Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Guidelines Development Process

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral (ARV) agents for the treatment of HIV infection in adults and adolescents in the United States.
Panel members	The Panel is composed of approximately 40 voting members who have expertise in HIV care and research. The Panel includes at least one representative from each of the following U.S. Department of Health and Human Services (HHS) agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resource Services Administration (HRSA), and National Institutes of Health (NIH). Approximately two-thirds of the Panel members are non-governmental scientific members. The Panel also includes four to five community members with knowledge in HIV treatment and care. The U.S. government representatives are appointed by their respective agencies; other Panel members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 4-year term with an option for reappointment for an additional term. A list of current members can be found in the Panel Roster.
Financial disclosure	All members of the Panel submit financial disclosure in writing annually, reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDS*info* website (http://aidsinfo.nih.gov/contentfiles/AA_financialDisclosures.pdf).
Users of the guidelines	HIV treatment providers
Developer	Panel on Antiretroviral Guidelines for Adults and Adolescents—a working group of the Office of AIDS Research Advisory Council (OARAC)
Funding source	Office of AIDS Research, NIH
Evidence collection	The recommendations in the guidelines are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	As described in Table 2
Method of synthesizing data	Each section of the guidelines is assigned to a working group of Panel members with expertise in the area of interest. The working groups synthesize the available data and propose recommendations to the Panel. The Panel discusses all proposals during monthly teleconferences. Recommendations endorsed by the Panel are included in the guidelines as official recommendations.
Other guidelines	These guidelines focus on treatment for HIV-infected adults and adolescents. Included is a brief discussion on the management of women of reproductive age and pregnant women. For more detailed and up-to-date discussion on the use of antiretroviral therapy (ART) for these women, as well as for children, and other special populations, please refer to guidelines specific to these groups. The guidelines are also available on the AIDS*info* website (http://www.aidsinfo.nih.gov).
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, dosing formulations, or frequency of dosing), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may post a warning announcement with recommendations on the AIDS*info* website in the interim until the guidelines can be updated with the appropriate changes. Updated guidelines are available on the AIDS*info* website (http://www.aidsinfo.nih.gov).
Public comments	A 2-week public comment period follows release of the updated guidelines on the AIDS*info* website. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov.

Table 2. Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	**II:** One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	**III:** Expert opinion

Table 3. Laboratory Monitoring Schedule for HIV-Infected Patients Before and After Initiation of Antiretroviral Therapy[a] (page 1 of 2)

Laboratory Test	Timepoint/Frequency of Testing								
	Entry into Care	Follow Up Before Initiation of ART	ART Initiation or Modification[b]	Follow-Up 2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated
HIV Serology	√ If HIV diagnosis has not been confirmed								
CD4 Count	√	√ Every 3–6 months	√		√ During first 2 years of ART or if viremia develops while patient on ART or CD4 count <300 cells/mm^3		√ After 2 years on ART with consistently suppressed viral load: *CD4 Count 300–500 cells/mm^3:* • Every 12 months *CD4 Count >500 cells/mm^3:* • CD4 monitoring is optional	√	√
HIV Viral Load	√	Repeat testing is optional	√	√[c]	√[d]	√[d]		√	√
Resistance Testing	√		√[e]					√	√
HLA-B*5701 Testing			√ If considering ABC						
Tropism Testing			√ If considering a CCR5 antagonist					√ If considering a CCR5 antagonist or for failure of CCR5 antagonist-based regimen	√

Table 3. Laboratory Monitoring Schedule for HIV-Infected Patients Before and After Initiation of Antiretroviral Therapy[a] (page 2 of 2)

Laboratory Test	Timepoint/Frequency of Testing								
	Entry into Care	Follow Up Before Initiation of ART	ART Initiation or Modification[b]	Follow-Up 2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated
Hepatitis B Serology[f]	√		√ May repeat if HBsAg (-) and HBsAb (-) at baseline						√
Hepatitis C Serology, with Confirmation of Positive Results	√								√
Basic Chemistry[g,h]	√	√ Every 6–12 months	√	√	√				√
ALT, AST, T. bilirubin	√	√ Every 6–12 months	√	√	√				√
CBC with Differential	√	√ Every 3–6 months	√	√ If on ZDV	√				√
Fasting Lipid Profile	√	√ If normal, annually	√	√ Consider 4–8 weeks after starting new ART regimen that affects lipids		√ If abnormal at last measure-ment	√ If normal at last measurement		√
Fasting Glucose or Hemoglobin A1C	√	√ If normal, annually	√		√ If abnormal at last measure-ment		√ If normal at last measurement		√
Urinalysis[g]	√		√			√ If on TDF[i]	√		√
Pregnancy Test			√ In women with child-bearing potential						√

[a] This table pertains to laboratory tests done to select an ARV regimen and monitor for treatment responses or ART toxicities. Please refer to the HIV Primary Care guidelines for guidance on other laboratory tests generally recommended for primary health care maintenance of HIV patients.[1]

[b] ART may be modified because of treatment failure, adverse effects, or for regimen simplification.

[c] If HIV RNA is detectable at 2 to 8 weeks, repeat every 4 to 8 weeks until viral load is suppressed to <200 copies/mL, and thereafter, every 3 to 6 months.

[d] In patients on ART, viral load typically is measured every 3 to 4 months. However, for adherent patients with consistently suppressed viral load and stable immunologic status for more than 2 years, monitoring can be extended to 6 month intervals.

[e] In ART-naive patients, if resistance testing was performed at entry into care, repeat testing before initiation of ART is optional. The exception is pregnant women; repeat testing is recommended in this case. In virologically suppressed patients who are switching therapy because of toxicity or for convenience, viral amplification will not be possible; therefore, resistance testing should not be performed. Results from prior resistance testing can be helpful in constructing a new regimen.

[f] If HBsAg is positive at baseline or before initiation of ART, TDF plus either FTC or 3TC should be used as part of the ARV regimen to treat both HBV and HIV infections. If HBsAg, and HBsAb, and anti-HBc are negative at baseline, hepatitis B vaccine series should be administered. Refer to HIV Primary Care guidelines for more detailed recommendations.[1]

[g] Serum Na, K, HCO_3, Cl, BUN, creatinine, glucose (preferably fasting). Some experts suggest monitoring the phosphorus levels of patients on TDF. Determination of renal function should include estimation of CrCl using the Cockcroft-Gault equation or estimation of glomerular filtration rate using the MDRD equation.

[h] For patients with renal disease, consult the Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America.[2]

[i] More frequent monitoring may be indicated for patients with evidence of kidney disease (e.g., proteinuria, decreased glomerular dysfunction) or increased risk of renal insufficiency (e.g., patients with diabetes, hypertension).

Key to Acronyms: 3TC = lamivudine, ABC = abacavir, ALT = alanine aminotransferase, ART = antiretroviral therapy, AST = aspartate aminotranserase, CBC = complete blood count, CrCl = creatinine clearance, EFV = efavirenz, FTC = emtricitabine, HBsAb = hepatitis B surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, MDRD = modification of diet in renal disease (equation), TDF = tenofovir, ZDV = zidovudine

Table 4. Recommendations on the Indications and Frequency of Viral Load and CD4 Count Monitoring[a]

Clinical Scenario	Viral Load Monitoring	CD4 Count Monitoring
Before initiating ART	At entry into care **(AIII)** If ART initiation is deferred, repeat before initiating ART **(AIII)**. In patients not initiating ART, repeat testing is optional **(CIII)**.	At entry into care **(AI)** If ART is deferred, every 3 to 6 months **(AIII)**.[b]
After initiating ART	Preferably within 2 to 4 weeks (and no later than 8 weeks) after initiation of ART **(AIII)**; thereafter, every 4 to 8 weeks until viral load suppressed **(BIII)**.	3 months after initiation of ART **(AIII)**
After modifying ART because of drug toxicities or for regimen simplification in a patient with viral suppression	4 to 8 weeks after modification of ART to confirm effectiveness of new regimen **(AIII)**.	Monitor according to prior CD4 count and duration on ART, as outlined below.
After modifying ART because of virologic failure	Preferably within 2 to 4 weeks (and no later than 8 weeks) after modification **(AIII)**; thereafter, every 4 to 8 weeks until viral load suppressed **(BIII)**. If viral suppression is not possible, repeat viral load every 3 months or more frequently if indicated **(AIII)**.	Every 3 to 6 months **(AI)**
During the first 2 years of ART	Every 3 to 4 months **(AIII)**	Every 3 to 6 months[a] **(BII)**
After 2 years of ART (VL consistently suppressed, CD4 consistently 300-500 cells/mm^3)	Can extend to every 6 months for patients with consistent viral suppression for ≥2 years **(AIII)**.	Every 12 months **(BII)**
After 2 years of ART (VL consistently suppressed, CD4 consistently >500 cells/mm^3)		Optional **(CIII)**
While on ART with detectable viremia (VL repeatedly >200 copies/mL)	Every 3 months **(AIII)** or more frequently if clinically indicated. (See Virologic Failure and Suboptimal Immunologic Response section)	Every 3 to 6 months **(AIII)**
Change in clinical status (e.g., new HIV clinical symptom or initiation of interferon, chronic systemic corticosteroids, or antineoplastic therapy)	Every 3 months **(AIII)**	Perform CD4 count and repeat as clinically indicated[c] **(AIII)**

[a] Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) has not proven clinically useful, adds to costs, and is not routinely recommended **(BIII)**.

[b] Some experts may repeat CD4 count every 3 months in patients with low baseline CD4 count (<200–300 cells/mm^3) before ART but every 6 months in those who initiated ART at higher CD4 cell count (e.g., >300 cells/mm^3).

[c] The following are examples of clinically indicated scenarios: changes in a patient's clinical status that may decrease CD4 count and thus prompt initiation of prophylaxis for opportunistic infections (OI), such as new HIV-associated symptoms, or initiation of treatment with medications which are known to reduce CD4 cell count.

Table 5. Recommendations for Using Drug-Resistance Assays (page 1 of 2)

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
In acute HIV infection: Drug-resistance testing is recommended regardless of whether antiretroviral therapy (ART) is initiated immediately or deferred **(AII)**. A genotypic assay is generally preferred **(AIII)**.	If ART is initiated immediately, drug-resistance testing can determine whether drug-resistant virus was transmitted. Test results will help in the design of initial regimens or to modify or change regimens if results are obtained after treatment initiation. Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If ART is deferred, repeat resistance testing should be considered at the time therapy is initiated **(CIII)**. A genotypic assay generally is preferred **(AIII)**.	If ART is deferred, testing should still be performed because of the greater likelihood that transmitted resistance-associated mutations will be detected earlier in the course of HIV infection. Results of resistance testing may be important when treatment is initiated. Repeat testing at the time ART is initiated should be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection).
In ART-naive patients with chronic HIV infection: Drug-resistance testing is recommended at entry into HIV care, regardless of whether therapy is initiated immediately or deferred **(AII)**. A genotypic assay is generally preferred **(AIII)**.	Transmitted HIV with baseline resistance to at least 1 drug is seen in 6% to 16% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations. Some drug-resistance mutations can remain detectable for years in untreated, chronically infected patients.
If therapy is deferred, repeat resistance testing should be considered before initiation of ART **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	Repeat testing before initiation of ART should be considered because the patient may have acquired a drug-resistant virus (i.e., a superinfection). Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If an INSTI is considered for an ART-naive patient and transmitted INSTI resistance is a concern, providers may supplement standard resistance testing with a specific INSTI genotypic resistance assay **(CIII)**.	Standard genotypic drug-resistance assays test only for mutations in the RT and PR genes.
If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-receptor Tropism Assays)	(see Co-receptor Tropism Assays)
In patients with virologic failure: Drug-resistance testing is recommended in patients on combination ART with HIV RNA levels >1,000 copies/mL **(AI)**. In patients with HIV RNA levels >500 copies/mL but <1,000 copies/mL, testing may not be successful but should still be considered **(BII)**.	Testing can help determine the role of resistance in drug failure and maximize the clinician's ability to select active drugs for the new regimen. Drug-resistance testing should be performed while the patient is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy.
A standard genotypic resistance assay is generally preferred for patients experiencing virologic failure on their first or second regimens **(AII)**.	Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant HIV.
In patients failing INSTI-based regimens, genotypic testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens **(AII)**.	Standard genotypic drug-resistance assays test only for mutations in the RT and PR genes.
If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-receptor Tropism Assays).	
Addition of phenotypic assay to genotypic assay is generally preferred in patients with known or suspected complex drug-resistance patterns, particularly to protease inhibitors (PIs) **(BIII)**.	Phenotypic testing can provide additional useful information in patients with complex drug-resistance mutation patterns, particularly to PIs.

Table 5. Recommendations for Using Drug-Resistance Assays (page 2 of 2)

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
In patients with suboptimal suppression of viral load: Drug-resistance testing is recommended in patients with suboptimal suppression of viral load after initiation of ART **(AII)**.	Testing can help determine the role of resistance and thus assist the clinician in identifying the number of active drugs available for a new regimen.
In HIV-infected pregnant women: Genotypic resistance testing is recommended for all pregnant women before initiation of ART **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**.	The goal of ART in HIV-infected pregnant women is to achieve maximal viral suppression for treatment of maternal HIV infection and for prevention of perinatal transmission of HIV. Genotypic resistance testing will assist the clinician in selecting the optimal regimen for the patient.
Drug-resistance assay not usually recommended	
After therapy is discontinued: Drug-resistance testing is not usually recommended more than 4 weeks after discontinuation of ARV drugs **(BIII)**.	Drug-resistance mutations may become minor species in the absence of selective drug pressure, and available assays may not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value; however, the absence of resistance does not rule out the presence of minor drug-resistant species.
In patients with low HIV RNA levels: Drug-resistance testing is not usually recommended in patients with a plasma viral load <500 copies/mL **(AIII)**.	Resistance assays cannot be consistently performed given low HIV RNA levels.

Table 6. Recommended and Alternative Antiretroviral Regimen Options for Treatment-Naive Patients

An antiretroviral regimen generally consists of two NRTIs plus one active drug from one of the following classes: NNRTI, PI (boosted with RTV), or INSTI. Selection of a regimen should be individualized on the basis of virologic efficacy, potential adverse effects, pill burden, dosing frequency, drug-drug interaction potential, a patient's resistance test results and comorbid conditions, and cost. Table 7 lists the advantages and disadvantages of the ARV components listed below. Appendix B, Tables 1–6 provides dosing information. The regimens in each category are listed in alphabetical order. For more detailed recommendations on ARV choices and dosing in HIV-infected pregnant women, refer to the latest perinatal guidelines available at http://aidsinfo.nih.gov/guidelines.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Recommended Initial ART Regimen Options for All Patients, Regardless of Pre-ART Viral Load or CD4 Cell Count
NNRTI-Based Regimen: • EFV/TDF/FTC[a] **(AI)**
PI-Based Regimens: • ATV/r plus TDF/FTC[a] **(AI)** • DRV/r plus TDF/FTC[a] **(AI)**
INSTI-Based Regimens: • DTG plus ABC/3TC[a] **(AI)—only** for patients who are HLA-B*5701 negative • DTG plus TDF/FTC[a] **(AI)** • EVG/cobi/TDF/FTC— **only** for patients with pre-treatment estimated CrCl ≥70 mL/min **(AI)** • RAL plus TDF/FTC[a] **(AI)**
In addition to the regimens listed above, the following regimens are also recommended, but only for patients with pre-ART plasma HIV RNA <100,000 copies/mL
NNRTI-Based Regimens: • EFV plus ABC/3TC[a] **(AI)—only** for patients who are HLA-B*5701 negative • RPV/TDF/FTC[a] **(AI)—only** for patients with CD4 cell count >200 cells/mm^3
PI-Based Regimen: • ATV/r plus ABC/3TC[a] **(AI)—only** for patients who are HLA-B*5701 negative
Alternative Initial ART Regimen Options
Regimens that are effective and tolerable, but that have potential disadvantages when compared with the recommended regimens listed above or have less data from randomized clinical trials. An alternative regimen may be the preferred regimen for some patients.
PI-Based Regimens: • DRV/r plus ABC/3TC[a] **(BII)—only** for patients who are HLA-B*5701 negative • LPV/r (once[b] or twice daily) plus ABC/3TC[a] **(BI)—only** for patients who are HLA-B*5701 negative • LPV/r (once[b] or twice daily) plus TDF/FTC[a] **(BI)**
INSTI-Based Regimen: • RAL plus ABC/3TC[a] **(BII)—only** for patients who are HLA-B*5701 negative

[a] 3TC may be substituted for FTC or vice versa. The following combinations in the recommended list above are available as co-formulated fixed-dose combinations: ABC/3TC, EFV/TDF/FTC, EVG/cobi/TDF/FTC, LPV/r, RPV/TDF/FTC, and TDF/FTC.

[b] Once daily LPV/r is not recommended for pregnant patients.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = ritonavir-boosted atazanavir; cobi = cobicistat; CrCl = creatinine clearance; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = ritonavir-boosted lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

Table 7. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 1 of 3)

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

ARV Class	ARV Agent(s)	Advantages	Disadvantages
Dual-NRTI Pairs	ABC/3TC	• Once-daily dosing • No food effect • No nephrotoxicity	• Inferior virologic responses in patients with baseline HIV RNA ≥100,000 copies/mL when given with EFV or ATV/r as compared with TDF/FTC in ACTG 5202 study. This difference not seen when ABC/3TC was used in combination with DTG. • Requires HLA-B*5701 testing before use • Potential for ABC HSR in patients with HLA-B*5701 allele • ABC use has been associated with cardiac events in some but not all observational studies.
	TDF/FTC	• Better virologic responses than with ABC/3TC in patients with baseline viral load ≥100,000 copies/mL when combined with ATV/r or EFV • Active against HBV; recommended dual-NRTI for HIV/HBV co-infected patients • Once-daily dosing • No food effect • Co-formulated in fixed-dose combinations that comprise an entire regimen in a single pill (EFV/TDF/FTC, EVG/cobi/TDF/FTC, and RPV/TDF/FTC)	• Potential for renal impairment, including proximal tubulopathy and acute or chronic renal insufficiency • Potential for decrease in BMD
NNRTIs	EFV	• Virologic responses non-inferior or superior to most comparators • Virologic potency persists regardless of baseline HIV RNA • Once-daily dosing • Co-formulated with TDF/FTC • Long-term clinical experience	• Transmitted resistance more common than with PIs • Short-and long-term neuropsychiatric side effects, including depression and suicidality • Teratogenic in non-human primates; avoid use in women who are trying to conceive or who are sexually active and not using contraception • Dyslipidemia • Greater risk of resistance at the time of treatment failure than with PIs • Skin rash • Potential for CYP450 drug interactions (see Tables 17, 18b, and 19a) • Should be taken on an empty stomach (food increases drug absorption and CNS toxicities)
	RPV	• Once-daily dosing • Co-formulated with TDF/FTC • Smaller pill size than co-formulated EFV/TDF/FTC or EVG/cobi/TDF/FTC • Compared with EFV: ◦ Fewer discontinuations for CNS adverse effects ◦ Fewer lipid effects ◦ Fewer rashes ◦ Smaller pill size	• Not recommended in patients with pre-ART HIV RNA >100,000 copies/mL or CD4 count <200 cells/mm^3 because of higher rate of virologic failure in these patients • Transmitted resistance more common than with PIs • More NNRTI-, TDF-, and 3TC-associated mutations at virological failure than with regimen containing EFV and two NRTIs • Potential for CYP450 drug interactions (see Tables 17, 18b, and 19a) • Meal requirement • Requires acid for adequate absorption • Contraindicated with PPIs • Use with H2 antagonists or antacids with caution (see Table 18a for detailed dosing information). • RPV-associated depression reported • Use with caution when co-administered with a drug having a known risk of torsades de pointes.

