely to be uncommon in this setting

The Panel also recommends using DTG/abacavir (ABC)/3TC **(BI)** when concerns about renal- or bone-associated adverse events preclude the use of TAF or TDF or when DTG/3TC cannot be used. Concerns about renal- or bone-associated adverse events should be weighed against cardiovascular disease risk when considering ABC use, especially in people with higher underlying atherosclerotic cardiovascular disease (ASCVD) risk or known ASCVD. See Cardiovascular Complications in People With HIV for more information. ABC should only be given to people who are documented to be HLA-B*5701-negative.

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*

Adverse Effects

BIC and DTG are generally well tolerated, although there are reports of insomnia in some people. Depression and suicidal ideation, primarily in people with a history of psychiatric illnesses, have been reported rarely in those receiving INSTI-based regimens.[2-5]

Among people with HIV who are ART-naive, initiation of INSTI-based regimens has been associated with greater weight increases than with non-nucleoside reverse transcriptase inhibitor (NNRTI)– or boosted protease inhibitor (PI)–based regimens.[6-11] 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 EVG/c or efavirenz (EFV).[8,12-14] Weight gain was also greater in those initiating TAF than in those initiating other nucleoside reverse transcriptase inhibitors (NRTIs).[7,8,15] These weight

increases appear to disproportionately affect women and Black and Hispanic people,[6-8,16] yet predictors and mechanisms for the weight increases are still unclear. Specific ARV classes or medications, including INSTI- or TAF-based regimens, should not be avoided to prevent or reduce weight gain.

Integrase Strand Transfer Inhibitor Use in Women of Reproductive Potential

Clinicians should refer to the Perinatal Guidelines for detailed recommendations on INSTI-based ARV regimens throughout conception, pregnancy, and postpartum care.

- Earlier data from a birth outcomes surveillance study in Botswana raised concern about an increased risk of neural tube defects (NTDs) of 0.9% in infants born to women who were receiving DTG at the time of conception.[17] 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 that of those on non-DTG regimens at the time of conception.[18] Based on these data, DTG (with [TDF or TAF] plus [3TC or FTC]) is now one of the *Preferred* INSTIs during pregnancy. See the Perinatal Guidelines for further discussion.
- BIC is also recommended as a *Preferred* INSTI during pregnancy based on safety and PK data in pregnancy. See the Perinatal Guidelines for more details.
- DTG/3TC is recommended as an *Alternative* ART regimen during pregnancy. See the Perinatal Guidelines for more details.

Bictegravir

BIC is approved by the U.S. Food and Drug Administration for initial therapy in adults with HIV as a component of a once-daily single-tablet regimen with TAF and FTC, given with or without food.

Efficacy in Clinical Trials

- The efficacy of BIC in ART-naive adults has been evaluated in two large Phase 3 randomized double-blind clinical trials that compared BIC/TAF/FTC 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.[15]
  - 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.[19]
  - Week 144 follow-up from both trials demonstrated non-inferiority of the BIC/TAF/FTC regimen to both DTG-containing regimens, with high levels of virologic suppression and no treatment-emergent resistance.[14]
  - The open-label, multicenter LAPTOP trial randomized 447 ART-naive participants with advanced HIV disease to receive either BIC/TAF/FTC or darunavir/cobicistat (DRV/c)/TAF/FTC. Through 48 weeks, the primary composite outcome (the time to first occurrence of specified virologic or clinical event) was observed in 22% of participants in the

BIC/TAF/FTC group and 32% in the DRV/c/TAF/FTC group, demonstrating non-inferiority of BIC/TAF/FTC. At Week 48, HIV RNA <50 copies/mL was achieved by 69% of participants in the BIC/TAF/FTC group and 61% in the DRV/c/TAF/FTC group. Compared with the DRV/c/TAF/FTC group, participants in the BIC/TAF/FTC group were more likely to achieve an HIV RNA <50 copies/mL at Week 4 (16% vs. 1%), Week 8 (35% vs. 7%), and Week 12 (46% vs. 17%).[20]

Adverse Effects

- BIC is generally well tolerated.
- Neuropsychiatric adverse events have been reported with INSTIs. BIC-associated serious neuropsychiatric effects were uncommon (<1%) in clinical trials and mainly occurred in the setting of preexisting depression, other psychiatric illness, or prior suicide attempt.[21]

Drug–Drug Interactions

Note: Refer to the Liverpool HIV Drug Interaction Checker for information on potential INSTI-related drug–drug interactions.

