Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Last updated June 3, 2021; last reviewed June 3, 2021) (page 1 of 5)

Note: All drugs within an ARV class are listed in alphabetical order.

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
Dual-NRTI	**ABC/3TC**	• Coformulated with DTG • Generic formulations are available for ABC/3TC, ABC, and 3TC.	• May cause life-threatening HSRs in patients who test positive for the HLA-B*5701 allele. As a result, HLA-B*5701 testing is required before use. • In the ACTG 5202 study, patients with baseline HIV RNA ≥100,000 copies/mL showed inferior virologic responses when ABC/3TC was given with EFV or ATV/r as opposed to TDF/FTC. This difference was not seen when ABC/3TC was used in combination with DTG. • ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies.
	TAF/FTC	• Coformulated with BIC, DRV/c, EVG/c, or RPV • Active against HBV; a recommended dual-NRTI option for patients with HBV/HIV coinfection • Smaller decline in renal function, less proteinuria, and smaller reductions in BMD than TDF/FTC • Approved for patients with eGFR ≥30 mL/min • Can be used in patients with eGFR <30 mL/min and on chronic hemodialysis	• TDF is associated with lower lipid levels than TAF, perhaps because TDF results in higher plasma levels of tenofovir, which lowers lipids. • See discussion in text regarding weight gain with TAF.
	TDF/3TC	• Coformulated with DOR • Generic formulations are available for TDF, 3TC, TDF/3TC, and EFV/TDF/3TC. • Long-term clinical experience • Active against HBV	• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency, especially when combined with pharmacologic boosters. • Osteomalacia has been reported as a consequence of proximal tubulopathy. • Decreased BMD has been associated with use of TDF, especially when combined with pharmacologic boosters.
	TDF/FTC	• Coformulated with EFV, EVG/c, and RPV as STRs • Active against HBV; a recommended dual-NRTI option for patients with HIV/HBV coinfection • Better virologic responses than ABC/3TC in patients with baseline viral loads ≥100,000 copies/mL when combined with ATV/r or EFV • Associated with lower lipid levels than ABC or TAF	• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency, especially when combined with pharmacologic boosters. • Osteomalacia has been reported as a consequence of proximal tubulopathy. • Decreased BMD has been associated with use of TDF, especially when combined with pharmacologic boosters.
Single NRTI	**3TC**	• Coformulated with DTG as STR • Avoids potential toxicities associated with TDF, TAF, ABC	• DTG/3TC **is not recommended** for individuals with HIV RNA >500,000 copies/mL, HBV co-infection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Last updated June 3, 2021; last reviewed June 3, 2021) (page 2 of 5)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
INSTI	**BIC**	• Coformulated with TAF/FTC • Higher barrier to resistance than EVG and RAL • No food requirement	• Oral absorption of BIC can be reduced by simultaneous administration with drugs or supplements containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 24d. • Inhibits tubular secretion of Cr without affecting glomerular function. • CYP3A4 and UGT1A1 substrate (but not a CYP3A4 inducer or inhibitor); potential for drug-drug interactions. • **Should not be used in pregnancy** because of lack of data for BIC. • See discussion in text regarding weight gain related to INSTIs.
	DTG	• Higher barrier to resistance than EVG or RAL • Coformulated with ABC/3TC and 3TC • No food requirement • Minimal CYP3A4 interactions • Favorable lipid profile	• Oral absorption of DTG can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 24d. • Inhibits renal tubular secretion of Cr and can increase serum Cr without affecting glomerular function. • UGT1A1 substrate; potential for drug interactions (see Table 24d). • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions). • See discussion in text regarding weight gain related to INSTIs. • Updated data from Botswana suggest that DTG exposure during conception may be associated with a small risk of NTDs in the infant compared with non-DTG ARV drugs (1.9 per 1,000 versus 1.1 per 1,000), with a prevalence difference that was not statistically significant. Clinicians should discuss with people of childbearing potential and refer to the Perinatal Guidelines.
	EVG/c	• Coformulated with TDF/FTC or TAF/FTC • Compared with ATV/r, EVG/c causes smaller increases in total and LDL cholesterol. • EVG/c/TAF/FTC can be used in patients on chronic hemodialysis.	• EVG/c/TDF/FTC is recommended only for patients with baseline CrCl ≥70 mL/min; this regimen should be discontinued if CrCl decreases to <50 mL/min. • COBI is a potent CYP3A4 inhibitor, which can result in **significant interactions** with CYP3A substrates. • Oral absorption of EVG can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements or multivitamin tablets with minerals). See dosing recommendations in Table 24d. • COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • Has a lower barrier to resistance than boosted PI-, BIC-, or DTG-based regimens. • Food requirement. • Depression and suicidal ideation (rare; usually in patients with preexisting psychiatric conditions). • EVG/c should be avoided in pregnancy, because levels of COBI and its boosted drugs are lower in the second and third trimesters. If women who are pregnant with suppressed virus on EVG/c elect to continue on the drug, frequent viral load monitoring is recommended. • See discussion in text regarding weight gain related to INSTIs.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Last updated June 3, 2021; last reviewed June 3, 2021) (page 3 of 5)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
INSTI, continued	RAL	• Compared to other INSTIs, has longest post-marketing experience • No food requirement • No CYP3A4 interactions • Favorable lipid profile	• Has a lower barrier to resistance than boosted PI-, BIC-, or DTG-based regimens. • Increases in creatine kinase, myopathy, and rhabdomyolysis have been reported. • Rare cases of severe HSRs (including SJS and TEN) have been reported. • Higher pill burden than other INSTI-based regimens. • No FDC formulation. • Oral absorption of RAL can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements or multivitamin tablets with minerals). See dosing recommendations in Table 24d. • UGT1A1 substrate; potential for drug interactions (see Table 24d). • Depression and suicidal ideation (rare; usually in patients with preexisting psychiatric conditions). • See discussion in text regarding weight gain related to INSTIs.
NNRTI	**DOR**	• Coformulated with TDF/3TC • Compared to EFV, fewer CNS side effects • No food requirement • Favorable lipid profile • Lack of association with weight gain compared with boosted DRV or EFV	• Shorter-term clinical experience than with EFV and RPV. • Potential for CYP450 drug interactions (see Tables 24b, 25a and 25b). • Treatment-emergent DOR resistance mutations may confer resistance to certain NNRTIs.
	EFV	• EFV 600 mg is coformulated with TDF/FTC and TDF/3TC. • EFV 400 mg is coformulated with TDF/3TC. • EFV 600-mg dose has long-term clinical experience and EFV-based regimens (except for EFV plus ABC/3TC) have well-documented efficacy in patients with high HIV RNA. • EFV 400 mg has fewer CNS side effects than EFV 600 mg. • EFV 600 mg can be given with rifamycin antibiotics (rifampin, rifabutin, or rifapentine).	• Short- and long-term neuropsychiatric (CNS) side effects, including depression and, in some studies, suicidality and catatonia. Late onset ataxia and encephalopathy have also been reported. • Periodic screening for depression and suicidality is recommended in people with HIV who are taking a regimen that includes EFV. • Dyslipidemia • Rash • QTc interval prolongation; consider using an alternative to EFV in patients taking medications with known risk of causing Torsades de Pointes or in those at higher risk of Torsades de Pointes. • Transmitted resistance is more common than with PIs and INSTIs. • Greater risk of resistance at the time of treatment failure than with PIs. • Potential for CYP450 drug interactions (see Tables 24b and 25a). • Should be taken on an empty stomach (food increases drug absorption and CNS toxicities).

