Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Updated January 10, 2011)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
NNRTI (in alphabetical order)		**NNRTI Class Advantages:** • Long half-lives	**NNRTI Class Disadvantages:** • Low genetic barrier to resistance (single mutation confers resistance for EFV, NVP, and DLV); greater risk of resistance at the time of failure or treatment interruption • Potential for cross resistance • Skin rash • Potential for CYP450 drug interactions (See Tables 14, 15b, and 16b.) • Transmitted resistance to NNRTIs more common than resistance to PIs
	EFV	• Virologic responses equivalent or superior to all comparators to date • Lowest pill burden; once-daily dosing • Fixed-dose combination with TDF/FTC	• Neuropsychiatric side effects • Teratogenic in nonhuman primates, and several cases of neural tube defect reported in infants of women with first-trimester exposure. EFV is contraindicated in first trimester of pregnancy; avoid use in women with pregnancy potential. • Dyslipidemia
	NVP	• No food effect • Fewer lipid effects than EFV	• Higher incidence of rash than with other NNRTIs, including rare but serious hypersensitivity reactions (Stevens-Johnson syndrome or toxic epidermal necrolysis) • Higher incidence of hepatotoxicity than with other NNRTIs, including serious and even fatal cases of hepatic necrosis • Contraindicated in patients with moderate or severe (Child-Pugh B or C) hepatic impairment • Some data suggest that ART-naïve patients with high pre-NVP CD4 counts (>250 cells/mm^3 for females, >400 cells/mm^3 for males) are at higher risk of symptomatic hepatic events. NVP is not recommended in these patients unless benefit clearly outweighs risk. • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials • Fewer clinical trial data than for EFV
PI (in alphabetical order)		**PI Class Advantages:** • Higher genetic barrier to resistance • PI resistance uncommon with failure (boosted PIs)	**PI Class Disadvantages:** • Metabolic complications (e.g., dyslipidemia, insulin resistance, hepatotoxicity) • Gastrointestinal adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (more pronounced with RTV-based regimens) (See Tables 14 and 15a.)
	ATV	• Fewer adverse effects on lipids than other PI • Once-daily dosing • Low pill burden (two pills per day) • Good GI tolerability • Signature mutation (I50L) not associated with broad PI cross resistance	• Indirect hyperbilirubinemia sometimes leading to jaundice or scleral icterus • PR interval prolongation: generally inconsequential unless combined with another drug with similar effect • Cannot be coadministered with TDF, EFV, or NVP (See ATV/r.) • Nephrolithiasis • Skin rash • Food requirement • Absorption depends on food and low gastric pH (See Table 15a for detailed information regarding interactions with H2 antagonists, antacids, and PPIs.)
	ATV/r	• RTV boosting: higher trough ATV concentration and greater antiviral effect • Once-daily dosing • Low pill burden (two pills per day)	• More adverse effects on lipids than unboosted ATV • More hyperbilirubinemia and jaundice than unboosted ATV • Food requirement • Absorption depends on food and low gastric pH (See Table 15a for interactions with H_2 antagonists, antacids, and PPIs.) • RTV boosting required with TDF and EFV. With EFV, use ATV 400 mg and RTV 100 mg once daily (PI-naïve patients only). • Should not be coadministered with NVP