- BIC is a cytochrome P450 (CYP) 3A4 substrate and a uridine diphosphate glucuronosyltransferase (UGT) 1A1 substrate; therefore, its metabolism may be affected by concomitant use of CYP3A4 and UGT1A1 inducers or inhibitors.
- BIC is an inhibitor of the drug transporters, organic cation transporter 2 (OCT2) and multidrug and toxic compound extrusion 1 (MATE1); therefore, BIC may increase concentrations of drugs that are substrates of these transporters. For this reason, dofetilide is **contraindicated** with BIC/TAF/FTC.
- 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; calcium or iron supplements).

Other Factors and Considerations

- 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 0.11 mg/dL by Week 144).[21] This increase is comparable to that seen with other ARV drugs that have a similar effect on creatinine secretion, including DTG, RPV, and COBI.
- Treatment-emergent mutations that confer BIC resistance have rarely been reported in people receiving BIC for initial therapy.[22] BIC has not been studied in prospective trials for people with prior INSTI failure or INSTI-related resistance mutations. A retrospective analysis of data from seven switch trials found 20 individuals with preexisting INSTI-related resistance mutations (based on history or proviral DNA testing) showed maintenance of viral suppression in 19 people after a switch to BIC and viral suppression after beginning BIC in 1 person without prior ARV treatment.[23] However, data are currently insufficient to recommend BIC use in such cases.

The Panel's Recommendation

The Panel recommends the use of BIC/TAF/FTC as a *Recommended Initial Regimen for Most People With HIV* **(AI)** who **do not** have a history of using CAB-LA as PrEP, unless INSTI sensitivity is documented on genotypic drug resistance testing (see *Recommended Initial Regimens for Most*

People With HIV and Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios for more detailed recommendations).

Dolutegravir

As initial ARV regimens, both DTG plus two NRTIs and DTG/3TC demonstrated high efficacy in achieving HIV suppression in clinical trials. DTG is given once daily, with or without food.

Efficacy in Clinical Trials

The efficacy of DTG in ART-naive individuals has been evaluated in several fully powered randomized controlled clinical trials. In these trials, DTG-based regimens were non-inferior 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.[12,24,25]

Dolutegravir Plus Two NRTIs Versus Other INSTIs Plus Two NRTIs

- DTG-based regimens (with TAF/FTC or ABC/3TC) have been compared with BIC/TAF/FTC in two randomized controlled trials. These regimens have virologic efficacy that is similar to BIC/TAF/FTC (see discussion in the BIC section above).[15,19,24,26]

Dolutegravir Plus Two NRTIs Versus Efavirenz 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.[27] At Week 144, DTG plus ABC/3TC remained superior to EFV/TDF/FTC.[28]
- 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 non-inferior to the EFV-based 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 group and was greater among women than men.[13]

Dolutegravir Plus Two NRTIs Versus Ritonavir-Boosted Darunavir Plus Two NRTIs

- The FLAMINGO study, a randomized open-label clinical trial, compared DTG 50 mg once daily to the boosted PI—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. More participants discontinued DRV/r-based regimens.[29] The difference in efficacy between the DTG and DRV/r regimens was more pronounced in people with pre-treatment HIV RNA levels >100,000 copies/mL. At Week 96, DTG remained superior to DRV/r.[30]
- The ADVANZ-4 trial, a Phase 4 open-label study, enrolled and randomized 104 ART-naive adults with advanced HIV (CD4 T lymphocyte [CD4] cell counts <100 cells/mm^3) to receive DTG plus ABC/3TC or DRV/r plus ABC/3TC. Virologic response was similar at 48 weeks but occurred

sooner in the DTG arm, with a significantly higher proportion of participants in the DTG arm achieving undetectable viral loads at Weeks 4 and 12.[31]