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Last updated June 3, 2021; last reviewed June 3, 2021) (page 4 of 5)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)

NNRTI, continued	**RPV**	• Coformulated with TDF/FTC and TAF/FTC
		• RPV/TDF/FTC and RPV/TAF/FTC have smaller pill sizes than other coformulated ARV drugs
		• Compared with EFV:
		  • Fewer CNS adverse effects
		  • Fewer lipid effects
		  • Fewer rashes
			• **Not recommended** in patients with pre-ART HIV RNA >100,000 copies/mL or CD4 counts <200 cells/mm^3 because of higher rate of virologic failure in these patients.
			• Depression and suicidality
			• QTc interval prolongation; consider using an alternative to RPV in patients taking medications with known risk of causing Torsades de Pointes or in those at higher risk of Torsades de Pointes.
			• Rash
			• Transmitted resistance is more common than with PIs and INSTIs.
			• More NNRTI-, TDF-, and 3TC-associated mutations at virologic failure than with regimens that contain EFV and 2 NRTIs.
			• Potential for CYP450 drug interactions (see Tables 24b and 25a).
			• Meal requirement (>390 kcal)
			• Requires acid for adequate absorption.
			  • **Contraindicated** with PPIs.
			  • Use with H2 antagonists or antacids with caution (see Table 24a for detailed dosing information).

PIs	**ATV/c** or **ATV/r**	• Higher barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure is uncommon with PK-enhanced PIs. • ATV/c and ATV/r have similar virologic activity and toxicity profiles. • Observational cohort studies have found an association between some PIs (DRV, LPV/r, FPV, IDV) and an increased risk of CV events; this risk has not been seen with ATV. Further study is needed. See text for discussion. • Individual ATV and RTV components are available as generics.	• Commonly causes indirect hyperbilirubinemia, which may manifest as scleral icterus or jaundice. • Food requirement • Absorption depends on food and low gastric pH (see Table 24a for interactions with H2 antagonists, antacids, and PPIs). • Nephrolithiasis, cholelithiasis, nephrotoxicity • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 24a).
	ATV/c Specific considerations	Coformulated tablet	• COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • Coadministration with TDF **is not recommended** in patients with CrCl <70 mL/min. • COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. • COBI should be avoided in pregnancy, because levels of COBI and its boosted drugs are lower in the second and third trimesters. If women who are pregnant with suppressed virus on ATV/c elect to continue on the drug, frequent viral load monitoring is recommended.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Last updated June 3, 2021; last reviewed June 3, 2021) (page 5 of 5)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
PIs, continued	**DRV/c** or **DRV/r**	• Higher barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure is uncommon with PK-enhanced PIs.	• Skin rash • Food requirement • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 24a). • Increased CV risk reported in one observational cohort study. • Hepatotoxicity has been reported, especially in those with pre-existing liver disease.
	DRV/c Specific considerations	• Coformulated as DRV/c and DRV/c/TAF/FTC.	• COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • Coadministration with TDF is not recommended in patients with CrCl <70 mL/min. • COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. • COBI should be avoided in pregnancy, because levels of COBI and its boosted drugs are lower in the second and third trimesters. If women who are pregnant with suppressed virus on DRV/c elect to continue on the drug, frequent viral load monitoring is recommended.

Key: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; Ca = calcium; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; Cr = creatinine; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; eGFR = estimated glomerular filtration rate; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FPV = fosamprenavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; Mg = magnesium; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson syndrome; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrosis; UGT = uridine diphosphate glucuronosyltransferase