Table 7. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 2 of 3)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs	ATV/r	• Once-daily dosing • Higher genetic barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure uncommon with RTV-boosted PIs	• Commonly causes indirect hyperbilirubinemia, which may manifest as scleral icterus or jaundice. • Food requirement • Absorption depends on food and low gastric pH (see Table 18a for interactions with H2 antagonists, antacids, and PPIs). • Nephrolithiasis, cholelithiasis, nephrotoxicity • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Tables 17 and 18a)
	DRV/r	• Once-daily dosing • Higher genetic barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure uncommon with RTV-boosted PIs	• Skin rash • Food requirement • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Tables 17 and 18a)
	LPV/r	• Only PI co-formulated with RTV ◦ May reduce the number of patient co-pays (out-of-pocket cost) ◦ Can prevent patient from inadvertently not taking RTV or the active PI • No food requirement • Once or twice daily dosing	• Requires 200 mg per day of RTV • Once-daily dosing not recommended in pregnant women • 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. • Possible nephrotoxicity • CYP3A4 inhibitors and substrates: potential for drug interactions (see Tables 17 and 18a)
INSTIs	DTG	• Once-daily dosing • DTG-containing regimens have higher rates of virologic suppression than EFV- or DRV/r-containing regimens, largely because of fewer drug discontinuations. • May have higher barrier to resistance than EVG or RAL • Demonstrated virologic potency with both TDF/FTC and ABC/3TC regardless of pre-ART HIV RNA level • Effective at double dose (50 mg twice daily) against some RAL- and EVG-resistant viruses • No food requirement • No CYP3A4 interactions	• Inhibits renal tubular secretion of creatinine and can increase serum creatinine, without affecting glomerular function • Oral absorption can be reduced by simultaneous administration with products containing polyvalent cations (e.g., Al^{+++}, Ca^{++}, or Mg^{++} containing antacids or supplements, or multivitamin tablets with minerals) (see dosing recommendations in Table 18d). • UGT substrate: potential for drug interactions (see Table 18d)

Table 7. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 3 of 3)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
INSTIs	EVG	• Co-formulated with cobi/TDF/FTC • Once daily dosing • Non-inferior to EFV/TDF/FTC and ATV/r plus TDF/FTC	• EVG is only recommended for patients with baseline CrCl ≥70 mL/min; therapy 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 can be reduced by simultaneous administration with antacids containing polyvalent cations, such as Al^{+++} or Mg^{++} (see dosing recommendations in Table 18d). • Cobi inhibits active tubular secretion of creatinine and can increase serum creatinine, without affecting renal glomerular function. • Has potential for new onset or worsening of renal impairment • May have lower genetic barrier to resistance than seen with boosted PI- or DTG-based regimens • Food requirement
	RAL	• Longest post marketing experience in comparison to other INSTIs • No food requirement • No CYP3A4 interactions	• Twice-daily dosing • May have lower genetic barrier to resistance than seen with boosted PI- or DTG-based regimens • Increase in creatine kinase, myopathy, and rhabdomyolysis have been reported. • Rare cases of severe hypersensitivity reactions (including SJS and TEN) have been reported. • Metal-containing antacids can reduce the absorption of RAL. Co-administration of RAL with Al^{+++} and/or Mg^{++}-containing antacids is not recommended. RAL may be co-administered with $CaCO_3$ containing antacids (see dosing recommendations in Table 18d). • UGT substrate: potential for drug interactions (see Table 18d)

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; Al^{+++} = aluminum; ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; BMD = bone mineral density; $CaCO_3$ = Calcium carbonate; CNS = central nervous system; cobi= cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; LPV/r = ritonavir-boosted lopinavir; Mg^{++} = magnesium; MI = myocardial infarction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson syndrome; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrosis

Table 8. Antiretroviral Components or Regimens Not Recommended as Initial Therapy (page 1 of 2)

ARV Drugs or Components	Reasons for Not Recommending as Initial Therapy
NRTIs	
ABC/3TC/ZDV (Co-Formulated) As triple-NRTI combination regimen	• Inferior virologic efficacy
ABC plus 3TC plus ZDV plus TDF As quadruple-NRTI combination regimen	• Inferior virologic efficacy
d4T plus 3TC	• Significant toxicities including lipoatrophy; peripheral neuropathy; and hyperlactatemia, including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis
ddI plus 3TC (or FTC)	• Inferior virologic efficacy • Limited clinical trial experience in ART-naive patients • ddI toxicities such as pancreatitis, peripheral neuropathy
ddI plus TDF	• High rate of early virologic failure • Rapid selection of resistance mutations • Potential for immunologic nonresponse/CD4 cell decline • Increased ddI drug exposure and toxicities
ZDV/3TC	• ZDV/3TC is generally not recommended as initial therapy because greater toxicities (including bone marrow suppression; GI toxicities; and mitochondrial toxicities such as lipoatrophy, lactic acidosis, and hepatic steatosis; skeletal muscle myopathy, and cardiomyopathy) than Recommended NRTIs.
NNRTIs	
DLV	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
ETR	• Insufficient data in ART-naive patients
NVP	• Associated with serious and potentially fatal toxicity (hepatic events, severe rash, including SJS and TEN) • When compared to EFV, NVP did not meet non-inferiority criteria
PIs	
ATV (Unboosted)	• Less potent than boosted ATV
DRV (Unboosted)	• Use without RTV has not been studied
FPV (Unboosted) or **FPV/r**	• Virologic failure with unboosted FPV-based regimen may result in selection of mutations that confer resistance to DRV. • Less clinical trial data for FPV/r than for other PI/r
IDV (Unboosted)	• Inconvenient dosing (three times daily with meal restrictions) • Fluid requirement • IDV toxicities such as nephrolithiasis, crystalluria
IDV/r	• Fluid requirement • IDV toxicities such as nephrolithiasis, crystalluria
NFV	• Inferior virologic efficacy • Diarrhea

Table 8. Antiretroviral Components or Regimens Not Recommended as Initial Therapy (page 2 of 2)

ARV Drugs or Components	Reasons for Not Recommending as Initial Therapy
NRTIs	
RTV as sole PI	• High pill burden • GI intolerance • Metabolic toxicity
SQV (Unboosted)	• Inadequate bioavailability • Inferior virologic efficacy
SQV/r	• High pill burden • Can cause QT and PR prolongation; requires pre-treatment and follow-up ECG
TPV/r	• Inferior virologic efficacy • Higher rate of adverse events than other PI/r • Higher dose of RTV required for boosting than other PI/r
CCR5 Antagonist	
Maraviroc	• Requires testing for CCR5 tropism before initiation of therapy • No virologic benefit when compared with other recommended regimens • Requires twice-daily dosing

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; d4T = stavudine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; ETR = etravirine; FPV = fosamprenavir; FPV/r = ritonavir-boosted fosamprenavir; FTC = emtricitabine; GI = gastrointestinal; IDV = indinavir; MVC = maraviroc; NFV = nelfinavir; NVP = nevirapine; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; SJS = Stevens Johnson Syndrome; SQV = saquinavir; SQV/r = ritonavir-boosted saquinavir; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; ZDV = zidovudine

Table 9. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time (page 1 of 2)

	Rationale	Exception
Antiretroviral Regimens Not Recommended		
Monotherapy with NRTI (AII)	• Rapid development of resistance • Inferior ARV activity when compared with combination of three or more ARV agents	• No exception
Dual-NRTI regimens (AI)	• Rapid development of resistance • Inferior ARV activity when compared with combination of three or more ARV agents	• No exception
Triple-NRTI regimens (AI) except for ABC/ZDV/3TC (BI) or possibly TDF + ZDV/3TC (BII)	• High rate of early virologic nonresponse seen when triple-NRTI combinations, including ABC/TDF/3TC and TDF/ddI/3TC, were used as initial regimen in ART-naive patients. • Other triple-NRTI regimens have not been evaluated.	• ABC/ZDV/3TC **(BI)** and possibly TDF + ZDV/3TC **(BII)** in patients in whom other combinations are not desirable
Antiretroviral Components Not Recommended as Part of an Antiretroviral Regimen		
ATV + IDV (AIII)	• Potential additive hyperbilirubinemia	• No exception
ddI + d4T (AII)	• High incidence of toxicities: peripheral neuropathy, pancreatitis, and hyperlactatemia • Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women	• No exception
ddI + TDF (AII)	• Increased ddI concentrations and serious ddI-associated toxicities • Potential for immunologic nonresponse and/or CD4 cell count decline • High rate of early virologic failure • Rapid selection of resistance mutations at failure	• Clinicians caring for patients who are clinically stable on regimens containing TDF + ddI should consider altering the NRTIs to avoid this combination.
2-NNRTI combination (AI)	• When EFV combined with NVP, higher incidence of clinical adverse events seen when compared with either EFV- or NVP-based regimen. • Both EFV and NVP may induce metabolism and may lead to reductions in ETR exposure; thus, they should not be used in combination with ETR.	• No exception
EFV in first trimester of pregnancy or in women with significant childbearing potential (AIII)	• Teratogenic in nonhuman primates	• When no other ARV options are available and potential benefits outweigh the risks **(BIII)**
FTC + 3TC (AIII)	• Similar resistance profiles • No potential benefit	• No exception
ETR + unboosted PI (AII)	• ETR may induce metabolism of these PIs; appropriate doses not yet established	• No exception
ETR + RTV-boosted ATV or FPV (AII)	• ETR may alter the concentrations of these PIs; appropriate doses not yet established	• No exception
ETR + RTV-boosted TPV (AII)	• ETR concentration may be significantly reduced by RTV-boosted TPV	• No exception

Table 9. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time (page 2 of 2)

	Rationale	Exception
NVP in ARV-naive women with CD4 count >250 cells/mm^3 or men with CD4 count >400 cells/mm^3 (BI)	• High incidence of symptomatic hepatotoxicity	• If no other ARV option available; if used, patient should be closely monitored
d4T + ZDV (AII)	• Antagonistic effect on HIV-1	• No exception
Unboosted DRV, SQV, or TPV (AII)	• Inadequate bioavailability	• No exception

Acronyms: 3TC = lamivudine, ABC = abacavir, ATV = atazanavir, d4T = stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FTC = emitricitabine, IDV = indinavir, NVP = nevirapine, RTV = ritonavir, SQV = saquinavir, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

Table 10a. Trough Concentrations of Antiretroviral Drugs for Patients Who Have Drug-Susceptible Virus

Drug	Concentration (ng/mL)
Suggested minimum target trough concentrations in patients with HIV-1 susceptible to the ARV drugs[2-9]	
Fosamprenavir (FPV)	400 (measured as amprenavir concentration)
Atazanavir (ATV)	150
Indinavir (IDV)	100
Lopinavir (LPV)	1000
Nelfinavir[a] (NFV)	800
Saquinavir (SQV)	100–250
Efavirenz (EFV)	1000
Nevirapine (NVP)	3000

[a] Measurable active (M8) metabolite

Table 10b. Trough Concentrations of Antiretroviral Drugs for Treatment-Experienced Patients with Virologic Failure

Drug	Concentration (ng/mL)
Suggested minimum target trough concentrations for ART-experienced patients who have resistant HIV-1 strains	
Maraviroc (MVC)	>50
Tipranavir (TPV)	20,500
Median (Range) Trough Concentrations from Clinical Trials[12-14]	
Darunavir (DRV) (600 mg twice daily)	3300 (1255–7368)
Etravirine (ETR)	275 (81–2980)
Raltegravir (RAL)	72 (29–118)

Table 11. Identifying, Diagnosing, and Managing Acute and Recent HIV-1 Infection

- **Suspecting acute HIV infection:** Signs or symptoms of acute HIV infection with recent (within 2 to 6 weeks) high risk of exposure to HIV[a]
  - Signs/symptoms/laboratory findings may include but are not limited to one or more of the following: fever, lymphadenopathy, skin rash, myalgia/arthralgia, headache, diarrhea, oral ulcers, leucopenia, thrombocytopenia, transaminase elevation.
  - High-risk exposures include sexual contact with an HIV-infected person or a person at risk of HIV infection, sharing injection drug use paraphernalia, or contact of mucous membranes or breaks in skin with potentially infectious fluids.
- **Differential diagnosis:** Includes but is not limited to viral illnesses such as Epstein-Barr virus (EBV)- and non-EBV (e.g., cytomegalovirus) infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, or syphilis.
- **Evaluation/diagnosis of acute HIV infection:**
  - Acute infection is defined as detectable HIV RNA or p24 antigen (the antigen used in currently available HIV antigen/antibody [Ag/Ab] combination assays), in serum or plasma in the setting of a negative or indeterminate HIV antibody test result
    - A reactive HIV antibody test or Ag/Ab test must be followed by supplemental confirmatory testing.
    - A negative or indeterminate HIV antibody test in a person with a positive Ag/Ab test or in whom acute HIV infection is suspected requires assessment of plasma HIV RNA[b] to assess for acute HIV infection.
    - A positive plasma HIV RNA test in the setting of a negative or indeterminate antibody result is consistent with acute HIV infection.
  - Patients presumptively diagnosed with acute HIV infection should have serologic testing repeated over the next 3 to 6 months to document seroconversion.
- **Considerations for antiretroviral therapy (ART) during early HIV infection:**
  - All pregnant women with early HIV infection should begin taking combination ART as soon as possible because of the high risk of perinatal HIV transmission **(AI)**.
  - Treatment for early HIV infection should be offered to all non-pregnant persons **(BII)**.
  - The risks of ART during early HIV infection are largely the same as those for ART initiated in chronically infected asymptomatic patients with high CD4 counts.
  - If therapy is initiated, the goal should be sustained plasma virologic suppression **(AIII)**.
  - Providers should consider enrolling patients with early HIV infection in clinical studies.

[a] In some settings, behaviors conducive to acquisition of HIV infection might not be ascertained or might not be perceived as high risk by the health care provider or the patient or both. Thus, symptoms and signs consistent with acute retroviral syndrome should motivate consideration of this diagnosis even in the absence of reported high-risk behaviors.

[b] Plasma HIV RNA can be measured by a variety of quantitative assays, including branched DNA (bDNA) and reverse transcriptase-polymerase chain reaction (RT-PCR)-based assays as well as by a qualitative transcription-mediated amplification assay (APTIMA, GenProbe).

Table 12. Drug Interactions between Antiretroviral Agents and Drugs Used to Treat Opioid Addiction (page 1 of 2)

Concomitant Drug	Antiretroviral Drug	Pharmacokinetic Interactions Clinical Comments/Recommendations
Buprenorphine	EFV	buprenorphine AUC ↓ 50%; norbuprenorphine[a] AUC ↓ 71% No withdrawal symptoms reported. No dosage adjustment recommended; however, monitor for withdrawal symptoms.
	ETR	buprenorphine AUC ↓ 25% No dosage adjustment necessary.
	ATV	buprenorphine AUC ↑ 93%; norbuprenorphine AUC ↑ 76%; ↓ ATV levels possible Do not co-administer buprenorphine with unboosted ATV.
	ATV/r	buprenorphine AUC ↑ 66%; norbuprenorphine AUC ↑ 105% Monitor for sedation. Buprenorphine dose reduction may be necessary.
	DRV/r	buprenorphine: no significant effect; norbuprenorphine AUC ↑ 46% and C_{min} ↑ 71% No dose adjustment necessary.
	FPV/r	buprenorphine: no significant effect; norbuprenorphine AUC ↓ 15% No dosage adjustment necessary.
	TPV/r	buprenorphine: no significant effect; norbuprenorphine AUC, C_{max}, and C_{min} ↓ 80%; TPV C_{min} ↓ 19%–40% Consider monitoring TPV level.
	3TC, ddI, TDF, ZDV, NVP, LPV/r, NFV	No significant effect No dosage adjustment necessary.
	ABC, d4T, FTC, ETR, IDV +/- RTV, SQV/r, RAL, MVC, T20	No data
Methadone	ABC	methadone clearance ↑ 22% No dosage adjustment necessary.
	d4T	d4T AUC ↓ 23% and C_{max} ↓ 44% No dosage adjustment necessary.
	ZDV	ZDV AUC ↑ 29%–43% Monitor for ZDV-related adverse effects.
	EFV	methadone AUC ↓ 52% Opioid withdrawal common; increased methadone dose often necessary.

Table 12. Drug Interactions between Antiretroviral Agents and Drugs Used to Treat Opioid Addiction (page 2 of 2)

Methadone, cont'd	NVP	methadone AUC ↓ 41% NVP: no significant effect Opioid withdrawal common; increased methadone dose often necessary.
	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	With ATV/r, DRV/r, FPV/r: R-methadone[b] AUC ↓ 16%–18%; With LPV/r: methadone AUC ↓ 26%–53%; With SQV/r 1000/100 mg BID: R-methadone AUC ↓ 19%; With TPV/r: R-methadone AUC ↓ 48% Opioid withdrawal unlikely but may occur. Adjustment of methadone dose usually not required; however, monitor for opioid withdrawal and increase methadone dose as clinically indicated.
	FPV	No data with FPV (unboosted) With APV: R-methadone C_{min} ↓ 21%, no significant change in AUC Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
	NFV	methadone AUC ↓ 40% Opioid withdrawal rarely occurs. Monitor and titrate dose as clinically indicated. May require increased methadone dose.
	ddI (EC capsule), 3TC, TDF, ETR, RTV, ATV, IDV, RAL	No significant effect No dosage adjustment necessary.
	FTC, MVC, T20	No data

[a] Norbuprenorphine is an active metabolite of buprenorphine.
[b] R-methadone is the active form of methadone.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, APV = amprenavir, ATV = atazanavir, ATV/r = atazanavir/ ritonavair, AUC = area under the curve, BID = twice daily, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, d4T = stavudine, ddI = didanosine, DRV/r = darunavir/ritonavir, EC = enteric coated, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, IDV = indinavir, IDV/r = indinavir/ritonavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NVP = nevirapine, RAL = raltegravir, RTV = ritonavir, SQV/r = sacquinavir/ritonavir, T20 = enfuvirtide, TDF = tenofovir, TPV = tipranavir, TPV/r = tipranavir/ritonavir, ZDV = zidovudine

Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care
(page 1 of 3)

Strategies	Examples
Use a multidisciplinary team approach. Provide an accessible, trustworthy health care team.	• Nonjudgmental providers, nurses, social workers, pharmacists, and medication managers
Strengthen early linkage to care and retention in care.	• Encourage healthcare team participation in linkage to and retention in care.
Assess patient readiness to start ART.	
Evaluate patient's knowledge about HIV disease, prevention and treatment and, on the basis of the assessment, provide HIV-related information.	• Considering the patient's current knowledge base, provide information about HIV, including the natural history of the disease, HIV viral load and CD4 count and expected clinical outcomes according to these parameters, and therapeutic and prevention consequences of non-adherence.
Identify facilitators, potential barriers to adherence, and necessary medication management skills before starting ART medication.	• Assess patient's cognitive competence and impairment. • Assess behavioral and psychosocial challenges including depression, mental illnesses, levels of social support, high levels of alcohol consumption and active substance use, non-disclosure of HIV serostatus and stigma. • Identify and address language and literacy barriers. • Assess beliefs, perceptions, and expectations about taking ART (e.g., impact on health, side effects, disclosure issues, consequences of non-adherence). • Ask about medication taking skills and foreseeable challenges with adherence (e.g., past difficulty keeping appointments, adverse effects from previous medications, issues managing other chronic medications, need for medication reminders and organizers). • Assess structural issues including unstable housing, lack of income, unpredictable daily schedule, lack of prescription drug coverage, lack of continuous access to medications.
Provide needed resources.	• Provide or refer for mental health and/or substance abuse treatment. • Provide resources to obtain prescription drug coverage, stable housing, social support, and income and food security.

Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care
(page 2 of 3)

Strategies	Examples
Involve the patient in ARV regimen selection.	• Review regimen potency, potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of nonadherence. • Assess daily activities and tailor regimen to predictable and routine daily events. • Consider preferential use of PI/r-based ART if poor adherence is predicted. • Consider use of fixed-dose combination formulation. • Assess if cost/co-payment for drugs can affect access to medications and adherence.
Assess adherence at every clinic visit.	• Monitor viral load as a strong biologic measure of adherence. • Use a simple behavioral rating scale. • Employ a structured format that normalizes or assumes less-than-perfect adherence and minimizes socially desirable or "white coat adherence" responses. • Ensure that other members of the health care team also assess adherence.
Use positive reinforcement to foster adherence success.	• Inform patients of low or non-detectable levels of HIV viral load and increases in CD4 cell counts. • When needed, consider providing incentives and rewards for achieving high levels of adherence and treatment success.
Identify the type of and reasons for nonadherence.	• Failure to fill the prescription(s) • Failure to understand dosing instructions • Complexity of regimen (e.g., pill burden, size, dosing schedule, food requirements) • Pill aversion • Pill fatigue • Adverse effects • Inadequate understanding of drug resistance and its relationship to adherence • Cost-related issues • Depression, drug and alcohol use, homelessness, poverty • Stigma • Non-disclosure • Other potential barriers
Select from among available effective treatment adherence interventions.	• See http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm. • Use adherence-related tools to complement education and counseling interventions (e.g., pill boxes, dose planners, reminder devices). • Use community resources to support adherence (e.g., visiting nurses, community workers, family, peer advocates). • Use patient prescription assistance programs. • Use motivational interviews.

Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care
(page 3 of 3)

Strategies	Examples
Systematically monitor retention in care.	• Record and follow up on missed visits.
On the basis of any problems identified through systematic monitoring, consider options to enhance retention in care given resources available.	• Provide outreach for those patients who drop out of care. • Use peer or paraprofessional treatment navigators. • Employ incentives to encourage clinic attendance or recognize positive clinical outcomes resulting from good adherence. • Arrange for directly observed therapy (if feasible).