Dolutegravir/Lamivudine

- 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 non-inferior to DTG plus TDF/FTC, with 86% of participants in the DTG plus 3TC group and 89.5% in the DTG plus TDF/FTC group achieving HIV RNA <50 copies/mL.[32] 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 treatment-emergent NRTI or INSTI resistance occurred in either treatment group. Among participants who started the study with CD4 counts <200 cells/mm^3, the rate of 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 non-inferiority to DTG plus TDF/FTC, with 82% versus 84% of participants maintaining viral load <50 copies/mL, respectively. The proportion of participants with 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% confidence interval, 0.63–0.92]).[32]
- In the DOLCE study, 230 treatment-naive individuals with CD4 count ≤200 cells/mm^3 were randomized 2:1 to DTG/3TC or DTG plus TDF/3TC or TDF/FTC. At baseline, the median CD4 count was 109 cells/mm^3 and viral load 180,000 copies/mL, with 23% having viral load >500,000 copies/mL. The study demonstrated non-inferiority between the study arms, with no emergent resistance to 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 the triple therapy arm. Although the GEMINI-1 and GEMINI-2 studies excluded those with baseline viral load >500,000 copies/mL, this study supports the use of DTG/3TC in this population.[33]

Adverse Effects

- DTG is generally well tolerated. The most reported adverse reactions of moderate-to-severe intensity were insomnia and headache.
- Some studies have shown greater weight increase among people initiating INSTI-based regimens, including regimens with DTG.[7-10] 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). The clinical significance of weight gain in this setting is unclear.[8]
- Neuropsychiatric adverse events (e.g., sleep disturbances, depression, anxiety, suicidal ideation) associated with the initiation of DTG and other INSTIs have been reported.[2,3,34,35] 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.[36] Neuropsychiatric events rarely led to DTG discontinuation.

Drug–Drug Interactions

Note: See the Liverpool HIV Drug Interaction Checker for a comprehensive list of potential INSTI-related drug–drug interactions.

- Whereas BIC is a major CYP3A4 substrate, DTG is a minor substrate and is therefore less impacted by CYP3A4-mediated interactions, allowing coadministration with certain medications that cannot be coadministered with BIC; dose adjustment to DTG twice daily may be necessary.
- DTG oral absorption may be reduced when the ARV drug is coadministered with polyvalent cations.

Other Factors and Considerations

- DTG decreases tubular secretion of creatinine without affecting glomerular function, with increases in serum creatinine observed within the first 4 weeks of treatment (with a mean increase of 0.15 mg/dL after 96 weeks).[37]
- Treatment-emergent mutations that confer DTG resistance have been rarely reported in people receiving DTG as part of a three-drug regimen for initial therapy.[38-40] 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

- The Panel classifies the following as *Recommended Initial Regimens for Most People With HIV* who **do not** have a history of using CAB-LA as PrEP, unless INSTI sensitivity is documented on genotypic drug resistance testing (see *Recommended Initial Regimens for Most People With HIV* and Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios for more detailed recommendations):
  - DTG plus (TAF or TDF) with (FTC or 3TC) **(AI)**
  - DTG/3TC **(AI)—not recommended** for those with HBV coinfection unless on another HBV-active drug (i.e., entecavir), those with unknown HBV serostatus, or those in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase are available. DTG/3TC is not appropriate for rapid ART initiation.
- The Panel recommends DTG/ABC/3TC **(BI)** in certain clinical scenarios for people with HIV who are documented to be HLA-B*5701-negative and have concerns about renal or bone toxicities associated with TAF or TDF or who cannot use DTG/3TC. Concerns about renal- or bone-associated adverse events should be weighed against cardiovascular disease risk when considering ABC use, especially in individuals with higher underlying ASCVD risk or known ASCVD. See Cardiovascular Complications in People With HIV for more information. This regimen should not be used in people with HBV unless an HBV-active drug (i.e., entecavir) other than 3TC is used.

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