ARV Class	ARV Agent(s)	Advantages	Disadvantages
	DRV/r	• Once-daily dosing	• Skin rash • Food requirement
	FPV	• No food effect	• Skin rash • Potential for PI resistance with failure, including emergence of mutations that can cause DRV cross resistance
	FPV/r	• Twice-daily dosing resulted in efficacy comparable to LPV/r • RTV boosting: higher trough APV concentration and greater antiviral effect • Once-daily dosing possible with RTV 100 mg or 200 mg daily • No food effect	• Skin rash • Hyperlipidemia • Once-daily dosing results in lower APV concentrations than twice-daily dosing • For FPV 1,400 mg + RTV 200 mg: requires 200 mg of RTV and no coformulation • Fewer data on FPV 1,400 mg + RTV 100 mg dose than on DRV/r and ATV/r
	LPV/r	• Coformulated • No food requirement • Recommended PI in pregnant women (twice daily only) • Greater CD4 count increase than with EFV-based regimens	•Requires 200 mg per day of RTV •Lower drug exposure in pregnant women—may need dose increase in third trimester • Once-daily dosing not recommended in pregnant women • Once-daily dosing: lower trough concentration than twice-daily dosing • Possible higher risk of MI associated with cumulative use of LPV/r • PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or receiving other drugs with similar effect.
	SQV/r	• Efficacy similar to LPV/r with less hyperlipidemia	• Highest pill burden among available PI regimens (6 pills per day) • Requires 200 mg of RTV • Food requirement • PR and/or QT interval prolongations in a healthy volunteer study • Pretreatment ECG recommended • SQV/r is not recommended for patients with any of the following conditions: (1) congenital or acquired QT prolongation; (2) pretreatment ECG >450 msec; (3) on concomitant therapy with other drugs that prolong QT interval; (4) complete AV block without implanted pacemakers; (5) risk of complete AV block.
INSTI	**RAL**	• Virologic response noninferior to EFV • Fewer drug-related adverse events and lipid changes than EFV • No food effect • Fewer drug-drug interactions than PI- or NNRTI-based regimens	•Less long-term experience in ART-naïve patients than with boosted PI- or NNRTI-based regimens •Twice-daily dosing •Lower genetic barrier to resistance than with boosted PI-based regimens •No data with NRTIs other than TDF/FTC in ART-naïve patients
CCR5 Antagonist	**MVC**	• Virologic response noninferior to EFV in post-hoc analysis of MERIT study (See text.) • Fewer adverse effects than EFV	• Requires viral tropism testing prior to initiation of therapy with additional cost and possible delay in initiation of therapy •More MVC-treated than EFV-treated patients discontinued therapy due to lack of efficacy in MERIT study •Less long-term experience in ART-naïve patients than with boosted PI- or NNRTI-based regimens •Limited experience with 2-NRTI other than ZDV/3TC •Twice-daily dosing •CYP 3A4 substrate, dosing depends on presence or absence of concomitant CYP3A4 inducer(s) or inhibitor(s)
Dual NRTIs		**Dual-NRTI Class Advantage:** Established backbone of combination ART	**Dual-NRTI Class Disadvantage:** Rare but serious cases of lactic acidosis with hepatic steatosis reported with d4T, ddI, and ZDV

Dual-NRTI pairs (in alphabetical order)	**ABC/3TC**	• Virologic response noninferior to ZDV/3TC • Better CD4 count response than with ZDV/3TC • Once-daily dosing • Coformulation • No food effect • No cumulative TAM-mediated resistance	• Potential for ABC HSR in patients with HLA-B*5701 • Potential for increased cardiovascular events, especially in patients with cardiovascular risk factors • Inferior virologic responses when compared with TDF/FTC in patients with baseline HIV RNA >100,000 copies/mL in ACTG 5202 study; however, this was not seen in the HEAT study.
	ddI + (3TC or FTC)	• Once-daily dosing • No cumulative TAM-mediated resistance	• Peripheral neuropathy, pancreatitis • Reports of noncirrhotic portal hypertension • Food effect; must be taken on an empty stomach • Requires dosing separation from some PIs • Increase in toxicities when used with ribavirin, TDF, d4T, or hydroxyurea • Preliminary data showed inferior virologic responses of ATV/ddI/FTC when compared with EFV/ZDV/3TC or EFV/TDF/FTC. Combination of ATV/ddI/FTC should be avoided.
	TDF/FTC or TDF + 3TC	• Better virologic responses than with ZDV/3TC • Better virologic responses than with ABC/3TC in patients with baseline HIV RNA >100,000 copies/mL in ACTG 5202 study; however, this was not seen in the HEAT study. • Active against HBV; recommended dual-NRTI for HBV/HIV coinfection • Once-daily dosing • No food effect • Coformulated (TDF/FTC) and (EFV/TDF/FTC) • No cumulative TAM-mediated resistance	• Potential for renal impairment, including rare reports of Fanconi syndrome and acute renal insufficiency • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials • Potential for decrease in bone mineral density
	ZDV/3TC	• Coformulated (ZDV/3TC and ZDV/3TC/ABC) • No food effect (although better tolerated with food) • Preferred 2 NRTI in pregnant women	• Bone marrow suppression, especially anemia and neutropenia • GI intolerance, headache • Mitochondrial toxicity, including lipoatrophy, lactic acidosis, hepatic steatosis • Inferior to TDF/FTC in combination with EFV • Diminished CD4 T-cell responses compared with ABC/3TC

Acronyms: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ARV = antiretroviral, ATV = atazanavir, ATV/r = atazanavir/ritonavir, AV = atrioventricular, CYP = cytochrome P, ddI = didanosine, DLV = delavirdine, DRV/r = darunavir/ritonavir, ECG = electrocardiogram, EFV = efavirenz, FPV = fosamprenavir, FPV/r = fosamprenavir/ ritonavir, FTC = emtricitabine, GI = gastrointestinal, HBV = hepatitis B virus, HSR = hypersensitivity reaction, INSTI = integrase strand transfer inhibitor, LPV/r = lopinavir/ritonavir, MI = myocardial infarction, msec = milliseconds, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PPI = proton pump inhibitor, SQV/r = saquinavir/ritonavir, TAM = thymidine analogue mutation, TDF = tenofovir, ZDV = zidovudine