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 1 of 7)

See Appendix B for additional information listed by drug. Empty cells in the table may mean that there are no reported cases for the particular side effect or that data for the specific ARV drug class are not available.

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Bleeding Events	N/A	N/A	PIs: Increased spontaneous bleeding, hematuria in patients with hemophilia reported with some PIs TPV: Reports of intracranial hemorrhage. Risks include CNS lesions, trauma, surgery, hypertension, alcohol abuse, coagulopathy, and concomitant use of anti-coagulant or anti-platelet agents, including vitamin E	N/A	N/A
Bone Density Effects	TDF: Associated with greater loss of BMD than ZDV, d4T, and ABC. Osteomalacia reported in association with proximal renal tubulopathy.	Decreases in BMD observed in studies of regimens containing different NRTIs combined with NNRTIs, PIs, or INSTIs.			N/A
Bone Marrow Suppression	ZDV: Anemia, neutropenia	N/A	N/A	N/A	N/A
CVD	ABC and ddI: Associated with an increased risk of MI in some, but not all, cohort studies. Absolute risk is greatest in patients with traditional CVD risk factors.	N/A	PIs: Associated with MI and stroke in some cohort studies. Data on newer PIs (ATV, DRV, and TPV) are limited. SQV/r, ATV/r, and LPV/r: PR interval prolongation. Risks include structural heart disease, conduction system abnormalities, cardiomyopathy, ischemic heart disease, and co-administration with drugs that prolong PR interval. SQV/r: QT interval prolongation in patients in a healthy volunteer study. Risks include underlying heart conditions, pre-existing prolonged QT or arrhythmia, or use with other QT-prolonging drugs. ECG is recommended before SQV initiation and should be considered during therapy.	N/A	N/A

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 2 of 7)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Cholelithiasis	N/A	N/A	ATV: • History of kidney stones increases risk. • Patients may present with cholelithiasis and kidney stones concurrently. • Typically presents as abdominal pain. • Reported complications include cholecystitis, pancreatitis, choledocholithiasis, and cholangitis. • Median time to onset is 42 months (range 1 to 90 months).	N/A	N/A
DM/Insulin Resistance	ZDV, d4T, and ddI	N/A	Reported for some PIs (IDV, LPV/r), but not all PIs	N/A	N/A
Dyslipidemia	d4T > ZDV > ABC: ↑LDL and TG	EFV: ↑TG, ↑LDL, ↑HDL	↑LDL, ↑TG, ↑HDL: All RTV-boosted PIs ↑TG: LPV/r = FPV/r and LPV/r > DRV/r and ATV/r	EVG/cobi/TDF/FTC: ↑TG, ↑LDL, ↑HDL	N/A
GI Effects	Nausea and vomiting: ddI and ZDV > other NRTIs Pancreatitis: ddI	N/A	GI intolerance (e.g., diarrhea, nausea, vomiting) Diarrhea: Common with NFV; also seen with LPV/r > DRV/r and ATV/r	Nausea and diarrhea: EVG/cobi/TDF/FTC	N/A

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 3 of 7)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Hepatic Effects	Reported with most NRTIs ddI: Prolonged exposure has been linked to non-cirrhotic portal hypertension, including some cases with esophageal varices. Steatosis: Most commonly seen with ZDV, d4T, or ddI Flares: HIV/HBV-co-infected patients may develop severe hepatic flares when TDF, 3TC, and FTC are withdrawn or when HBV resistance develops.	NVP > Other NNRTIs NVP: • Severe hepatotoxicity with NVP is often associated with skin rash or symptoms of hypersensitivity. • In ARV-naive patients, risk is greater for women with pre-NVP CD4 count >250 cells/mm^3 and men with pre-NVP CD4 count >400 cells/mm^3. Overall risk is higher for women than men. • Risk is greatest in the first few months of treatment. • 2-week dose escalation of NVP reduces risk of rash and possibly hepatotoxicity if related to hypersensitivity. • NVP is contraindicated in patients with moderate to severe hepatic insufficiency (Child-Pugh classification B or C). • Liver failure observed in HIV-uninfected individuals receiving NVP for post-exposure prophylaxis. NVP should **never** be used for this indication.	All PIs: Drug-induced hepatitis and hepatic decompensation (and rare cases of fatalities) have been reported with all PIs. The frequency of hepatic events is higher with TPV/r than with other PIs. IDV, ATV: Jaundice due to indirect hyperbilirubinemia TPV/r: Contraindicated in patients with moderate to severe hepatic insufficiency (Child Pugh classification B or C)	N/A	MVC: Hepatotoxicity with or without rash or HSRs reported

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 4 of 7)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
HSR Excluding rash alone or SJS	ABC: • HLA-B*5701 screening should be performed before initiation of ABC. ABC should not be started if the HLA-B*5701 test result is positive. • Symptoms of HSR (in descending frequency): fever, skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms • Symptoms worsen with continuation of ABC. • Median onset of reactions is 9 days; approximately 90% of reactions occur within the first 6 weeks of treatment. • Patients, regardless of HLA-B*5701 status, should not be re-challenged with ABC if HSR is suspected.	NVP: • Hypersensitivity syndrome of hepatic toxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction. • In ARV-naive patients, risk is greater for women with pre-NVP CD4 count >250 cells/mm^3 and men with pre-NVP CD4 count >400 cells/mm^3. Overall, risk is higher for women than men. • 2-week dose escalation of NVP reduces risk.	N/A	RAL: HSR reported when RAL given in combination with other drugs known to cause HSR. All ARVs should be stopped if HSR occurs. DTG: Reported in <1% of patients in clinical development program	MVC: Reported as part of a syndrome related to hepatotoxicity

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 5 of 7)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Lactic Acidosis	NRTIs, Especially d4T, ZDV, and ddI: • Insidious onset with GI prodrome, weight loss, and fatigue. May be rapidly progressive with tachycardia, tachypnea, jaundice, muscular weakness, mental status changes, respiratory distress, pancreatitis, and organ failure. • Mortality up to 50% in some case series, especially in patients with serum lactate >10 mmol/L • Females and obese patients at increased risk Laboratory Findings: • ↑ lactate (often >5 mmol/L), anion gap, AST, ALT, PT, bilirubin • ↑ amylase and lipase in patients with pancreatitis • ↓ arterial pH, serum bicarbonate, serum albumin	N/A	N/A	N/A	N/A
Lipodystrophy	Lipoatrophy: Thymidine analogs (d4T > ZDV). May be more likely when NRTIs combined with EFV than with a RTV-boosted PI.	Lipohypertophy: Trunk fat increase observed with EFV-, PI-, and RAL-containing regimens; however, causal relationship has not been established.			N/A
Myopathy/ Elevated CPK	ZDV: Myopathy	N/A	N/A	RAL: ↑ CPK Muscle weakness and rhabdomyolysis	N/A

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 6 of 7)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Nervous System/ Psychiatric Effects	Peripheral neuropathy (pain and/or paresthesia, lower extremities > upper extremities): d4T > ddI and ddC (can be irreversible) d4T: Associated with rapidly progressive, ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare)	EFV: Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, and suicidal ideation. Symptoms usually subside or diminish after 2–4 weeks. Bedtime dosing may reduce symptoms. Risks include history of psychiatric illness, concomitant use of agents with neuropsychiatric effects, and increased plasma EFV concentrations because of genetic factors or increased absorption with food. An association between EFV and suicidal ideation, suicide, and attempted suicide (especially among younger patients and those with history of mental illness or substance abuse) was found in one retrospective analysis of several comparative trials.	N/A	All INSTIs: insomnia RAL: Depression and suicidal ideation (uncommon)	N/A
Rash	FTC: Hyperpigmentation	All NNRTIs	ATV, DRV, FPV, LPV/r, TPV	RAL, EVG/cobi/ TDF/FTC: Uncommon	MVC
Renal Effects/ Urolithiasis	TDF: ↑ SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, non-anion gap metabolic acidosis Concurrent use with PI appears to increase risk.	N/A	ATV and LPV/r: Associated with increased risk of chronic kidney disease in a large cohort study. IDV: ↑ SCr, pyuria; hydronephrosis or renal atrophy IDV, ATV: Stone, crystal formation; adequate hydration may reduce risk.	cobi (a component of EVG/cobi/TDF/ FTC) and DTG: Can increase SCr by reducing tubular secretion of Cr without reducing renal glomerular function; however, assess for renal dysfunction, especially if SCr increase by >0.4 mg/dL.	N/A

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 7 of 7)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
SJS/TEN	ddI, ZDV: Reported cases	NVP > DLV, EFV, ETR, RPV	FPV, DRV, IDV, LPV/r, ATV: Reported cases	RAL	N/A

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ALT = alanine aminotransferase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; BMD = bone mineral density; CrCl = creatinine clearance; CNS = central nervous system; cobi= cobicistat; CPK = creatine phosphokinase; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delavirdine; DM = diabetes mellitus; DRV = darunavir; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FPV/r = ritonavir-boosted fosamprenavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = ritonavir-boosted lopinavir; MI = myocardial infarction; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PT = prothrombin time; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr. = serum creatinine; SJS = Stevens-Johnson syndrome; SQV = saquinavir; SQV/r = ritonavir-boosted saquinavir; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrosis; TG = triglyceride; TPV = tipranavir; TPV/r = ritonavir-boosted tipranavir; ZDV = zidovudine

Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 1 of 3)

Switching a successful ARV regimen should be done carefully and only when the potential benefits of the change outweigh the potential complications of altering treatment. The fundamental principle of regimen switching is to maintain viral suppression. Before any treatment switch is implemented, it is critical to review the patient's medical and full ARV history including the patient's prior virologic responses, resistance test results, viral tropism (when MVC is being considered), HLA B*5701 status (when ABC is being considered), co-morbidities, adherence history, concomitant medications and supplements and their potential for drug interactions, and prior intolerances to any ARV drugs.

Adverse Event	ARV Agent(s)/Drug Class		Comments
	Switch from	Switch to	
Bone Density Effects	TDF[a]	ABC[b]	Declines in BMD have been observed with the start of most ART. Modification of ART because of reduced BMD should be predicated on the clinical significance of the decline. Switching from TDF to alternative ARV agents has been shown to increase bone density, but the clinical significance of this increase remains uncertain.
Bone Marrow Suppression Anemia, leukopenia	ZDV	TDF or ABC[b]	N/A
CNS/Neuropsychiatric Side Effects Dizziness, suicidal ideation, sleep disturbance, abnormal dreams, depression	EFV	Alternative NNRTI (RPV, ETR, NVP), a PI, or an INSTI	In most patients, EFV-related CNS effects subside within 4 weeks after initiation of the drug. Persistent or intolerable effects should prompt substitution of EFV with an alternate ARV agent.
Dyslipidemia Hypertriglyceridemia (with or without high low-density LDL level)	RTV- or cobi-boosted regimens or EFV	RAL, DTG, RPV, NVP, or unboosted ATV[c]	Elevated TG and LDL levels are more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improved TG and LDL levels have been seen following a switch from LPV/r to RTV-boosted and -unboosted ATV.[c]
GI Effects Nausea, diarrhea	LPV/r	ATV/r, DRV/r, RAL, DTG, EVG/cobi/TDF/FTC	GI intolerance is relatively common with boosted PIs and is linked to the total dose of RTV. More GI toxicity is seen with LPV/r than with ATV/r or DRV/r. GI effects are often transient in nature, and do not warrant switching therapy. If GI adverse effects are persistent or intolerable, consider drug substitution.
	Other RTV-boosted regimens or EVG/cobi/TDF/FTC	RAL, DTG, unboosted ATV,[c] NNRTIs	In a trial of treatment-naive patients, rates of diarrhea and nausea were similar for boosted EVG/cobi/TDF/FTC and ATV/r plus TDF/FTC.

Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 2 of 3)

Adverse Event	ARV Agent(s)/Drug Class		Comments
	Switch from	Switch to	
HSR	ABC	TDF	Never re-challenge with ABC following a suspected HSR, regardless of the patient's HLA B*5701 status.
	NVP, EFV, ETR, RPV	Non-NNRTI ART	Risk of HSR with NVP is higher for women and those with high CD4 cell counts.
	DTG, RAL MVC	Non-INSTI ART Suitable alternative ART	Reactions to NVP, ETR, RAL, DTG and MVC may be accompanied by elevated liver transaminases.
Insulin Resistance	LPV/r, FPV/r	NNRTI (NVP or RPV), INSTI, unboosted ATV[c]	Results of switch studies have been inconsistent. Studies in HIV-negative patients given short courses of a PI suggest a direct causal effect of LPV/r (and IDV) on insulin resistance. However, traditional risk factors, such as obesity and family history of diabetes, may be stronger risk factors for insulin resistance than use of any PIs.
Jaundice and Icterus	ATV, ATV/r	DRV/r, INSTI, or NNRTI	Increases in unconjugated bilirubin are commonly seen with ATV and generally do not require modification of therapy unless jaundice/icterus is distressing to the patient.
Lipoatrophy Subcutaneous fat wasting of limbs, face, buttocks	d4T, ZDV	TDF or ABC[b]	Peripheral lipoatrophy is a legacy of prior thymidine analog (d4T and ZDV) use. Switching from these ARVs prevents worsening lipoatrophy, but fat recovery is typically slow, incomplete, and may take years.
Lipohypertrophy Accumulation of visceral abdominal, truncal, dorsocervical, and breast fat	Lipohypertrophy has been observed during ART, particularly during use of older PI-based regimens (e.g., IDV), but whether ART directly causes increases in fat depots remains unclear. There is no clinical evidence that switching to any currently recommended first line regimen will reverse weight or visceral fat gain.		
Rash	NNRTIs (especially NVP and EFV)	PI- or INSTI- based regimen	Rash can be seen with any NNRTI but occurs more frequently and is more severe with use of NVP, followed by EFV. Mild rashes developing after initiation of NNRTIs other than NVP rarely require treatment switch. When serious rash develops with use of any NNRTI, a switch to an agent from another ARV drug class is recommended.
	DRV/r	ATV/r or another class, such as INSTI	Mild rashes following DRV/r initiation do not necessarily require treatment switch. Close follow-up until the rash subsides is recommended. For more severe reactions, therapy can be changed to an alternative RTV-boosted PI or an agent from another drug class.

Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 3 of 3)

Adverse Event	ARV Agent(s)/Drug Class		Comments
	Switch from	Switch to	
Renal Effects Including proximal renal tubulopathy, elevated creatinine	TDF [a]	ABC [b]	Phosphate wasting as a consequence of TDF nephrotoxicity may lead to osteomalacia.
	ATV/r, LPV/r	DTG, RAL, or NNRTI	cobi and DTG, and to a lesser extent RTV, RPV, and RAL, can increase SCr soon after treatment initiation because of inhibition of tubular secretion of creatinine. This effect does not affect glomerular filtration. However, assess for renal dysfunction, especially if SCr increases by >0.4 mg/dL.
Stones Nephrolithiasis and cholelithiasis	ATV, ATV/r	DRV/r, INSTI, or NNRTI	Nephrolithiasis (a frequent complication of IDV) has been observed with ATV. Cholelithiasis is also reported with ATV.

[a] For patients with chronic active HBV infection, another agent active against HBV should be added to substitute for TDF.

[b] ABC should be used only in patients known to be HLA-B*5701 negative.

[c] TDF reduces ATV levels; therefore, unboosted ATV should not be co-administered with TDF. Long term data for unboosted ATV are unavailable.

Key to Abbreviations: ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; BMD = bone mineral density; CNS = central nervous system; cobi = cobicistat; d4T = stavudine; ddI = didanosine; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV/r = ritonavir-boosted fosamprenavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = ritonavir-boosted lopinavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; TDF = tenofovir disoproxil fumarate; TG = triglycerides; ZDV = zidovudine

Table 16: Monthly Average Wholesale Price[a] of Antiretroviral Drugs (Last updated January 2014; last reviewed January 2014) (page 1 of 4)

ARV Drug (Generic and Brand Names)	Strength	Dosing	Tablets/Capsules/ mLs per Month	AWP[a] (Monthly)
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)				
Abacavir				
• Generic	300 mg tab	2 tabs daily	60 tabs	$602.66
• Ziagen	300 mg tab	2 tabs daily	60 tabs	$670.30
• Ziagen	20 mg/mL soln	30 mL daily	900 mL	$660.86
Didanosine Delayed-Release				
• Generic	400 mg cap	1 cap daily	30 caps	$368.72
• Videx EC	400 mg cap	1 cap daily	30 caps	$515.84
Emtricitabine				
• Emtriva	200 mg cap	1 cap daily	30 tabs	$602.27
• Emtriva	10 mg/mL soln	24 mL daily	680 mL (28-day supply)	$568.88
Lamivudine				
• Generic	300 mg tab	1 tab daily	30 tabs	$429.66
• Epivir	300 mg tab	1 tab daily	30 tabs	$498.89
• Epivir	10 mg/mL soln	30 mL daily	900 mL	$498.90
Stavudine				
• Generic	40 mg cap	1 cap twice daily	60 caps	$410.70
• Zerit	40 mg cap	1 cap twice daily	60 caps	$553.12
Tenofovir				
• Viread	300 mg tab	1 tab daily	30 tabs	$1,047.73
Zidovudine				
• Generic	300 mg tab	1 tab twice daily	60 tabs	$360.97
• Retrovir	300 mg tab	1 tab twice daily	60 tabs	$476.70

Table 16: Monthly Average Wholesale Price[a] of Antiretroviral Drugs (Last updated January 2014; last reviewed January 2014) (page 2 of 4)

ARV Drug (Generic and Brand Names)	Strength	Dosing	Tablets/Capsules/ mLs per Month	AWP[a] (Monthly)
NRTI Combination Products				
Abacavir/Lamivudine				
• Epzicom	600/300 mg tab	1 tab daily	30 tabs	$1,239.41
Tenofovir Disoproxil Fumarate/ Emtricitabine				
• Truvada	300/150 mg tab	1 tab daily	30 tabs	$1,539.90
Zidovudine/Lamivudine				
• Generic	300/150 mg tab	1 tab twice daily	60 tabs	$931.61
• Combivir	300/150 mg tab	1 tab twice daily	60 tabs	$1,081.70
Abacavir Sulfate/Zidovudine/ Lamivudine				
• Generic	300/300/150 mg tab	1 tab twice daily	60 tabs	$1,738.46
• Trizivir	300/300/150 mg tab	1 tab twice daily	60 tabs	$1,931.64
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)				
Efavirenz				
• Sustiva	600 mg tab	1 tab daily	30 tabs	$862.14
Etravirine				
• Intelence	200 mg tab	1 tab twice daily	60 tabs	$1,123.52
Nevirapine				
• Generic	200 mg tab	1 tab twice daily	60 tabs	$650.05
• Viramune	200 mg tab	1 tab twice daily	60 tabs	$812.45
• Viramune XR (nevirapine extended release)	400 mg tab	1 tab daily	30 tabs	$753.52
Rilpivirine				
• Endurant	25 mg tab	1 tab daily	30 tabs	$923.47
Protease Inhibitors (PIs)				
Atazanavir				
• Reyataz	150 mg cap[b]	2 caps daily	60 caps	$1,422.83
• Reyataz	200 mg cap	2 caps daily	60 caps	$1,422.83
• Reyataz	300 mg cap[b]	1 cap daily	30 caps	$1,409.39
Darunavir				
• Prezista	600 mg tab[b]	1 tab twice daily	60 tabs	$1,399.25
• Prezista	800 mg tab[b]	1 tab daily	30 tabs	$1,399.25
• Prezista	100 mg/mL soln[b]	8 mL daily 6 mL twice daily	240 mL 360 mL	$932.83 $1,399.25
Fosamprenavir				
• Lexiva	700 mg tab	2 tabs twice daily	120 tabs	$2,088.40
• Lexiva	700 mg tab	1 tab twice daily[b]	60 tabs	$1,044.20
• Lexiva	700 mg tab	2 tabs once daily[b]	60 tabs	$1,044.20

Table 16: Monthly Average Wholesale Price[a] of Antiretroviral Drugs (Last updated January 2014; last reviewed January 2014) (page 3 of 4)

ARV Drug (Generic and Brand Names)	Strength	Dosing	Tablets/Capsules/ mLs per Month	AWP[a] (Monthly)
Protease Inhibitors (PIs), continued				
Lopinavir/Ritonavir				
• Kaletra	200 mg/50 mg tab	2 tabs twice daily or 4 tabs once daily	120 tabs	$977.22
• Kaletra	80 mg/20 mg per mL soln	5 mL twice daily	300 mL	$916.13
Ritonavir Total Daily Dose Depends On Concomitant PI				
• Norvir	100 mg tab	1 tab once daily	30 tabs	$308.60
• Norvir	100 mg tab	1 tab twice daily	60 tabs	$617.20
• Norvir	100 mg tab	2 tabs twice daily	120 tabs	$1,234.40
Saquinavir				
• Invirase	500 mg tab[b]	2 tabs twice daily	120 tabs	$1,177.58
Tipranavir				
• Aptivus	250 mg cap[b]	2 caps twice daily	120 caps	$1,500.17
Integrase Strand Transfer Inhibitors (INSTIs) Please refer to Co-formulated Combination Antiretroviral Drugs for cost of elvitegravir/cobicistat/tenofovir/emtricitabine (Stribild)				
Dolutegravir				
• Tivicay	50 mg tab	1 tab once daily	30 tabs	$1,410.48
• Tivicay	50 mg tab	1 tab twice daily	60 tabs	$2,820.96
Raltegravir				
• Isentress	400 mg tab	1 tab twice daily	60 tabs	$1,352.05
Fusion Inhibitor				
Enfuviritide				
• Fuzeon	90 mg injection kit	1 injection twice daily	60 doses (1 kit)	$3,513.49
CCR5 Antagonist				
Maraviroc				
• Selzentry	150 mg tab	1 tab twice daily	60 tabs	$1,297.62
• Selzentry	300 mg tab	1 tab twice daily	60 tabs	$1,297.62
• Selzentry	300 mg tab	2 tabs twice daily	120 tabs	$2,595.24
Co-Formulated Combination Products as Complete Antiretroviral Regimens				
Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine				
• Atripla	600/300/200 mg tab	1 tab daily	30 tabs	$2,402.04
Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine				
• Complera	25/300/200 mg tab	1 tab daily	30 tabs	$2,463.37
Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/ Emtricitabine				
• Stribild	150/150/300/200 mg tab	1 tab daily	30 tabs	$2,948.70

Table 16: Monthly Average Wholesale Price[a] of Antiretroviral Drugs (Last updated January 2014; last reviewed January 2014) (page 4 of 4)

[a] AWP = Average Wholesale Price. Note that this price may not represent the pharmacy acquisition price or the price paid by consumers.

Source: Red Book Online. Available at http://aapredbook.aappublications.org. Accessed January 2014

[b] Should be used in combination with ritonavir. Please refer to Appendix B, Table 3 for ritonavir doses.

Key to Abbreviations: cap = capsule; EC = enteric coated; soln = solution; AWP = average wholesale price; tab = tablet; XR = extended release

Table 17. Drugs That Should Not Be Used With Antiretroviral Agents (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 2)

This table only lists drugs that should not be co-administered at any dose and regardless of RTV enhancing. See Tables 18 and 19 for more detailed PK interaction data.

ARV Agents and Contraindicated Drugs by Drug Category										
ARV Agents[a,b]	Cardiac Agents	Lipid-Lowering Agents	Antimyco-bacterials	GI Drugs	Neuro-leptics	Psycho-tropics	Ergot Derivatives (Vasoconstrictors)	Herbs	ARV Agents	Others
ATV +/− RTV	Amiodarone Dronedarone	Lovastatin Simvastatin	Rifampin Rifapentine[c]	Cisapride[e]	Pimozide	Midazolam[f] Triazolam	Dihydroergotamine Ergonovine Ergotamine Methylergonovine	St. John's wort	ETR NVP	Alfuzosin Irinotecan Salmeterol Sildenafil for PAH
DRV/r	Amiodarone Dronedarone	Lovastatin Simvastatin	Rifampin Rifapentine[c]	Cisapride[e]	Pimozide	Midazolam[f] Triazolam	Dihydroergotamine Ergonovine Ergotamine Methylergonovine	St. John's wort	None	Alfuzosin Salmeterol Sildenafil for PAH
FPV +/− RTV	Amiodarone Dronedarone Flecainide Propafenone	Lovastatin Simvastatin	Rifampin Rifapentine[c]	Cisapride[e]	Pimozide	Midazolam[f] Triazolam	Dihydroergotamine Ergonovine Ergotamine Methylergonovine	St. John's wort	ETR	Alfuzosin Salmeterol Sildenafil for PAH
LPV/r	Amiodarone Dronedarone	Lovastatin Simvastatin	Rifampin[d] Rifapentine[c]	Cisapride[e]	Pimozide	Midazolam[f] Triazolam	Dihydroergotamine Ergonovine Ergotamine Methylergonovine	St. John's wort	None	Alfuzosin Salmeterol Sildenafil for PAH
SQV/r	Amiodarone Dronedarone Dofetilide Flecainide Lidocaine Propafenone Quinidine	Lovastatin Simvastatin	Rifampin[d] Rifapentine[c]	Cisapride[e]	Pimozide	Midazolam[f] Triazolam Trazodone	Dihydroergotamine Ergonovine Ergotamine Methylergonovine	St. John's wort Garlic supp-lements	None	Alfuzosin Salmeterol Sildenafil for PAH
TPV/r	Amiodarone Dronedarone Flecainide Propafenone Quinidine	Lovastatin Simvastatin	Rifampin Rifapentine[c]	Cisapride[e]	Pimozide	Midazolam[f] Triazolam	Dihydroergotamine Ergonovine Ergotamine Methylergonovine	St. John's wort	ETR	Alfuzosin Salmeterol Sildenafil for PAH
EFV	None	None	Rifapentine[c]	Cisapride[e]	Pimozide	Midazolam[f] Triazolam	Dihydroergotamine Ergonovine Ergotamine Methylergonovine	St. John's wort	Other NNRTIs	None
ETR	None	None	Rifampin Rifapentine[c]	None	None	None	None	St John's wort	Unboosted PIs, ATV/r, FPV/r, or TPV/r other NNRTIs	Carbamazepine Phenobarbital Phenytoin Clopidogrel
NVP	None	None	Rifapentine[c]	None	None	None	None	St. John's wort	ATV +/- RTV DTG other NNRTIs	Ketoconazole

Table 17. Drugs That Should Not Be Used With Antiretroviral Agents (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 2)

ARV Agents and Contraindicated Drugs by Drug Category										
ARV Agents[a,b]	Cardiac Agents	Lipid-Lowering Agents	Antimyco-bacterials	GI Drugs	Neuro-leptics	Psycho-tropics	Ergot Derivatives (Vasoconstrictors)	Herbs	ARV Agents	Others
RPV	None	None	Rifabutin Rifampin Rifapentine[c]	Proton pump inhibitors	None	None	None	St. John's wort	Other NNRTIs	Carbamazepine Oxcarbazepine Phenobarbital Phenytoin
MVC	None	None	Rifapentine[c]	None	None	None	None	St. John's wort	None	None
EVG/ cobi/TDF/ FTC	None	Lovastatin Simvastatin	Rifabutin Rifampin Rifapentine[c]	Cisapride[e]	Pimozide	Midazolam[f] Triazolam	Dihydroergotamine Ergotamine Methylergonovine	St. John's wort	All other ARVs	Alfuzosin Salmeterol Sildenafil for PAH
DTG	Dofetilide	None	Rifapentine[c]	None	None	None	None	St. John's wort	NVP	Carbamazepine Oxcarbazepine Phenobarbital Phenytoin

[a] DLV, IDV, NFV, and RTV (as sole PI) are not included in this table. Refer to the appropriate FDA package insert for information regarding DLV-, IDV-, NFV-, and RTV (as sole PI)-related drug interactions.

[b] Certain listed drugs are contraindicated on the basis of theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with CYP450 3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

[c] HIV-infected patients who received rifapentine as part of a treatment regimen for TB had a higher rate of TB relapse and acquired rifamycin resistance than those treated with other rifamycin-based regimens. Therefore an alternative agent to rifapentine is recommended for TB treatment.

[d] A high rate of Grade 4 serum transaminase elevation was seen when a higher dose of RTV was added to LPV/r or SQV or when double-dose LPV/r was used with rifampin to compensate for rifampin's induction effect and therefore, these dosing strategies should not be used.

[e] The manufacturer of cisapride has a limited-access protocol for patients who meet specific clinical eligibility criteria.

[f] Use of oral midazolam is contraindicated. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.

Suggested alternatives to:

- **Lovastatin, simvastatin:** Fluvastatin, pitavastatin, and pravastatin (except for pravastatin with DRV/r) have the least potential for drug-drug interactions (see Table 18a). Use atorvastatin and rosuvastatin with caution; start with the lowest possible dose and titrate based on tolerance and lipid-lowering efficacy.
- **Rifampin:** Rifabutin (with dosage adjustment, see Tables 18a and 18b)
- **Midazolam, triazolam:** temazepam, lorazepam, oxazepam

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; cobi = cobicistat; CYP = cytochrome P; DLV = delavirdine; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FDA = Food and Drug Administration; FPV = fosamprenavir; FPV/r = ritonavir-boosted fosamprenavir; FTC = emtricitabine; IDV = indinavir; LPV/r = ritonavir-boosted lopinavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PAH = pulmonary arterial hypertension; PI = protease inhibitor; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = ritonavir-boosted saquinavir; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; TPV/r = ritonavir-boosted tipranavir

Table 18a. Drug Interactions between Protease Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 12)

This table provides information relating to PK interactions between PIs and non-ARV drugs. When information is available, interactions with boosted and unboosted PIs are listed separately. For interactions between ARV agents and for dosing recommendations, refer to Tables 18c, 19a, and 19b.

[a] NFV and IDV are **not** included in this table. Please refer to the FDA product labels for NFV and IDV for information regarding drug interactions with these PIs.

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV, ATV/r	When given simultaneously, ↓ ATV expected	Give ATV at least 2 hours before or 1 hour after antacids or buffered medications.
	FPV	APV AUC ↓ 18%; no significant change in APV C_{min}	Give FPV simultaneously with (or at least 2 hours before or 1 hour after) antacids.
	TPV/r	TPV AUC ↓ 27%	Give TPV at least 2 hours before or 1 hour after antacids.
H2 Receptor Antagonists	**RTV-Boosted PIs**		
	ATV/r	↓ ATV	H2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40 mg BID in ART-naive patients or 20 mg BID in ART-experienced patients. Give ATV 300 mg + RTV 100 mg simultaneously with and/or ≥10 hours after the H2 receptor antagonist. If using TDF and H2 receptor antagonist in ART-experienced patients, use ATV 400 mg + RTV 100 mg.
	DRV/r, LPV/r	No significant effect	No dosage adjustment necessary.
	PIs without RTV		
	ATV	↓ ATV	H2 receptor antagonist single dose should not exceed a dose equivalent of famotidine 20 mg or total daily dose equivalent of famotidine 20 mg BID in ART-naive patients. Give ATV at least 2 hours before and at least 10 hours after the H2 receptor antagonist.
	FPV	APV AUC ↓ 30%; no significant change in APV C_{min}	If concomitant use is necessary, give FPV at least 2 hours before H2 receptor antagonist. Consider boosting FPV with RTV.
PPIs	ATV	↓ ATV	**PPIs are not recommended in patients receiving unboosted ATV.** In these patients, consider alternative acid-reducing agents, RTV boosting, or alternative PIs.
	ATV/r	↓ ATV	PPIs should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naive patients. PPIs should be administered at least 12 hours before ATV/r. **PPIs are not recommended in PI-experienced patients.**
	DRV/r, TPV/r	↓ omeprazole PI: no significant effect	May need to increase omeprazole dose when using TPV/r.
	FPV, FPV/r, LPV/r	No significant effect	No dosage adjustment necessary.
	SQV/r	SQV AUC ↑ 82%	Monitor for SQV toxicities.

Table 18a. Drug Interactions between Protease Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 12)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants			
Warfarin	All PIs	↑ or ↓ warfarin possible	Monitor INR closely when stopping or starting PI and adjust warfarin dose accordingly.
Rivaroxaban	All PIs	↑ rivaroxaban	Avoid concomitant use. Co-administration is expected to result in increased rivaroxaban exposure, which may lead to risk of increased bleeding.
Anticonvulsants			
Carbamazepine	**RTV-Boosted PIs**		
	ATV/r, FPV/r, LPV/r, SQV/r, TPV/r	↑ carbamazepine possible TPV/r ↑ carbamazepine AUC 26% May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not co-administer with LPV/r once daily.**
	DRV/r	carbamazepine AUC ↑ 45% DRV: no significant change	Monitor anticonvulsant level and adjust dose accordingly.
	PIs without RTV		
	ATV, FPV	May ↓ PI levels substantially	**Do not co-administer.** Consider alternative anticonvulsant or RTV boosting for ATV and FPV.
Lamotrigine	LPV/r	Lamotrigine AUC ↓ 50% LPV: no significant change	A dose increase of lamotrigine may be needed and therapeutic concentration monitoring for lamotrigine may be indicated, particularly during dosage adjustment. Alternatively, consider another anticonvulsant. A similar interaction is possible with other RTV-boosted PIs.
Phenobarbital	All PIs	May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not co-administer with LPV/r once daily, ATV without RTV, or FPV without RTV.**
Phenytoin	**RTV-Boosted PIs**		
	ATV/r, DRV/r, SQV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	FPV/r	phenytoin AUC ↓ 22% APV AUC ↑ 20%	Monitor phenytoin level and adjust dose accordingly. No change in FPV/r dose recommended.
	LPV/r	phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not co-administer with LPV/r once daily.**
	PIs without RTV		
	ATV, FPV	May ↓ PI levels substantially	**Do not co-administer.** Consider alternative anticonvulsant or RTV boosting for ATV and FPV.
Valproic Acid	LPV/r	↓ or ⇔VPA possible LPV AUC ↑ 75%	Monitor VPA levels and virologic response. Monitor for LPV-related toxicities.

Table 18a. Drug Interactions between Protease Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 3 of 12)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants			
Bupropion	LPV/r	bupropion AUC ↓ 57%	Titrate bupropion dose based on clinical response.
	TPV/r	bupropion AUC ↓ 46%	
Paroxetine	DRV/r	paroxetine AUC ↓ 39%	Titrate paroxetine dose based on clinical response.
	FPV/r	paroxetine AUC ↓ 55%	
Sertraline	DRV/r	sertraline AUC ↓ 49%	Titrate sertraline dose based on clinical response.
Trazodone	ATV/r, ATV, DRV/r, FPV/r, FPV, LPV/r, TPV/r	RTV 200 mg BID (for 2 days) ↑ trazodone AUC 240%	Use lowest dose of trazodone and monitor for CNS and cardiovascular adverse effects.
	SQV/r	↑ trazodone expected	**Contraindicated. Do not co-administer.**
Tricyclic Antidepressants Amitriptyline, Desipramine, Imipramine, Nortriptyline	All RTV-boosted PIs	↑ TCA expected	Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.
Antifungals			
Fluconazole	**RTV-Boosted PIs**		
	ATV/r	No significant effect	No dosage adjustment necessary.
	SQV/r	No data with RTV boosting SQV (1200 mg TID) AUC ↑ 50%	No dosage adjustment necessary.
	TPV/r	TPV AUC ↑ 50%	Fluconazole >200 mg daily is not recommended. If high-dose fluconazole is indicated, consider alternative PI or another class of ARV drug.
Itraconazole	All PIs	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended with RTV-boosted PIs unless dose is guided by itraconazole levels.
Posaconazole	ATV/r	ATV AUC ↑ 146%	Monitor for adverse effects of ATV.
	ATV	ATV AUC ↑ 268%	Monitor for adverse effects of ATV.
	FPV	Compared with FPV/r (700 mg/100 mg), FPV (1400 mg BID) ↓ posaconazole AUC 23%, ↓ APV AUC 65%	**Do not co-administer.**

Table 18a. Drug Interactions between Protease Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 4 of 12)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals, continued			
Voriconazole	**RTV-Boosted PIs**		
	All RTV-boosted PIs	RTV 400 mg BID ↓ voriconazole AUC 82% RTV 100 mg BID ↓ voriconazole AUC 39%	**Do not co-administer voriconazole and RTV unless benefit outweighs risk.** If administered, consider monitoring voriconazole level and adjust dose accordingly.
	PIs without RTV		
	ATV, FPV	↑ voriconazole possible ↑ PI possible	Monitor for toxicities.
Antimalarials			
Artemether/ Lumefantrine	DRV/r	artemether AUC ↓ 16%; DHA[a] AUC ↓ 18%; lumefantrine AUC ↑ 2.5-fold	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy and lumefantrine toxicity.
	LPV/r	artemether AUC ↓ 40%; DHA AUC ↓ 17%; lumefantrine AUC ↑ 470%	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy and lumefantrine toxicity.
Atovaquone/ Proguanil	ATV/r, LPV/r	ATV/r ↓ atovaquone AUC 46% and ↓ proguanil AUC 41% LPV/r ↓ atovaquone AUC 74% and ↓ proguanil AUC 38%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.
Mefloquine	RTV	With RTV 200 mg BID: RTV AUC ↓ 31%, C_{min} ↓ 43%; ⇔ mefloquine	Use with caution. Effect on exposure of RTV-boosted PIs is unknown.
Antimycobacterials			
Bedaquiline	All RTV-boosted PIs	With LPV/r: bedaquiline AUC ↑ 22%; C_{max} ⇔ With other PI/r: ↑ bedaquiline possible	Clinical significance unknown. Use with caution if benefit outweighs the risk and monitor for QTc prolongation and liver function tests.
Clarithromycin	ATV/r, ATV	clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy (e.g., azithromycin).
	DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	DRV/r ↑ clarithromycin AUC 57% FPV/r ↑ clarithromycin possible LPV/r ↑ clarithromycin expected RTV 500 mg BID ↑ clarithromycin 77% SQV unboosted ↑ clarithromycin 45% TPV/r ↑ clarithromycin 19% clarithromycin ↑ unboosted SQV 177% clarithromycin ↑ TPV 66%	Monitor for clarithromycin-related toxicities or consider alternative macrolide (e.g., azithromycin). Reduce clarithromycin dose by 50% in patients with CrCl 30–60 mL/min. Reduce clarithromycin dose by 75% in patients with CrCl <30 mL/min.
	FPV	APV AUC ↑ 18%	No dosage adjustment necessary.

Table 18a. Drug Interactions between Protease Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 5 of 12)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials, continued			
Rifabutin	**RTV-Boosted PIs**		
	ATV/r	Compared with rifabutin (300 mg daily) administered alone, when rifabutin (150 mg once daily) is administered with ATV/r, rifabutin AUC ↑ 110% and metabolite AUC ↑ 2101%	Rifabutin 150 mg once daily or 300 mg three times a week. Monitor for antimycobacterial activity and consider therapeutic drug monitoring. PK data reported in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in HIV-infected patients than in the healthy study participants.
	DRV/r	Compared with rifabutin (300 mg once daily) administered alone, when rifabutin (150 mg every other day) is administered with DRV/r, rifabutin AUC not significantly changed and metabolite AUC ↑ 881%	
	FPV/r	Compared with rifabutin (300 mg once daily) administered alone, when rifabutin (150 mg every other day) is administered with FPV/r, rifabutin and metabolite AUC ↑ 64%.	
	LPV/r	Compared with rifabutin (300 mg daily) administered alone, when rifabutin (150 mg once daily) is administered with LPV/r, rifabutin and metabolite AUC ↑ 473%.	
	SQV/r	↑ rifabutin with unboosted SQV	
	TPV/r	rifabutin and metabolite AUC ↑ 333%	
	PIs without RTV		
	ATV, FPV	↑ rifabutin AUC expected	Rifabutin 150 mg daily or 300 mg three times a week
Rifampin	All PIs	↓ PI concentration by >75%	**Do not co-administer rifampin and PIs.** Additional RTV does not overcome this interaction and increases hepatotoxicity. Consider rifabutin if a rifamycin is indicated.
Rifapentine	All PIs	↓ PI expected	**Do not co-administer rifapentine and PIs.**
Benzodiazepines			
Alprazolam **Diazepam**	All PIs	↑ benzodiazepine possible RTV (200 mg BID for 2 days) ↑ alprazolam half-life 222% and AUC 248%	Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam.
Lorazepam **Oxazepam** **Temazepam**	All PIs	No data	These benzodiazepines are metabolized via non-CYP450 pathways; there is less interaction potential than with other benzodiazepines.
Midazolam	All PIs	↑ midazolam expected SQV/r ↑ midazolam (oral) AUC 1144% and C_{max} 327%	**Do not co-administer oral midazolam and PIs.** Parenteral midazolam can be used with caution when given as a single dose in a monitored situation for procedural sedation.
Triazolam	All PIs	↑ triazolam expected RTV (200 mg BID) ↑ triazolam half-life 1200% and AUC 2000%	**Do not co-administer triazolam and PIs.**

Table 18a. Drug Interactions between Protease Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 6 of 12)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications			
Bosentan	All PIs	LPV/r ↑ bosentan 48-fold (day 4) and 5-fold (day 10) ↓ ATV expected	**Do not co-administer bosentan and ATV without RTV.** In Patients on a PI (Other than Unboosted ATV) >10 Days: • Start bosentan at 62.5 mg once daily or every other day. In Patients on Bosentan who Require a PI (Other than Unboosted ATV): • Stop bosentan ≥36 hours before PI initiation and restart 10 days after PI initiation at 62.5 mg once daily or every other day.
Digoxin	RTV, SQV/r	RTV (200 mg BID) ↑ digoxin AUC 29% and ↑ half-life 43% SQV/r ↑ digoxin AUC 49%	Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased.
Calcium Channel Blockers	All PIs	↑ dihydropyridine possible	Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when CCB used with ATV.
Diltiazem	ATV/r, ATV	diltiazem AUC ↑ 125%	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/r, FPV/r, FPV, LPV/r, SQV/r, TPV/r	↑ diltiazem possible	Use with caution. Adjust diltiazem according to clinical response and toxicities.
Corticosteroids			
Beclomethasone Inhaled	DRV/r	RTV 100 mg BID ↑ 17-BMP AUC 2-fold and ↑ C_{max} 1.6-fold (DRV 600 mg plus RTV 100 mg) BID ↓ 17-BMP AUC 11% and ↓ C_{max} 19%	No dosage adjustment necessary. Significant interaction between beclomethasone (inhaled or intranasal) and other RTV-boosted PIs is not expected.
Budesonide Systemic	All PIs	↓ PI levels possible ↑ glucocorticoids	Co-administration can result in adrenal insufficiency, including Cushing's syndrome. **Do not co-administer unless potential benefits of systemic budesonide outweigh the risks of systemic corticosteroid adverse effects.**
Budesonide Inhaled or Intranasal	All RTV-boosted PIs	↑ glucocorticoids	Co-administration can result in adrenal insufficiency, including Cushing's syndrome. **Do not co-administer unless potential benefits of inhaled or intranasal budesonide outweigh the risks of systemic corticosteroid adverse effects.** Consider alternative therapy (e.g., beclomethasone).
Dexamethasone	All PIs	↓ PI levels possible	Use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use.

Table 18a. Drug Interactions between Protease Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 7 of 12)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids, continued			
Fluticasone Inhaled or Intranasal	All RTV-boosted PIs	RTV 100 mg BID ↑ fluticasone AUC 350-fold and ↑ C_{max} 25-fold	Co-administration can result in adrenal insufficiency, including Cushing's syndrome. **Do not co-administer unless potential benefits of inhaled or intranasal fluticasone outweigh the risks of systemic corticosteroid adverse effects.** Consider alternative therapy (e.g., beclomethasone).
Prednisone	LPV/r All PIs	↑ prednisolone AUC 31% ↑ prednisolone possible	Use with caution. Co-administration can result in adrenal insufficiency, including Cushing's syndrome. **Do not co-administer unless potential benefits of prednisone outweigh the risks of systemic corticosteroid adverse effects.**
Methylprednisolone, Prednisolone, Triamcinolone (local injections, including intra-articular, epidural, intra-orbital)	All RTV-boosted PIs	↑ glucocorticoids expected	Co-administration can result in adrenal insufficiency, including Cushing's syndrome. **Do not co-administer.** Consider alternative non-steroidal therapies. If intra-articular corticosteroid therapy required, change to alternative non-CYP3A-modulating ART (e.g., RAL, DTG).
Hepatitis C NS3/4A Protease Inhibitors			
Boceprevir	ATV/r	ATV AUC ↓ 35%, C_{min} ↓ 49% RTV AUC ↓ 36% boceprevir AUC ↔	**Co-administration is not recommended.**
	DRV/r	DRV AUC ↓ 44%, C_{min} ↓ 59% RTV AUC ↓ 26% boceprevir AUC ↓ 32%, C_{min} ↓ 35%	**Co-administration is not recommended.**
	LPV/r	LPV AUC ↓ 34%, C_{min} ↓ 43% RTV AUC ↓ 22% boceprevir AUC ↓ 45%, C_{min} ↓ 57%	**Co-administration is not recommended.**
Simeprevir	All PIs	DRV/r 800/100 mg daily plus simeprevir 50 mg: simeprevir AUC ↑ 159% compared with simeprevir 150 mg alone RTV 100 mg BID ↑ simeprevir AUC 618%	**Co-administration is not recommended.**
Telaprevir	ATV/r	telaprevir AUC ↓ 20%	No dose adjustment necessary.
	DRV/r	telaprevir AUC ↓ 35% DRV AUC ↓ 40%	**Co-administration is not recommended.**
	FPV/r	telaprevir AUC ↓ 32% APV AUC ↓ 47%	**Co-administration is not recommended.**
	LPV/r	telaprevir AUC ↓ 54% LPV: no significant change	**Co-administration is not recommended.**

Table 18a. Drug Interactions between Protease Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 8 of 12)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Herbal Products			
St. John's Wort	All PIs	↓ PI expected	**Do not co-administer.**
Hormonal Contraceptives			
Hormonal Contraceptives	**RTV-Boosted PIs**		
	ATV/r	ethinyl estradiol AUC ↓ 19% and C_{min} ↓ 37% norgestimate ↑ 85%	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.[b]
	DRV/r	ethinyl estradiol AUC ↓ 44% norethindrone AUC ↓ 14%	Recommend alternative or additional contraceptive method.
	FPV/r	ethinyl estradiol AUC ↓ 37% norethindrone AUC ↓ 34%	Recommend alternative or additional contraceptive method.
	LPV/r	ethinyl estradiol AUC ↓ 42% norethindrone AUC ↓ 17%	Recommend alternative or additional contraceptive method.
	SQV/r	↓ ethinyl estradiol	Recommend alternative or additional contraceptive method.
	TPV/r	ethinyl estradiol AUC ↓ 48% norethindrone: no significant change	Recommend alternative or additional contraceptive method.
	PIs without RTV		
	ATV	ethinyl estradiol AUC ↑ 48% norethindrone AUC ↑ 110%	Prescribe oral contraceptive that contains no more than 30 mcg of ethinyl estradiol or recommend alternative contraceptive method. Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.[c]
	FPV	With APV: ↑ ethinyl estradiol and ↑ norethindrone C_{min}; APV C_{min} ↓ 20%	Recommend alternative contraceptive method.
HMG-CoA Reductase Inhibitors			
Atorvastatin	ATV/r, ATV	↑ atorvastatin possible	Titrate atorvastatin dose carefully and use lowest dose necessary.
	DRV/r, FPV/r, FPV, SQV/r	DRV/r plus atorvastatin 10 mg similar to atorvastatin 40 mg administered alone; FPV +/– RTV ↑ atorvastatin AUC 130% to 153%; SQV/r ↑ atorvastatin AUC 79%	Titrate atorvastatin dose carefully and use the lowest necessary dose. Do not exceed 20 mg atorvastatin daily.
	LPV/r	LPV/r ↑ atorvastatin AUC 488%	Use with caution and use the lowest atorvastatin dose necessary.
	TPV/r	↑ atorvastatin AUC 836%	**Do not co-administer.**
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated. Do not co-administer.**

Table 18a. Drug Interactions between Protease Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 9 of 12)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors, continued			
Pitavastatin	All PIs	ATV ↑ pitavastatin AUC 31% and C_{max} ↑ 60% ATV: no significant effect DRV/r: no significant effect LPV/r ↓ pitavastatin AUC 20% LPV: no significant effect	No dose adjustment necessary.
Pravastatin	DRV/r	pravastatin AUC • ↑ 81% following single dose of pravastatin • ↑ 23% at steady state	Use lowest possible starting dose of pravastatin with careful monitoring.
	LPV/r	pravastatin AUC ↑ 33%	No dose adjustment necessary.
	SQV/r	pravastatin AUC ↓ 47% to 50%	No dose adjustment necessary.
Rosuvastatin	ATV/r, LPV/r	ATV/r ↑ rosuvastatin AUC 3-fold and C_{max} ↑ 7-fold LPV/r ↑ rosuvastatin AUC 108% and C_{max} ↑ 366%	Titrate rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed 10 mg rosuvastatin daily.
	DRV/r	rosuvastatin AUC ↑ 48% and C_{max} ↑ 139%	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.
	FPV +/- RTV	No significant effect on rosuvastatin	No dosage adjustment necessary.
	SQV/r	No data available	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.
	TPV/r	rosuvastatin AUC ↑ 26% and C_{max} ↑ 123%	No dosage adjustment necessary.
Simvastatin	All PIs	Significant ↑ simvastatin level; SQV/r 400 mg/400 mg BID ↑ simvastatin AUC 3059%	**Contraindicated. Do not co-administer.**
Immunosuppressants			
Cyclosporine **Sirolimus** **Tacrolimus**	All PIs	↑ immunosuppressant expected	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	ATV	buprenorphine AUC ↑ 93% norbuprenorphine[d] AUC ↑ 76% ↓ ATV possible	**Do not co-administer buprenorphine with unboosted ATV.**
	ATV/r	buprenorphine AUC ↑ 66% norbuprenorphine[d] AUC ↑ 105%	Monitor for sedation. Buprenorphine dose reduction may be necessary.
	DRV/r	buprenorphine: no significant effect norbuprenorphine[d] AUC ↑ 46% and C_{min} ↑ 71%	No dosage adjustment necessary. Clinical monitoring is recommended.

Table 18a. Drug Interactions between Protease Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 10 of 12)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Narcotics/Treatment for Opioid Dependence, continued			
Buprenorphine, continued	FPV/r	buprenorphine: no significant effect norbuprenorphine[d] AUC ↓ 15%	No dosage adjustment necessary. Clinical monitoring is recommended.
	LPV/r	No significant effect	No dosage adjustment necessary.
	TPV/r	buprenorphine: no significant effect norbuprenorphine[d] AUC, C_{max}, and C_{min} ↓ 80% TPV C_{min} ↓ 19%–40%	Consider monitoring TPV level.
Oxycodone	LPV/r	oxycodone AUC ↑ 2.6-fold	Monitor for opioid-related adverse effects. Oxycodone dose reduction may be necessary.
Methadone	**RTV-Boosted PIs**		
	ATV/r, DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	ATV/r, DRV/r, FPV/r: ↓ R-methadone[e] AUC 16% to 18%; LPV/r ↓ methadone AUC 26% to 53% SQV/r 1000/100 mg BID ↓ R-methadone[e] AUC 19% TPV/r ↓ R-methadone[e] AUC 48%	Opioid withdrawal unlikely but may occur. Dosage adjustment of methadone is not usually required, but monitor for opioid withdrawal and increase methadone dose as clinically indicated.
	PIs without RTV		
	ATV	No significant effect	No dosage adjustment necessary.
	FPV	No data with unboosted FPV APV ↓ R-methadone[e] C_{min} 21%, AUC no significant change	Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Avanafil	ATV, ATV/r, DRV/r, FPV/r, SQV/r, LPV/r	RTV (600 mg BID for 5 days) ↑ avanafil AUC 13-fold, C_{max} 2.4-fold	**Co-administration is not recommended.**
	FPV	No data	Avanafil dose should not exceed 50 mg once every 24 hours.
Sildenafil	All PIs	DRV/r plus sildenafil 25 mg similar to sildenafil 100 mg alone; RTV 500 mg BID ↑ sildenafil AUC 1000% SQV unboosted ↑ sildenafil AUC 210%	For Treatment of Erectile Dysfunction: • Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil. For treatment of PAH: • **Contraindicated**

Table 18a. Drug Interactions between Protease Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 11 of 12)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Phosphodiesterase Type 5 (PDE5) Inhibitors, continued			
Tadalafil	All PIs	RTV 200 mg BID ↑ tadalafil AUC 124% TPV/r (1st dose) ↑ tadalafil AUC 133% TPV/r steady state: no significant effect	For Treatment of Erectile Dysfunction: Start with tadalafil 5-mg dose and do not exceed a single dose of 10 mg every 72 hours. Monitor for adverse effects of tadalafil. For Treatment of PAH: *In Patients on a PI >7 Days:* • Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability. *In Patients on Tadalafil who Require a PI:* • Stop tadalafil ≥24 hours before PI initiation, restart 7 days after PI initiation at 20 mg once daily, and increase to 40 mg once daily based on tolerability. For Treatment of Benign Prostatic Hyperplasia: • Maximum recommended daily dose is 2.5 mg per day
Vardenafil	All PIs	RTV 600 mg BID ↑ vardenafil AUC 49-fold	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Miscellaneous Interactions			
Colchicine	All PIs	RTV 100 mg BID ↑ colchicine AUC 296%, C_{max} 184% With all PIs: significant ↑ in colchicine AUC expected	For Treatment of Gout Flares: • Colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. *With FPV without RTV:* • 1.2 mg x 1 dose and no repeat dose for at least 3 days For Prophylaxis of Gout Flares: • Colchicine 0.3 mg once daily or every other day *With FPV without RTV:* • Colchicine 0.3 mg BID or 0.6 mg once daily or 0.3 mg once daily For Treatment of Familial Mediterranean Fever: • Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID. *With FPV without RTV:* • Do not exceed 1.2 mg once daily or 0.6 mg BID. **Do not co-administer in patients with hepatic or renal impairment.**

Table 18a. Drug Interactions between Protease Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 12 of 12)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Interactions, continued			
Quetiapine	All PIs	↑ quetiapine AUC expected	Initiation of Quetiapine in a Patient Receiving a PI: • Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine effectiveness and adverse effects. Initiation of a PI in a Patient Receiving a Stable Dose of Quetiapine: • Reduce quetiapine dose to 1/6 of the original dose. Closely monitor for quetiapine effectiveness and adverse effects.
Salmeterol	All PIs	↑ salmeterol possible	**Do not co-administer** because of potential increased risk of salmeterol-associated cardiovascular events.

[a] DHA is an active metabolite of artemether.

[b] The following products contain at least 35 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulation may also be available): Ovcon 35, 50; Femcon Fe; Brevicon; Modicon; Ortho-Novum 1/35, 10/11, 7/7/7; Norinyl 1/35; Tri-Norinyl; Ortho-Cyclen; Ortho Tri-Cyclen.

[c] The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulation may also be available): Loestrin 1/20, 1.5/30; Loestrin Fe 1/20, 1.5/30; Loestrin 24 Fe; Ortho Tri-Cyclen Lo.

[d] Norbuprenorphine is an active metabolite of buprenorphine.

[e] R-methadone is the active form of methadone.

Key to Acronyms: 17-BMP = beclomethasone 17-monopropionate; APV = amprenavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; AUC = area under the curve; BID = twice daily; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CNS = central nervous system; CrCl = creatinine clearance; CYP = cytochrome P; DHA = dihydroartemisinin; DRV = darunavir; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; ECG = electrocardiogram; FDA = Food and Drug Administration; FPV = fosamprenavir; FPV/r = ritonavir-boosted fosamprenavir; IDV = indinavir; INR = international normalized ratio; LPV = lopinavir; LPV/r = ritonavir-boosted lopinavir; NFV = nelfinavir; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RAL = raltegravir; RTV = ritonavir; SQV = saquinavir; SQV/r = ritonavir-boosted saquinavir; TDF = tenofovir disoproxil fumarate; TID = three times a day; TPV = tipranavir; TPV/r = ritonavir-boosted tipranavir

Note: FPV is a pro-drug of APV

Table 18b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 7)

This table provides information relating to PK interactions between NNRTIs and non- ARV drugs. For interactions between ARV agents and for dosing recommendations, refer to Tables 18c, 19a, and 19b.

[a] DLV is **not** included in this table. Please refer to the DLV FDA package insert for information regarding drug interactions.

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	RPV	↓ RPV expected when given simultaneously	Give antacids at least 2 hours before or at least 4 hours after RPV.
H2 Receptor Antagonists	RPV	↓ RPV	Give H2-receptor antagonists at least 12 hours before or at least 4 hours after RPV.
PPIs	RPV	With omeprazole 20 mg daily, ↓ RPV AUC 40%, C_{min} 33%	**Contraindicated. Do not co-administer.**
Anticoagulants/Antiplatelets			
Warfarin	EFV, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
	ETR	↑ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Clopidogrel	ETR	↓ activation of clopidogrel possible	ETR may prevent metabolism of clopidogrel (inactive) to its active metabolite. Avoid co-administration, if possible.
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	EFV	Carbamazepine plus EFV: • Carbamazepine AUC ↓ 27%, and • EFV AUC ↓ 36% Phenytoin plus EFV: • ↓ EFV, and • ↓ phenytoin possible	Monitor anticonvulsant and EFV levels or, if possible, use alternative anticonvulsant to those listed.
	ETR	↓ anticonvulsant and ETR possible	**Do not co-administer.** Consider alternative anticonvulsant.
	NVP	↓ anticonvulsant and NVP possible	Monitor anticonvulsant and NVP levels and virologic responses or consider alternative anticonvulsant.
	RPV	↓ RPV possible	**Contraindicated. Do not co-administer.** Consider alternative anticonvulsant.
Antidepressants			
Bupropion	EFV	bupropion AUC ↓ 55%	Titrate bupropion dose based on clinical response.
Paroxetine	EFV, ETR	No significant effect	No dosage adjustment necessary.
Sertraline	EFV	sertraline AUC ↓ 39%	Titrate sertraline dose based on clinical response.

Table 18b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	EFV	No significant effect	No dosage adjustment necessary.
	ETR	ETR AUC ↑ 86%	No dosage adjustment necessary. Use with caution.
	NVP	NVP AUC ↑ 110%	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative ARV agent.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection (RPV 150 mg/day reduces ketoconazole exposure; no data on interaction with fluconazole).
Itraconazole	EFV	itraconazole and OH-itraconazole AUC, C_{max} and C_{min} ↓ 35%–44%	Failure to achieve therapeutic itraconazole concentrations has been reported. Avoid this combination if possible. If co-administered, closely monitor itraconazole concentration and adjust dose accordingly.
	ETR	↓ itraconazole possible ↑ ETR possible	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.
	NVP	↓ itraconazole possible ↑ NVP possible	Avoid combination if possible. If co-administered, monitor itraconazole concentration and adjust dose accordingly.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection. (RPV 150 mg/day reduces ketoconazole exposure; no data on interaction with itraconazole.)
Posaconazole	EFV	posaconazole AUC ↓ 50% ↔ EFV	Avoid concomitant use unless the benefit outweighs the risk. If co-administered, monitor posaconazole concentration and adjust dose accordingly.
	ETR	↑ ETR possible	No dosage adjustment necessary.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection (RPV 150 mg/day reduces ketoconazole exposure; no data on interaction with posaconazole).

Table 18b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 3 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals, continued			
Voriconazole	EFV	voriconazole AUC ↓ 77% EFV AUC ↑ 44%	**Contraindicated at standard doses.** Dose: voriconazole 400 mg BID, EFV 300 mg daily.
	ETR	voriconazole AUC ↑ 14% ETR AUC ↑ 36%	No dosage adjustment necessary; use with caution. Consider monitoring voriconazole level.
	NVP	↓ voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal response and/or voriconazole level.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection (RPV 150 mg/day reduces ketoconazole exposure; no data on interaction with voriconazole).
Antimalarials			
Artemether/ Lumefantrine	EFV	artemether AUC ↓ 79% DHA AUC ↓ 75% lumefantrine AUC ↓ 56%	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy
	ETR	artemether AUC ↓ 38% DHA AUC ↓ 15% lumefantrine AUC ↓ 13% ETR AUC ↑ 10%	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy
	NVP	artemether AUC ↓ 72% DHA AUC ↓ 37% lumefantrine: no difference in one study, but AUC ↑ 55.6% in another study	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy and lumefantrine toxicity.
Atovaquone/ Proguanil	EFV	↓ atovaquone AUC 75% ↓ proguanil AUC 43%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.
Antimycobacterials			
Bedaquiline	EFV, NVP	↔ bedaquiline AUC	No dosage adjustment necessary.
Clarithromycin	EFV	clarithromycin AUC ↓ 39%	Monitor for effectiveness or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	ETR	clarithromycin AUC ↓ 39% ETR AUC ↑ 42%	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	NVP	clarithromycin AUC ↓ 31%	Monitor for effectiveness or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	RPV	↔ clarithromycin expected ↑ RPV possible	Consider alternative macrolide, such as azithromycin, for MAC prophylaxis and treatment.

Table 18b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 4 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Rifabutin	EFV	rifabutin ↓ 38%	Dose: rifabutin 450–600 mg once daily or 600 mg 3 times a week if EFV is not co-administered with a PI.
	ETR	rifabutin and metabolite AUC ↓ 17% ETR AUC ↓ 37%	**If ETR is used with an RTV-boosted PI, rifabutin should not be co-administered.** Dose: rifabutin 300 mg once daily **if** ETR is not co-administered with an RTV-boosted PI.
	NVP	rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C_{min} ↓ 16%	No dosage adjustment necessary. Use with caution.
	RPV	RPV AUC ↓ 46%	**Contraindicated. Do not co-administer.**
Rifampin	EFV	EFV AUC ↓ 26%	Maintain EFV dose at 600 mg once daily and monitor for virologic response. Consider therapeutic drug monitoring. Some clinicians suggest EFV 800 mg dose in patients who weigh more than 60 kg.
	ETR	Significant ↓ ETR possible	**Do not co-administer.**
	NVP	NVP ↓ 20% to 58%	**Do not co-administer.**
	RPV	RPV AUC ↓ 80%	**Contraindicated. Do not co-administer.**
Rifapentine	EFV, ETR, NVP, RPV	↓ NNRTI expected	**Do not co-administer.**
Benzodiazepines			
Alprazolam	EFV, ETR, NVP, RPV	No data	Monitor for therapeutic effectiveness of alprazolam.
Diazepam	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary.
Lorazepam	EFV	lorazepam C_{max} ↑ 16%, AUC ↔	No dosage adjustment necessary.
Midazolam	EFV	Significant ↑ midazolam expected	**Do not co-administer with oral midazolam.** Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	EFV	Significant ↑ triazolam expected	**Do not co-administer.**
Cardiac Medications			
Dihydropyridine Calcium Channel Blockers	EFV, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem Verapamil	EFV	diltiazem AUC ↓ 69% ↓ verapamil possible	Titrate diltiazem or verapamil dose based on clinical response.
	NVP	↓ diltiazem or verapamil possible	
Corticosteroids			
Dexamethasone	EFV, ETR, NVP	↓ EFV, ETR, NVP possible	Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.
	RPV	Significant ↓ RPV possible	**Contraindicated with more than a single dose of dexamethasone.**

Table 18b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 5 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C NS3/4A—PIs			
Boceprevir	EFV	EFV AUC ↑ 20% boceprevir AUC ↓ 19%, C_{min} ↓ 44%	**Co-administration is not recommended.**
	ETR	ETR AUC ↓ 23% boceprevir AUC, C_{max} ↑ 10%	No dosage adjustment necessary.
Simeprevir	EFV	Simeprevir AUC ↓ 71%, C_{min} ↓ 91% EFV ↔	**Co-administration is not recommended.**
	ETR, NVP	↓ simeprevir expected	**Co-administration is not recommended.**
	RPV	Simeprevir ↔ and RPV ↔	No dosage adjustment necessary.
Telaprevir	EFV	EFV AUC ↔ telaprevir AUC ↓ 26%, C_{min} ↓ 47% With TDF: • EFV AUC ↓ 15% to 18% • Telaprevir AUC ↓ 18% to 20%	Increase telaprevir dose to 1125 mg q8h.
	ETR	ETR AUC ↔ telaprevir AUC ↓ 16%, C_{min} ↓ 25%	No dosage recommendation.
Herbal Products			
St. John's Wort	EFV, ETR, NVP, RPV	↓ NNRTI	**Do not co-administer.**
Hormonal Contraceptives			
Hormonal Contraceptives	EFV	ethinyl estradiol ↔ levonorgestrel AUC ↓ 83% norelgestromin AUC ↓ 64% ↓ etonogestrel (implant) possible	Use alternative or additional contraceptive methods. Norelgestromin and levonorgestrel are active metabolites of norgestimate.
	ETR	ethinyl estradiol AUC ↑ 22% norethindrone: no significant effect	No dosage adjustment necessary.
	NVP	ethinyl estradiol AUC ↓ 20% norethindrone AUC ↓ 19%	Use alternative or additional contraceptive methods.
		DMPA: no significant change	No dosage adjustment necessary.
	RPV	ethinyl estradiol AUC ↑ 14% norethindrone: no significant change	No dosage adjustment necessary.
Levonorgestrel (for emergency contraception)	EFV	levonorgestrel AUC ↓ 58%	Effectiveness of emergency post-coital contraception may be diminished.

Table 18b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 6 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors			
Atorvastatin	EFV, ETR	atorvastatin AUC ↓ 32% to 43%	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
	RPV	atorvastatin AUC ↔ atorvastatin metabolites ↑	No dosage adjustment necessary.
Fluvastatin	ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary.
Lovastatin Simvastatin	EFV	simvastatin AUC ↓ 68%	Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If EFV used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
	ETR, NVP	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If ETR or NVP used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
Pitavastatin	EFV	pitavastatin AUC ↓ 11%, C_{max} ↑ 20%	No dosage adjustment necessary.
	ETR, NVP, RPV	No data	No significant effect expected. No dosage adjustment necessary.
Pravastatin Rosuvastatin	EFV	pravastatin AUC ↓ 44% rosuvatatin: no data	Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	No significant effect expected	No dosage adjustment necessary.
Immunosuppressants			
Cyclosporine Sirolimus Tacrolimus	EFV, ETR, NVP	↓ immunosuppressant possible	Increase in immunosuppressant dose may be necessary. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	EFV	buprenorphine AUC ↓ 50% norbuprenorphine[b] AUC ↓ 71%	No dosage adjustment recommended; monitor for withdrawal symptoms.
	ETR	buprenorphine AUC ↓ 25%	No dosage adjustment necessary.
	NVP	No significant effect	No dosage adjustment necessary.
Methadone	EFV	methadone AUC ↓ 52%	Opioid withdrawal common; increased methadone dose often necessary.
	ETR	No significant effect	No dosage adjustment necessary.
	NVP	methadone AUC ↓ 37% to 51% NVP: no significant effect	Opioid withdrawal common; increased methadone dose often necessary.
	RPV	R-methadone[c] AUC ↓ 16%	No dosage adjustment necessary, but monitor for withdrawal symptoms.

Table 18b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors[a] and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 7 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors			
Avanafil	EFV, ETR, NVP, RPV	No data	**Co-administration is not recommended.**
Sildenafil	ETR	sildenafil AUC ↓ 57%	May need to increase sildenafil dose based on clinical effect.
	RPV	sildenafil ↔	No dosage adjustment necessary.
Tadalafil	ETR	↓ tadalafil possible	May need to increase tadalafil dose based on clinical effect.
Vardenafil	ETR	↓ vardenafil possible	May need to increase vardenafil dose based on clinical effect.

[a] Approved dose for RPV is 25 mg once daily. Most PK interaction studies were performed using 75 to 150 mg per dose.

[b] Norbuprenorphine is an active metabolite of buprenorphine.

[c] R-methadone is the active form of methadone.

Key to Acronyms: ARV = antiretroviral; AUC = area under the curve; BID = twice daily; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; DHA = dihydroartemisinin; DLV = delavirdine; DMPA = depot medroxyprogesterone acetate; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; INR = international normalized ratio; MAC = *Mycobacterium avium* complex; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; OH-clarithromycin = active metabolite of clarithromycin; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PPI = proton pump inhibitor; RPV = rilpivirine; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

Table 18c. Drug Interactions between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 2)

Concomitant Drug Class/Name	NRTI	Effect on NRTI or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
Non-ARV—Antivirals			
Adefovir	TDF	No data	**Do not co-administer.** Serum concentrations of TDF and/or other renally eliminated drugs may be increased.
Boceprevir	TDF	No significant effect	No dose adjustment necessary.
Ganciclovir **Valganciclovir**	TDF	No data	Serum concentrations of these drugs and/or TDF may be increased. Monitor for dose-related toxicities.
	ZDV	No significant effect	Potential increase in hematologic toxicities
Ribavirin	ddI	↑ intracellular ddI	**Contraindicated. Do not co-administer.** Fatal hepatic failure and other ddI-related toxicities have been reported with co-administration.
	ZDV	Ribavirin inhibits phosphorylation of ZDV.	Avoid co-administration if possible, or closely monitor HIV virologic response and possible hematologic toxicities.
Simeprevir	TDF	No significant PK effects	No dose adjustment necessary.
Telaprevir	TDF	TDF AUC ↑ 30%, C_{min} ↑ 6% to 41%	Monitor for TDF-associated toxicity.
INSTIs			
DTG	TDF	TDF AUC ↑ 12%, C_{min} ↑ 19% DTG ↔	No dosage adjustment necessary.
RAL	TDF	RAL AUC ↑ 49%	No dosage adjustment necessary.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	3TC, ddI, TDF, ZDV	No significant effect	No dosage adjustment necessary.
Methadone	ABC	methadone clearance ↑ 22%	No dosage adjustment necessary.
	d4T	d4T AUC ↓ 23%	No dosage adjustment necessary.
	ZDV	ZDV AUC ↑ 29% to 43%	Monitor for ZDV-related adverse effects.
NRTIs			
ddI	d4T	No significant PK interaction	**Do not co-administer.** Additive toxicities of peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination.
	TDF	ddI-EC AUC and C_{max} ↑ 48% to 60%	**Avoid co-administration.**
Other			
Allopurinol	ddI	ddI AUC ↑ 113% In Patients with Renal Impairment: • ddI AUC ↑ 312%	**Contraindicated.** Potential for increased ddI-associated toxicities.
Atovaquone	ZDV	ZDV AUC ↑ 31%	Monitor for ZDV-related adverse effects.

Table 18c. Drug Interactions between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 2)

Concomitant Drug Class/Name	NRTI	Effect on NRTI or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
PIs			
ATV	ddI	With ddI-EC Plus ATV (with Food): • ddI AUC ↓ 34% • ATV no change	Administer ATV with food 2 hours before or 1 hour after ddI.
	TDF	ATV AUC ↓ 25%, C_{min} ↓ 23% to 40% (higher C_{min} with RTV than without RTV) TDF AUC ↑ 24% to 37%	Dose: ATV/r 300/100 mg daily co-administered with TDF 300 mg daily. Avoid concomitant use without RTV. If using TDF and H2 receptor antagonist in ART-experienced patients, use ATV/r 400 mg/100 mg daily. Monitor for TDF-associated toxicity.
	ZDV	ZDV C_{min} ↓ 30%, no change in AUC	Clinical significance unknown.
DRV/r	TDF	TDF AUC ↑ 22%, C_{min} ↑ 37%	Clinical significance unknown. Monitor for TDF toxicity.
LPV/r	TDF	LPV/r AUC ↓ 15% TDF AUC ↑ 34%	Clinical significance unknown. Monitor for TDF toxicity.
TPV/r	ABC	ABC AUC ↓ 35% to 44%	Appropriate doses for this combination have not been established.
	ddI	ddI-EC AUC ↔ and C_{min} ↓ 34% TPV/r ↔	Separate doses by at least 2 hours.
	TDF	TDF AUC ↔ TPV/r AUC ↓ 9%–18%, C_{min} ↓ 12% to 21%	No dosage adjustment necessary.
	ZDV	ZDV AUC ↓ 35% TPV/r AUC ↓ 31% to 43%	Appropriate doses for this combination have not been established.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral; ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; AUC = area under the curve; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; d4T = stavudine; ddI = didanosine; DRV/r = ritonavir-boosted darunavir; EC = enteric coated; LPV/r = ritonavir-boosted lopinavir; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TPV/r = ritonavir-boosted tipranavir; ZDV = zidovudine

Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 8)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Aluminium, Magnesium +/- Calcium Containing Antacids Please refer to the Miscellaneous Interactions section below for recommendations on use with other polyvalent cation products (e.g., iron, calcium supplements, multivitamins).	DTG	DTG AUC ↓ 74% if given simultaneously; DTG AUC ↓ 26% if given 2 hours before antacid	Give DTG at least 2 hours before or at least 6 hours after medications containing polyvalent cations.
	EVG/cobi/TDF/FTC	EVG AUC ↓ 40% to 50% if given simultaneously, ↓ 15% to 20% if given 2 hours before or after antacid; ↔ with 4-hour interval	Separate EVG/cobi/FTC/TDF and antacid administration by more than 2 hours.
	RAL	Al-Mg Hydroxide Antacid: • RAL C_{min} ↓ 54% to 63% if given simultaneously or 2 hours before or after antacid $CaCO_3$ Antacid: • RAL AUC ↓ 54%, C_{min} ↓ 32%	**Do not co-administer RAL and Al-Mg hydroxide antacids either simultaneously or within 2 hours.** No dosing separation necessary when co-administering RAL and $CaCO_3$ antacids.
H2-Receptor Antagonists	EVG/cobi/TDF/FTC	No significant effect	No dosage adjustment necessary.
Proton Pump Inhibitors	DTG	No significant effect	No dosage adjustment necessary.
	EVG/cobi/TDF/FTC	No significant effect	No dosage adjustment necessary.
	RAL	RAL AUC ↑ 212%, C_{min} ↑ 46%	No dosage adjustment necessary.
Anticoagulants			
Warfarin	EVG/cobi/TDF/FTC	No data, but warfarin levels may be affected	Monitor INR and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine	DTG	↓ DTG possible	Consider alternative anticonvulsant.
Oxcarbazepine **Phenobarbital** **Phenytoin**	EVG/cobi/TDF/FTC	↑ carbamazepine possible ↓ EVG possible ↓ cobi possible	Consider alternative anticonvulsant.
Ethosuximide	EVG/cobi/TDF/FTC	↑ ethosuximide possible	Clinically monitor for ethosuxamide toxicities.
Antidepressants			
SSRIs	EVG/cobi/TDF/FTC	↑ SSRI possible	Initiate with lowest dose of SSRI and titrate dose carefully based on antidepressant response.
TCAs Amitriptyline Desipramine Imipramine Nortriptyline	EVG/cobi/TDF/FTC	Desipramine AUC ↑ 65%	Initiate with lowest dose and titrate dose of TCA carefully.
Trazodone	EVG/cobi/TDF/FTC	↑ trazodone possible	Initiate with lowest dose and titrate dose of trazodone carefully.

Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 8)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Itraconazole	EVG/cobi/TDF/FTC	↑ itraconazole expected ↑ EVG and cobi possible	Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended unless dose is guided by itraconazole levels.
Posaconazole	EVG/cobi/TDF/FTC	↑ EVG and cobi possible ↑ posaconazole possible	If co-administered, monitor posaconazole concentrations
Voriconazole	EVG/cobi/TDF/FTC	↑ voriconazole expected ↑ EVG and cobi possible	Risk/benefit ratio should be assessed to justify use of voriconazole. If administered, consider monitoring voriconazole level. Adjust dose accordingly.
Antimycobacterials			
Clarithromycin	EVG/cobi/TDF/FTC	↑ clarithromycin possible ↑ cobi possible	CrCl ≥60 mL/min: • No dose adjustment is necessary. CrCl 50–60 mL/min: • Reduce clarithromycin dose by 50%. CrCl <50 mL/min: • EVG/cobi/TDF/FTC is not recommended.
Rifabutin	DTG	Rifabutin (300 mg once daily): • DTG AUC ↔, C_{min} ↓ 30%	No dosage adjustment necessary.
	EVG/cobi/TDF/FTC	Compared with rifabutin (300 mg daily) administered alone, when **rifabutin (150 mg every other day)** administered with EVG/cobi/TDF/ FTC, no significant change in rifabutin AUC; For 25-O-desacetyl-rifabutin, AUC ↑ 625% EVG AUC ↓ 21%, C_{min} ↓ 67%	**Do not co-administer.**
	RAL	RAL AUC ↑ 19%, C_{min} ↓ 20%	No dosage adjustment necessary.

Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 3 of 8)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials, continued			
Rifampin	DTG	Rifampin with DTG 50 mg BID Compared with DTG 50 mg BID Alone: • DTG AUC ↓ 54%, C_{min} ↓ 72% Rifampin with DTG 50 mg BID Compared with DTG 50 mg Once Daily Alone: • DTG AUC ↑ 33%, C_{min} ↑ 22%	Dose: DTG 50 mg BID (instead of 50 mg once daily) for patients without suspected or documented INSTI mutation. **Avoid concomitant use in patients with certain suspected or determined INSTI-associated resistance substitutions. Consider using rifabutin.**
	EVG/cobi/TDF/FTC	Significant ↓ EVG and cobi expected	**Do not co-administer.**
	RAL	RAL 400 mg: • RAL AUC ↓ 40%, C_{min} ↓ 61% Compared with RAL 400 mg BID Alone, Rifampin with RAL 800 mg BID: • RAL AUC ↑ 27%, C_{min} ↓ 53%	Dose: RAL 800 mg BID Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin.
Rifapentine	EVG/cobi/TDF/FTC	Significant ↓ EVG and cobi expected	**Do not co-administer.**
Benzodiazepines			
Clonazepam **Clorazepate** **Diazepam** **Estazolam** **Flurazepam**	EVG/cobi/TDF/FTC	↑ benzodiazepines possible	Dose reduction of benzodiazepine may be necessary. Initiate with low dose and clinically monitor. Consider alternative benzodiazepines to diazepam, such as lorazepam, oxazepam, or temazepam.
Midazolam **Triazolam**	DTG	DTG 25 mg: • midazolam AUC ↔	No dosage adjustment necessary.
	EVG/cobi/TDF/FTC	↑ midazolam expected ↑ triazolam expected	**Do not co-administer triazolam or oral midazolam and EVG/cobi/TDF/FTC.** Parenteral midazolam can be used with caution in a closely monitored setting. Consider dose reduction, especially if more than one dose is administered.
Cardiac Medications			
Anti-Arrhythmics Amiodarone, bepridil, digoxin, disopyramide, dronedarone, flecainide, systemic lidocaine, mexilitine, propafenone, quinidine	EVG/cobi/TDF/FTC	↑ anti-arrhythmics possible digoxin C_{max} ↑ 41%, AUC no significant change	Use anti-arrhythmics with caution. Therapeutic drug monitoring, if available, is recommended for anti-arrhythmics.

Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 4 of 8)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications, continued			
Bosentan	EVG/cobi/TDF/FTC	↑ bosentan possible	In Patients on EVG/cobi/FTC/TDF ≥10 Days: • Start bosentan at 62.5 mg once daily or every other day based on individual tolerability. In Patients on Bosentan who Require EVG/cobi/FTC/TDF: • Stop bosentan ≥36 hours before EVG/cobi/FTC/TDF initiation. After at least 10 days following initiation of EVG/cobi/FTC/TDF, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.
Beta-blockers	EVG/cobi/TDF/FTC	↑ beta-blockers possible	Adjust beta-blockers according to clinical response. Beta-blocker dose may need to be decreased. Some beta-blockers (e.g., metoprolol, timolol) are metabolized via CYP450 pathway. Consider using other beta-blockers (e.g., atenolol, labetalol, nadolol, sotalol) as these agents are not metabolized by CYP450 enzymes.
Dofetilide	DTG	↑ dofetilide expected	**Do not co-administer.**
Dihydropyridine and Non-Dihydropyridine CCBs	EVG/cobi/TDF/FTC	↑ CCBs possible	Co-administer with caution. Monitor for CCB efficacy and toxicities.
Corticosteroids			
Dexamethasone	EVG/cobi/TDF/FTC	↓ EVG and cobi possible	Co-administer with caution and monitor HIV virologic response.
Fluticasone Inhaled/Intranasal	EVG/cobi/TDF/FTC	↑ fluticasone possible	Co-administration may result in adrenal insufficiency, including Cushing's syndrome. Consider alternative therapy (e.g., beclomethasone), particularly for long-term use.
Methylprednisolone, Prednisolone, Triamcinolone Local injections, including intra-articular, epidural, intra-orbital	EVG/cobi/TDF/FTC	↑ glucocorticoids expected	Co-administration may result in adrenal insufficiency, including Cushing's syndrome. **Do not co-administer.** Consider alternative non-steroidal therapies. If intra-articular corticosteroid therapy required, change to alternative non-CYP3A-modulating ART (e.g., RAL, DTG).
Hepatitis C NS3/4A—PIs			
Boceprevir	DTG	DTG AUC ↔	No dosage adjustment necessary.
	EVG/cobi/TDF/FTC	No data	**Do not co-administer.**
	RAL	No significant effect	No dosage adjustment necessary.

Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 5 of 8)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C NS3/4A—PIs, continued			
Simeprevir	EVG/cobi/TDF/FTC	↑ simeprevir expected	**Co-administration is not recommended.**
	RAL	No significant effect	No dosage adjustment necessary.
Telaprevir	DTG	DTG AUC ↑ 25%	No dosage adjustment necessary.
	EVG/cobi/TDF/FTC	EVG AUC ↓ 31%, C_{min} ↑ 29% Telaprevir AUC ↔	No dosage adjustment necessary.
	RAL	RAL AUC ↑ 31% Telaprevir ↔	No dosage adjustment necessary.
Herbal Products			
St. John's Wort	DTG	↓ DTG possible	**Do not co-administer.**
Hormonal Contraceptives			
Hormonal Contraceptives	RAL	No clinically significant effect	Safe to use in combination
Norgestimate/ethinyl estradiol	DTG	No significant effect	No dosage adjustment necessary.
	EVG/cobi/TDF/FTC	Norgestimate AUC, C_{max}, C_{min} ↑ >2-fold Ethinyl estradiol AUC ↓ 25%, C_{min} ↓ 44%	The effects of increases in progestin (norgestimate) are not fully known and can include insulin resistance, dyslipidemia, acne, and venous thrombosis. Weigh the risks and benefits of the drug, and consider alternative contraceptive method.
HMG-CoA Reductase Inhibitors			
Atorvastatin	EVG/cobi/TDF/FTC	↑ atorvastatin possible	Titrate statin dose slowly and use the lowest dose possible.
Lovastatin	EVG/cobi/TDF/FTC	Significant ↑ lovastatin expected	**Contraindicated. Do not co-administer.**
Pitavastatin **Pravastatin**	EVG/cobi/TDF/FTC	No data	No dosage recommendation
Rosuvastatin	EVG/cobi/TDF/FTC	Rosuvastatin AUC ↑ 38%, C_{max} ↑ 89%	Titrate statin dose slowly and use the lowest dose possible.
Simvastatin	EVG/cobi/TDF/FTC	Significant ↑ simvastatin expected	**Contraindicated. Do not co-administer.**
Immunosuppressants			
Cyclosporine **Sirolimus** **Tacrolimus**	EVG/cobi/TDF/FTC	↑ immunosuppressant possible	Initiate with an adjusted immunosuppressant dose to account for potential increased concentration and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.

Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 6 of 8)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	EVG/cobi/TDF/FTC	Buprenorphine: AUC ↑ 35%, C_{max} ↑ 12%, C_{min} ↑ 66% Norbuprenorphine: AUC ↑ 42%, C_{max} ↑ 24%, C_{min} ↑ 57%	No dosage adjustment necessary. Clinical monitoring is recommended.
	RAL	No significant effect	No dosage adjustment necessary.
Methadone	DTG	No significant effect	No dosage adjustment necessary.
	EVG/cobi/TDF/FTC	No significant effect	No dosage adjustment necessary.
	RAL	No significant effect	No dosage adjustment necessary.
Neuroleptics			
Perphenazine **Risperidone** **Thioridazine**	EVG/cobi/TDF/FTC	↑ neuroleptic possible	Initiate neuroleptic at a low dose. Decrease in neuroleptic dose may be necessary.
PDE5 Inhibitors			
Avanafil	EVG/cobi/TDF/FTC	No data	**Co-administration is not recommended.**
Sildenafil	EVG/cobi/TDF/FTC	↑ sildenafil expected	For Treatment of Erectile Dysfunction: • Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil. For treatment of PAH: • **Contraindicated**
Tadalafil	EVG/cobi/TDF/FTC	↑ tadalafil expected	For Treatment of Erectile Dysfunction: • Start with tadalafil 5-mg dose and do not exceed a single dose of 10 mg every 72 hours. Monitor for adverse effects of tadalafil. For Treatment of PAH *In Patients on EVG/cobi/TDF/FTC >7 Days:* • Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability. *In Patients on Tadalafil who Require EVG/cobi/TDF/FTC:* • Stop tadalafil ≥24 hours before EVG/cobi/TDF/FTC initiation. Seven days after EVG/cobi/TDF/FTC initiation restart tadalafil at 20 mg once daily, and increase to 40 mg once daily based on tolerability.

Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 7 of 8)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors, continued			
Vardenafil	EVG/cobi/TDF/FTC	↑ vardenafil expected	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Sedatives/Hypnotics			
Buspirone	EVG/cobi/TDF/FTC	↑ buspirone possible	Initiate buspirone at a low dose. Dose reduction may be necessary.
Zolpidem	EVG/cobi/TDF/FTC	↑ zolpidem possible	Initiate zolpidem at a low dose. Dose reduction may be necessary.
Miscellaneous Interactions			
Colchicine	EVG/cobi/TDF/FTC	↑ colchicine expected	**Do not co-administer in patients with hepatic or renal impairment.** For Treatment of Gout Flares: • Colchicine 0.6 mg for 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For Prophylaxis of Gout Flares: • If original regimen was colchicine 0.6 mg BID, the regimen should be decreased to 0.3 mg once daily. If regimen was 0.6 mg once daily, the regimen should be decreased to 0.3 mg every other day. For Treatment of Familial Mediterranean Fever: • Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.
Metformin	DTG	↑ metformin possible	Monitor clinically when starting or stopping DTG. Dose adjustment of metformin may be necessary.
Polyvalent Cations Mg, Al, Fe, Ca, Zn, including multivitamins with minerals	All INSTIs	↓ INSTI possible if co-administered with these products	Give INSTI at least 2 hours before or at least 6 hours after medications containing polyvalent cations, including but not limited to the following products: cation-containing antacids or laxatives; iron, calcium, or magnesium supplements; and sucralfate. Many oral multivitamins also contain varying amounts of polyvalent cations. Exception: No dosing separation necessary when co-administering RAL and $CaCO_3$ antacids.

Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 8 of 8)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Interactions, continued			
Quetiapine	EVG/cobi/TDF/FTC	↑ quetiapine AUC expected.	Initiation of Quetiapine in a Patient Receiving EVG/cobi/TDF/FTC: • Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine efficacy and adverse effects. Initiation of EVG/cobi/TDF/FTC in a Patient Receiving a Stable Dose of Quetiapine: • Reduce quetiapine dose to 1/6 of the original dose, and closely monitor for quetiapine efficacy and adverse effects.
Salmeterol	EVG/cobi/TDF/FTC	↑ salmeterol possible	**Do not co-administer** because of potential increased risk of salmeterol-associated cardiovascular events.

Key to Acronyms: Al = aluminum; ART = antiretroviral therapy; AUC = area under the curve; BID = twice daily; Ca = calcium; $CaCO_3$ = calcium carbonate; CCB = calcium channel blocker; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; cobi = cobicistat; CrCl = creatinine clearance; DTG = dolutegravir; EVG = elvitegravir; Fe = iron; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; Mg = magnesium; PAH = pulmonary arterial hypertension; RAL = raltegravir; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic anti-depressants; TDF = tenofovir disoproxil fumarate; Zn = zinc

Table 18e. Drug Interactions between CCR5 Antagonist and Other Drugs (Including Antiretroviral Agents) (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 2)

Concomitant Drug Class/Name	CCR5 Antagonist	Effect on CCR5 Antagonist or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine **Phenobarbital** **Phenytoin**	MVC	↓ MVC possible	If used without a strong CYP3A inhibitor, use MVC 600 mg BID or an alternative antiepileptic agent.
Antifungals			
Itraconazole	MVC	↑ MVC possible	Dose: MVC 150 mg BID
Voriconazole	MVC	↑ MVC possible	Consider dose reduction to MVC 150 mg BID
Antimycobacterials			
Clarithromycin	MVC	↑ MVC possible	Dose: MVC 150 mg BID
Rifabutin	MVC	↓ MVC possible	If used without a strong CYP3A inducer or inhibitor, use MVC 300 mg BID. If used with a strong CYP3A inhibitor, use MVC 150 mg BID.
Rifampin	MVC	MVC AUC ↓ 64%	**Co-administration is not recommended.** If co-administration is necessary, use MVC 600 mg BID. If co-administered with a strong CYP3A inhibitor, use MVC 300 mg BID.
Rifapentine	MVC	↓ MVC expected	**Do not co-administer.**
Hepatitis C NS3/4A—PIs			
Boceprevir	MVC	MVC AUC ↑ 202%	Dose: MVC 150 mg BID
Telaprevir	MVC	MVC AUC ↑ 850%	**Co-administration is not recommended.**
Herbal Products			
St. John's Wort	MVC	↓ MVC possible	**Co-administration is not recommended.**
Hormonal Contraceptives			
Hormonal Contraceptives	MVC	No significant effect on ethinyl estradiol or levonorgestrel	Safe to use in combination
Antiretroviral Drugs			
INSTIs			
EVG/cobi/TDF/FTC	MVC	↑ MVC possible	**Do not co-administer.**
RAL	MVC	RAL AUC ↓ 37% MVC AUC ↓ 21%	Dose: standard
NNRTIs			
EFV	MVC	MVC AUC ↓ 45%	Dose: MVC 600 mg BID

Table 18e. Drug Interactions between CCR5 Antagonist and Other Drugs (Including Antiretroviral Agents) (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 2)

Concomitant Drug Class/Name	CCR5 Antagonist	Effect on CCR5 Antagonist or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
NNRTIs, continued			
ETR	MVC	MVC AUC ↓ 53%	Dose: MVC 600 mg BID in the absence of a potent CYP3A inhibitor
NVP	MVC	MVC AUC ↔	Without HIV PI: • MVC 300 mg BID With HIV PI (except TPV/r): • MVC 150 mg BID
PIs			
ATV **+/-** **RTV**	MVC	With Unboosted ATV: • MVC AUC ↑ 257% With (ATV 300 mg and RTV 100 mg) Once Daily: • MVC AUC ↑ 388%	Dose: MVC 150 mg BID
DRV/r	MVC	With (DRV 600 mg and RTV 100 mg) BID: • MVC AUC ↑ 305% With (DRV 600 mg and RTV 100 mg) BID and ETR: • MVC AUC ↑ 210%	Dose: MVC 150 mg BID
FPV **+/-** **RTV**	MVC	With (FPV 700 mg plus RTV 100 mg) BID plus MVC 300 mg BID: • MVC AUC ↑ 149%, C_{min} ↑ 374% With (FPV 1400 mg plus RTV 200 mg) Once Daily and MVC 300 mg Once Daily: • MVC AUC ↑ 126%, C_{min} ↑ 80%	Dose: MVC 150 mg BID
LPV/r	MVC	MVC AUC ↑ 295% With LPV/r and EFV: • MVC AUC ↑ 153%	Dose: MVC 150 mg BID
RTV	MVC	With RTV 100 mg BID: • MVC AUC ↑ 161%	Dose: MVC 150 mg BID
SQV/r	MVC	With SQV 1000 mg and RTV 100 mg BID: • MVC: AUC ↑ 877% With SQV 1000 mg and RTV 100 mg BID plus EFV: • MVC AUC ↑ 400%	Dose: MVC 150 mg BID
TPV/r	MVC	With TPV 500 mg and RTV 200 mg) BID: • MVC AUC ↔; • No data for TPV	Dose: MVC 300 mg BID

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; AUC = area under the curve; BID = twice daily; cobi = cobicistat; CYP = cytochrome P; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = ritonavir-boosted lopinavir; MVC = maraviroc; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RTV = ritonavir; SQV/r= ritonavir-boosted saquinavir; TDF = tenofovir disoproxil fumarate

Note: FPV is a pro-drug of APV

Table 19a. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors, and Protease Inhibitors[a] (Last updated March 27, 2012; last reviewed May 1, 2014) (Page 1 of 2)

[a] DLV, IDV, and NFV are **not** included in this table. Refer to the DLV, IDV, and NFV Food and Drug Administration package inserts for information regarding drug interactions.

PIs		NNRTIs			
		EFV	ETR	NVP	RPV[a]
ATV +/- RTV	PK data	With Unboosted ATV: • ATV: AUC ↓ 74% • EFV: no significant change With ATV 300 mg plus RTV 100 mg Once Daily with Food: • ATV concentrations similar to those with unboosted ATV without EFV	With Unboosted ATV: • ETR: AUC ↑ 50%, C_{min} ↑ 58% • ATV: AUC ↓ 17%, C_{min} ↓ 47% With ATV 300 mg plus RTV 100 mg Once Daily: • ETR: AUC and C_{min} ↑ approximately 30% • ATV: AUC ↓ 14%, C_{min} ↓ 38%	With ATV 300 mg plus RTV 100 mg Once Daily: • ATV: AUC ↓ 42%, C_{min} ↓ 72% • NVP: AUC ↑ 25%	With Boosted and Unboosted ATV: • ↑ RPV possible
	Dose	**Do not co-administer with unboosted ATV.** In ART-Naive Patients: • (ATV 400 mg plus RTV 100 mg) once daily **Do not co-administer in ART-experienced patients.**	**Do not co-administer with ATV +/– RTV.**	**Do not co-administer with ATV +/– RTV.**	Standard
DRV Always use with RTV	PK data	With DRV 300 mg plus RTV 100 mg BID: • DRV: AUC ↓ 13%, C_{min} ↓ 31% • EFV: AUC ↑ 21%	ETR 100 mg BID with DRV 600 mg plus RTV 100 mg BID: • DRV: no significant change • ETR: AUC ↓ 37%, C_{min} ↓ 49%	With DRV 400 mg plus RTV 100 mg BID: • DRV: AUC ↑ 24%[b] • NVP: AUC ↑ 27%, C_{min} ↑ 47%	RPV 150 mg Once Daily with DRV 800 mg plus RTV 100 mg Once Daily: • DRV: no significant change • RPV: AUC ↑ 130%, C_{min} ↑ 178%
	Dose	Clinical significance unknown. Use standard doses and monitor patient closely. Consider monitoring drug levels.	Standard (ETR 200 mg BID) Safety and efficacy of this combination, despite decreased ETR concentration, have been established in a clinical trial.	Standard	Standard
FPV	PK data	With FPV 1400 mg plus RTV 200 mg Once Daily: • APV: C_{min} ↓ 36%	With FPV 700 mg plus RTV 100 mg BID: • APV: AUC ↑ 69%, C_{min} ↑ 77%	With Unboosted FPV 1400 mg BID: • APV: AUC ↓ 33% • NVP: AUC ↑ 29% With FPV 700 mg plus RTV 100 mg BID: • NVP: C_{min} ↑ 22%	With Boosted and Unboosted FPV: • ↑ RPV possible
	Dose	FPV 1400 mg plus RTV 300 mg once daily or FPV 700 mg plus RTV 100 mg BID EFV standard	**Do not co-administer with FPV +/– RTV.**	FPV 700 mg plus RTV 100 mg BID NVP standard	Standard

Table 19a. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors, and Protease Inhibitors[a] (Last updated March 27, 2012; last reviewed May 1, 2014) (Page 2 of 2)

PIs		NNRTIs			
		EFV	ETR	NVP	RPV[a]
LPV/r	PK data	With LPV/r Tablets 500/125 mg BID[c] plus EFV 600 mg: • LPV levels similar to LPV/r 400/100 mg BID without EFV	With LPV/r Tablets: • ETR: AUC ↓ 35% (comparable to the decrease with DRV/r) • LPV: AUC↓ 13%	With LPV/r Capsules: • LPV: AUC ↓ 27%, C_{min} ↓51%	RPV 150 mg Once Daily with LPV/r Capsules: • LPV: no significant change • RPV: AUC ↑ 52%, C_{min} ↑ 74%
	Dose	LPV/r tablets 500/125 mg[c] BID; LPV/r oral solution 533/133 mg BID EFV standard	Standard	LPV/r tablets 500/125 mg[c] BID; LPV/r oral solution 533/133 mg BID NVP standard	Standard
RTV	PK data	Refer to information for boosted PI.	Refer to information for boosted PI.	Refer to information for boosted PI.	Refer to information for boosted PI.
	Dose				
SQV Always use with RTV	PK data	With SQV 1200 mg TID: • SQV: AUC ↓ 62% • EFV: AUC ↓ 12%	With SQV 1000 mg plus RTV 100 mg BID: • SQV: AUC unchanged • ETR: AUC ↓ 33%, C_{min} ↓ 29% Reduced ETR levels similar to reduction with DRV/r	With 600 mg TID: • SQV: AUC ↓ 24% • NVP: no significant change	↑ RPV possible
	Dose	SQV 1000 mg plus RTV 100 mg BID	SQV 1000 mg plus RTV 100 mg BID	Dose with SQV/r not established	Standard
TPV Always use with RTV	PK data	With TPV 500 mg plus RTV 100 mg BID: • TPV: AUC ↓ 31%, C_{min} ↓ 42% • EFV: no significant change With TPV 750 mg plus RTV 200 mg BID: • TPV: no significant change • EFV: no significant change	With TPV 500 mg plus RTV 200 mg BID: • ETR: AUC ↓ 76%, C_{min} ↓ 82% • TPV: AUC ↑ 18%, C_{min} ↑ 24%	With (TPV 250 mg plus RTV 200 mg) BID and with (TPV 750 mg plus RTV 100 mg) BID: • NVP: no significant change • TPV: no data	↑ RPV possible
	Dose	Standard	**Do not co-administer.**	Standard	Standard

[a] Approved dose for RPV is 25 mg once daily. Most PK interaction studies were performed using 75 mg to 150 mg RPV per dose.

[b] Based on between-study comparison.

[c] Use a combination of two LPV/r 200 mg/50 mg tablets plus one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg.

Key to Acronyms: APV = amprenavir; ART = antiretroviral therapy; ATV = atazanavir; AUC = area under the curve; BID = twice daily; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CYP = cytochrome P; DLV = delavirdine; DRV = darunavir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; FPV = fosamprenavir; IDV = indinavir; LPV = lopinavir; LPV/r = ritonavir-boosted lopinavir; MVC = maraviroc; NFV = nelfinavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = ritonavir-boosted saquinavir; TDF: tenofovir disoproxil fumarate; TID = three times a day; TPV = tipranavir

Table 19b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 3)

Drug Class/ARV		INSTI		
		DTG	EVG/cobi/TDF/FTC	RAL
NNRTIs				
EFV	**PK Data**	With DTG 50 mg Once Daily: • DTG: AUC ↓ 57%, C_{min} ↓ 75%	↑ or ↓ EVG, cobi, EFV possible	EFV: AUC ↓ 36%
	Dose	DTG 50 mg BID in patients without INSTI resistance Consider alternative combination in patients with certain INSTI-associated resistance[a] or clinically suspected INSTI resistance.	**Do not co-administer.**	Standard
ETR	**PK Data**	With ETR 200 mg BID plus DTG 50 mg Once Daily: • DTG: AUC ↓ 71%, C_{min} ↓ 88% With ETR 200 mg BID plus DRV/r 600/100 mg BID plus DTG 50 mg Once Daily: • DTG: AUC ↓ 25%, C_{min} ↓ 37% With ETR 200 mg BID plus LPV/r 400 mg/100 mg BID plus DTG 50 mg Once Daily: • DTG: AUC ↑ 11%, C_{min} ↑ 28%	↑ or ↓ EVG, cobi, ETR possible	ETR: C_{min} ↓ 17% RAL: C_{min} ↓ 34%
	Dose	**Do not co-administer ETR and DTG without concurrently administering ATV/r, DRV/r, or LPV/r.** In Patients without INSTI Resistance: • DTG 50 mg daily with ETR (concurrently with ATV/r, DRV/r, or LPV/r) In Patients with Certain INSTI-Associated Resistance or Clinically Suspected INSTI Resistance: • DTG 50mg BID with ETR (concurrently with ATV/r, DRV/r, or LPV/r)	**Do not co-administer.**	Standard

Table 19b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 3)

Drug Class/ARV		INSTI		
		DTG	EVG/cobi/TDF/FTC	RAL
NNRTIs				
NVP	**PK Data**	↓ DTG possible	↑ or ↓ EVG, cobi, NVP possible	No data
	Dose	**Do not co-administer.**	**Do not co-administer.**	Standard
RPV	**PK Data**	With DTG 50 mg Daily: • DTG: AUC ↔, C_{min} ↑ 22% • RPV: AUC ↔, C_{min} ↑ 21%	↑ or ↓ EVG, cobi, RPV possible	No data
	Dose	Standard	**Do not co-administer.**	No data
PIs				
ATV +/- RTV	**PK Data**	With Unboosted ATV plus DTG 30 mg Once Daily: • DTG: AUC↑ 91%, C_{min} ↑ 180% With (ATV 300 mg plus RTV 100 mg) Once Daily plus DTG 30 mg Once Daily: • DTG: AUC ↑ 62%, C_{min} ↑ 121%	↑ or ↓ EVG, cobi, ATV possible	With unboosted ATV: • RAL: AUC ↑ 72% With ATV 300 mg plus RTV 100 mg Once Daily: • RAL: AUC ↑ 41%
	Dose	Standard	**Do not co-administer.**	Standard
DRV Always use with RTV	**PK Data**	With (DRV 600 mg plus RTV 100 mg) BID plus DTG 30 mg Once Daily: • DTG: AUC ↓ 22%, C_{min} ↓ 38%	↑ or ↓ EVG, cobi, DRV possible	With DRV 600 mg plus RTV 100 mg BID: • RAL: AUC ↓ 29% and C_{min} ↑ 38%
	Dose	Standard Can use either once or twice daily dosing of DRV/r without dose adjustments.	**Do not co-administer.**	Standard
FPV +/- RTV	**PK Data**	With (FPV 700 mg plus RTV 100 mg) BID plus DTG 50 mg Once Daily: • DTG: AUC ↓ 35%, C_{min} ↓ 49%	↑ or ↓ EVG, cobi, FPV possible	FPV: No significant effect
	Dose	DTG 50 mg BID in patients without INSTI resistance **Consider alternative combination** in patients with certain INSTI-associated resistance[a] or clinically suspected INSTI resistance.	**Do not co-administer.**	Standard

Table 19b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated May 1, 2014; last reviewed May 1, 2014) (page 3 of 3)

Drug Class/ARV		INSTI		
		DTG	EVG/cobi/TDF/FTC	RAL
PIs, continued				
LPV/r	**PK Data**	With LPV/r 400 mg/100 mg BID plus DTG 30 mg Once Daily: • DTG: no significant effect	↑ or ↓ EVG, cobi, LPV possible RTV and cobi have similar effects on CYP3A.	↓ RAL ↔ LPV/r
	Dose	Standard Can use either once or twice daily dosing of LPV/r without dose adjustments.	**Do not co-administer.**	Standard
RTV	**PK Data**	No data with RTV alone	↑ or ↓ EVG, cobi possible RTV and cobi have similar effects on CYP3A.	With RTV 100 mg BID: • RAL: AUC ↓ 16%
	Dose	Refer to other PI/r for dosage recommendation.	**Do not co-administer.**	Standard
SQV Always use with RTV	**PK Data**	No data	↑ or ↓ EVG, cobi, SQV possible RTV and cobi have similar effects on CYP3A.	No data
	Dose	No dosage recommendation	**Do not co-administer.**	Standard
TPV Always use with RTV	**PK Data**	With (TPV 500 mg plus RTV 200 mg) BID plus DTG 50 mg Once Daily: • DTG: AUC ↓ 59%, C_{min} ↓ 76%	↑ or ↓ EVG, cobi, TPV possible RTV and cobi have similar effects on CYP3A.	With TPV 500 mg plus RTV 200 mg BID: • RAL: AUC ↓ 24%
	Dose	DTG: 50 mg BID in patients without INSTI resistance **Consider alternative combination** in patients with certain INSTI-associated resistance or clinically suspected INSTI-associated resistance substitutions.[a]	**Do not co-administer.**	Standard

[a] Refer to Tivicay product label for details.

Key to Acronyms: APV = amprenavir; ART = antiretroviral therapy; ATV = atazanavir; AUC = area under the curve; BID = twice daily; cobi= cobicistat; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CYP = cytochrome P; DLV = delavirdine; DRV = darunavir; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; ETR = etravirine; FDA = Food and Drug Administration; FPV = fosamprenavir; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = ritonavir-boosted lopinavir; MVC = maraviroc; NFV = nelfinavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = ritonavir-boosted saquinavir; TDF = tenofovir disoproxil fumarate; TID = three times a day; TPV = tipranavir

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs) (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 5)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Abacavir (ABC) *Ziagen* **Note:** Generic available in tablet formulation **Also available as a component of fixed-dose combinations.**	Ziagen: • 300 mg tablet • 20 mg/mL oral solution	Ziagen: • 300 mg BID, or • 600 mg once daily • Take without regard to meals.	Metabolized by alcohol dehydrogenase and glucuronyl transferase Renal excretion of metabolites: 82% Dosage adjustment for ABC is recommended in patients with hepatic insufficiency (see Appendix B, Table 7).	1.5 hours/ 12–26 hours	• HSRs: Patients who test positive for HLA-B*5701 are at highest risk. HLA screening should be done before initiation of ABC. Re-challenge is not recommended. • Symptoms of HSR may include fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, or fatigue or respiratory symptoms such as sore throat, cough, or shortness of breath. • Some cohort studies suggest increased risk of MI with recent or current use of ABC, but this risk is not substantiated in other studies.
Trizivir ABC with ZDV + 3TC **Note:** Generic available	Trizivir: • ABC 300 mg + ZDV 300 mg + 3TC 150 mg tablet	Trizivir: • 1 tablet BID			
Epzicom ABC with 3TC	Epzicom: • ABC 600 mg + 3TC 300 mg tablet	Epzicom: • 1 tablet once daily			
Didanosine (ddI) *Videx EC* **Note:** Generic available; dose same as Videx EC	Videx EC: • 125, 200, 250, and 400 mg capsules Videx: • 10 mg/mL oral solution	Body Weight ≥60 kg: • 400 mg once daily *With TDF:* • 250 mg once daily Body Weight <60 kg: • 250 mg once daily *With TDF:* • 200 mg once daily Take 1/2 hour before or 2 hours after a meal. **Note:** Preferred dosing with oral solution is BID (total daily dose divided into 2 doses)	Renal excretion: 50% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	1.5 hours/ >20 hours	• Pancreatitis • Peripheral neuropathy • Retinal changes, optic neuritis • Lactic acidosis with hepatic steatosis +/- pancreatitis (rare but potentially life-threatening toxicity) • Nausea, vomiting • Potential association with non-cirrhotic portal hypertension; in some cases, patients presented with esophageal varices • One cohort study suggested increased risk of MI with recent or current use of ddI, but this risk is not substantiated in other studies. • Insulin resistance/diabetes mellitus

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs) (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 5)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Emtricitabine (FTC) *Emtriva* **Also available as a component of fixed-dose combinations.**	Emtriva: • 200 mg hard gelatin capsule • 10 mg/mL oral solution	Emtriva *Capsule:* • 200 mg once daily *Oral Solution:* • 240 mg (24 mL) once daily Take without regard to meals.	Renal excretion: 86% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	10 hours/ >20 hours	• Minimal toxicity • Hyperpigmentation/skin discoloration • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue FTC.
Atripla FTC with EFV + TDF	Atripla: • FTC 200 mg + EFV 600 mg + TDF 300 mg tablet	Atripla: • 1 tablet at or before bedtime • Take on an empty stomach to reduce side effects.			
Complera FTC with RPV + TDF	Complera: • FTC 200 mg + RPV 25 mg + TDF 300 mg tablet	Complera: • 1 tablet once daily with a meal			
Stribild FTC with EVG + cobi + TDF	Stribild: • FTC 200 mg + EVG 150 mg + cobi 150 mg + TDF 300 mg tablet	Stribild: • 1 tablet once daily with food			
Truvada FTC with TDF	Truvada: • FTC 200 mg + TDF 300 mg tablet	Truvada: • 1 tablet once daily			

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs) (Last updated May 1, 2014; last reviewed May 1, 2014) (page 3 of 5)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Lamivudine (3TC) *Epivir* **Note:** Generic available in tablet formulation **Also available as a component of fixed-dose combinations.**	Epivir: • 150 and 300 mg tablets • 10 mg/mL oral solution	Epivir: • 150 mg BID, or • 300 mg once daily • Take without regard to meals.	Renal excretion: 70% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	5–7 hours/ 18–22 hours	• Minimal toxicity • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue 3TC.
Combivir 3TC with ZDV **Note:** Generic available	Combivir: • 3TC 150 mg + ZDV 300 mg tablet	Combivir: • 1 tablet BID			
Epzicom 3TC with ABC	Epzicom: • 3TC 300 mg + ABC 600 mg tablet	Epzicom: • 1 tablet once daily			
Trizivir 3TC with ZDV + ABC **Note:** Generic available	Trizivir: • 3TC 150 mg + ZDV 300 mg + ABC 300 mg tablet	Trizivir: • 1 tablet BID			
Stavudine (d4T) *Zerit* **Note:** Generic available	Zerit: • 15, 20, 30, and 40 mg capsules • 1 mg/mL oral solution	Body Weight ≥60 kg: • 40 mg BID Body Weight <60 kg: • 30 mg BID Take without regard to meals. **Note:** WHO recommends 30 mg BID dosing regardless of body weight.	Renal excretion: 50% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	1 hour/ 7.5 hours	• Peripheral neuropathy • Lipoatrophy • Pancreatitis • Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Insulin resistance/diabetes mellitus • Rapidly progressive ascending neuromuscular weakness (rare)

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIS) (Last updated May 1, 2014; last reviewed May 1, 2014) (page 4 of 5)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Tenofovir Disoproxil Fumarate (TDF) *Viread* **Also available as a component of fixed-dose combinations.**	Viread: • 150, 200, 250, 300 mg tablets • 40 mg/g oral powder	Viread: • 300 mg once daily or • 7.5 level scoops once daily (dosing scoop dispensed with each prescription; one level scoop contains 1 g of oral powder). • Take without regard to meals. Mix oral powder with 2–4 ounces of a soft food that does not require chewing (e.g., applesauce, yogurt). **Do not mix oral powder with liquid.**	Renal excretion – primary route of elimination Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	17 hours/ >60 hours	• Renal insufficiency, Fanconi syndrome, proximal tubulopathy • Osteomalacia, decrease in bone mineral density • Potential decrease in bone mineral density • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF. • Asthenia, headache, diarrhea, nausea, vomiting, and flatulence
Atripla TDF with EFV + FTC	Atripla: • TDF 300 mg + EFV 600 mg + FTC 200 mg tablet	Atripla: • 1 tablet at or before bedtime • Take on an empty stomach to reduce side effects.			
Complera TDF with RPV + FTC	Complera: • TDF 300 mg + RPV 25 mg + FTC 200 mg tablet	Complera: • 1 tablet once daily • Take with a meal.			
Stribild TDF with EVG + cobi + FTC	Stribild: • TDF 300 mg + EVG 150 mg + cobi 150 mg + FTC 200 mg tablet	Stribild: • 1 tablet once daily • Take with food.			
Truvada TDF with FTC	Truvada: • TDF 300 mg + FTC 200 mg tablet	Truvada: • 1 tablet once daily • Take without regard to meals.			

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIS) (Last updated May 1, 2014; last reviewed May 1, 2014) (page 5 of 5)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Zidovudine (ZDV) *Retrovir* **Note:** Generic available **Also available as a component of fixed-dose combinations.**	Retrovir: • 100 mg capsule • 300 mg tablet • 10 mg/mL intravenous solution • 10 mg/mL oral solution	Retrovir: • 300 mg BID, or • 200 mg TID • Take without regard to meals.	Metabolized to GAZT Renal excretion of GAZT Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	1.1 hours/ 7 hours	• Bone marrow suppression: macrocytic anemia or neutropenia • Nausea, vomiting, headache, insomnia, asthenia • Nail pigmentation • Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Insulin resistance/diabetes mellitus • Lipoatrophy • Myopathy
Combivir ZDV with 3TC **Note:** Generic available	Combivir: • ZDV 300 mg + 3TC 150 mg tablet	Combivir: • 1 tablet BID • Take without regard to meals.			
Trizivir ZDV with 3TC + ABC **Note:** Generic available	Trizivir: • ZDV 300 mg + 3TC 150 mg + ABC 300 mg tablet	Trizivir: • 1 tablet BID • Take without regard to meals.			

[a] For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; BID = twice daily; cobi = cobicistat; d4T = stavudine; ddI = didanosine; EC = enteric coated; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; GAZT = azidothymidine glucuronide; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; MI = myocardial infarction; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate; TID = three times a day; WHO = World Health Organization; ZDV = zidovudine

Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 2)

Note: Delavirdine (DLV) is not included in this table. Please refer to the DLV FDA package insert for related information.

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Half-Life	Adverse Events[b]
Efavirenz (EFV) *Sustiva* **Also available as a component of fixed-dose combination.**	• 50 and 200 mg capsules • 600 mg tablet	600 mg once daily, at or before bedtime Take on an empty stomach to reduce side effects.	Metabolized by CYPs 2B6 and 3A4 CYP3A4 mixed inducer/inhibitor (more an inducer than an inhibitor)	40–55 hours	• Rash[c] • Neuropsychiatric symptoms[d] • Increased transaminase levels • Hyperlipidemia • False-positive results with some cannabinoid and benzodiazepine screening assays reported. • Teratogenic in non-human primates and potentially teratogenic in humans
Atripla EFV with TDF + FTC	Atripla: EFV 600 mg + FTC 200 mg + TDF 300 mg tablet	1 tablet once daily, at or before bedtime			
Etravirine (ETR) *Intelence*	• 25, 100, and 200 mg tablets	200 mg BID Take following a meal.	CYP3A4, 2C9, and 2C19 substrate 3A4 inducer; 2C9 and 2C19 inhibitor	41 hours	• Rash, including Stevens-Johnson syndrome[c] • HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure, have been reported. • Nausea
Nevirapine (NVP) *Viramune* or *Viramine XR* Generic available for 200 mg tablets	• 200 mg tablet • 400 mg XR tablet • 50 mg/5 mL oral suspension	200 mg once daily for 14 days (lead-in period); thereafter, 200 mg BID, or 400 mg (Viramune XR tablet) once daily Take without regard to meals. Repeat lead-in period if therapy is discontinued for more than 7 days. In patients who develop mild-to-moderate rash without constitutional symptoms, continue lead-in period until rash resolves but not longer than 28 days total.	CYP450 substrate, inducer of 3A4 and 2B6; 80% excreted in urine (glucuronidated metabolites, <5% unchanged); 10% in feces	25–30 hours	• Rash, including Stevens-Johnson syndrome[c] • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported: ◦ Rash reported in approximately 50% of cases. ◦ Occurs at significantly higher frequency in ARV-naive female patients with pre-NVP CD4 counts >250 cells/mm^3 and in ARV-naive male patients with pre-NVP CD4 counts >400 cells/mm^3. NVP should not be initiated in these patients unless the benefit clearly outweighs the risk.

Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 2)

Note: Delavirdine (DLV) is not included in this table. Please refer to the DLV FDA package insert for related information.

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Half-Life	Adverse Events[b]
Rilpivirine (RPV) *Edurant* **Also available as a component of fixed-dose combination.**	• 25 mg tablet	25 mg once daily Take with a meal.	CYP3A4 substrate	50 hours	• Rash[c] • Depression, insomnia, headache • Hepatotoxicity
Complera RPV with TDF + FTC	Complera: • RPV 25 mg + TDF 300 mg + FTC 200 mg tablet	1 tablet once daily Take with a meal.			

[a] For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

[c] Rare cases of Stevens-Johnson syndrome have been reported with most NNRTIs; the highest incidence of rash was seen with NVP.

[d] Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, depression, suicidality, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Approximately 50% of patients receiving EFV may experience any of these symptoms. Symptoms usually subside spontaneously after 2 to 4 weeks but may necessitate discontinuation of EFV in a small percentage of patients.

Key to Abbreviations: ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte; CYP = cytochrome P; DLV = delavirdine; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; FTC = emtricitabine; HSR = hypersensitivity reaction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate; XR = extended release

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs) (Last updated February 12, 2013; last reviewed May 1, 2014) (page 1 of 5)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Atazanavir (ATV) *Reyataz*	100, 150, 200, and 300 mg capsules	ARV-Naive Patients: • ATV 300 mg + RTV 100 mg once daily; or • ATV 400 mg once daily With TDF or in ARV-Experienced Patients: • ATV 300 mg + RTV 100 mg once daily With EFV in ARV-Naive Patients: • ATV 400 mg + RTV 100 mg once daily Take with food. **For recommendations on dosing with H2 antagonists and PPIs, refer to Table 18a.**	CYP3A4 inhibitor and substrate Dosage adjustment in patients with hepatic insufficiency is recommended (see Appendix B, Table 7).	7 hours	Room temperature (up to 25° C or 77° F)	• Indirect hyperbilirubinemia • PR interval prolongation: First degree symptomatic AV block reported. Use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation. • Hyperglycemia • Fat maldistribution • Cholelithiasis • Nephrolithiasis • Renal insufficiency • Serum transaminase elevations • Hyperlipidemia (especially with RTV boosting) • Skin rash
Darunavir (DRV) *Prezista*	75, 150, 600, and 800 mg tablets 100 mg/mL oral suspension	ARV-Naive Patients or ARV-Experienced Patients with no DRV Mutations: • DRV 800 mg + RTV 100 mg once daily ARV-Experienced Patients with at Least 1 DRV Mutation: • (DRV 600 mg + RTV 100 mg) BID Unboosted DRV is **not** recommended. Take with food.	CYP3A4 inhibitor and substrate	15 hours (when combined with RTV)	Room temperature (up to 25° C or 77° F)	• Skin rash (10%): DRV has a sulfonamide moiety; Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythrema multiforme have been reported. • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs) (Last updated February 12, 2013; last reviewed May 1, 2014) (page 2 of 5)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Fosamprenavir (FPV) *Lexiva* (a prodrug of amprenavir [APV])	700 mg tablet 50 mg/mL oral suspension	ARV-Naive Patients: • FPV 1400 mg BID, or • FPV 1400 mg + RTV 100–200 mg once daily, or • FPV 700 mg + RTV 100 mg BID PI-Experienced Patients (Once-Daily Dosing **Not** Recommended): • FPV 700 mg + RTV 100 mg BID With EFV: • FPV 700 mg + RTV 100 mg BID, or • FPV 1400 mg + RTV 300 mg once daily *Tablet:* • Without RTV tablet: Take without regard to meals. • With RTV tablet: Take with meals. *Oral Suspension:* • Take without food.	APV is a CYP3A4 substrate, inhibitor, and inducer. Dosage adjustment in patients with hepatic insufficiency is recommended (see Appendix B, Table 7).	7.7 hours (APV)	Room temperature (up to 25° C or 77° F)	• Skin rash (12% to 19%): FPV has a sulfonamide moiety. • Diarrhea, nausea, vomiting • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Nephrolithiasis
Indinavir (IDV) *Crixivan*	100, 200, and 400 mg capsules	800 mg every 8 hours Take 1 hour before or 2 hours after meals; may take with skim milk or a low-fat meal. With RTV: • IDV 800 mg + RTV 100–200 mg BID Take without regard to meals.	CYP3A4 inhibitor and substrate Dosage adjustment in patients with hepatic insufficiency is recommended (see Appendix B, Table 7).	1.5–2 hours	Room temperature (15° to 30° C/59° to 86° F) Protect from moisture.	• Nephrolithiasis • GI intolerance, nausea • Hepatitis • Indirect hyperbilirubinemia • Hyperlipidemia • Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs) (Last updated February 12, 2013; last reviewed May 1, 2014) (page 3 of 5)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Ritonavir-Boosted Lopinavir (LPV/r) *Kaletra*	Tablets: • LPV 200 mg + RTV 50 mg, or • LPV 100 mg + RTV 25 mg Oral Solution: • Each 5 mL contains (LPV 400 mg + RTV 100 mg) • Oral solution contains 42% alcohol.	LPV/r 400 mg/100 mg BID or LPV/r 800 mg/200 mg once daily Once-daily dosing is not recommended for patients with ≥3 LPV-associated mutations, pregnant women, or patients receiving EFV, NVP, FPV, NFV, carbamazepine, phenytoin, or phenobarbital. With EFV or NVP (PI-Naive or PI-Experienced Patients): • LPV/r 500 mg/125 mg tablets BID (use a combination of 2 LPV/r 200 mg/50 mg tablets + 1 LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg), or • LPV/r 533 mg/133 mg oral solution BID *Tablet:* • Take without regard to meals. *Oral Solution:* • Take with food.	CYP3A4 inhibitor and substrate	5–6 hours	Oral tablet is stable at room temperature. Oral solution is stable at 2° to 8° C (36° to 46° F) until date on label and is stable for up to 2 months when stored at room temperature (up to 25° C or 77° F).	• GI intolerance, nausea, vomiting, diarrhea • Pancreatitis • Asthenia • Hyperlipidemia (especially hypertriglyceridemia) • Serum transaminase elevation • Hyperglycemia • Insulin resistance/diabetes mellitus • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • PR interval prolongation • QT interval prolongation and torsades de pointes have been reported; however, causality could not be established.
Nelfinavir (NFV) *Viracept*	250 and 625 mg tablets 50 mg/g oral powder	1250 mg BID or 750 mg TID Dissolve tablets in a small amount of water, mix admixture well, and consume immediately. Take with food.	CYP2C19 and 3A4 substrate—metabolized to active M8 metabolite; CYP3A4 inhibitor	3.5–5 hours	Room temperature (15° to 30° C/59° to 86° F)	• Diarrhea • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Serum transaminase elevation

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs) (Last updated February 12, 2013; last reviewed May 1, 2014) (page 4 of 5)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Ritonavir (RTV) *Norvir*	100 mg tablet 100 mg soft gel capsule 80 mg/mL oral solution Oral solution contains 43% alcohol.	As PK Booster for Other PIs: • 100–400 mg per day in 1 or 2 divided doses (refer to other PIs for specific dosing recommendations) *Tablet:* • Take with food. *Capsule and Oral Solution:* • To improve tolerability, take with food if possible.	CYP3A4 >2D6 substrate; potent 3A4, 2D6 inhibitor	3–5 hours	Tablets do not require refrigeration. Refrigerate capsules. Capsules can be left at room temperature (up to 25° C or 77° F) for up to 30 days. Oral solution should **not** be refrigerated; store at room temperature (20° to 25° C/68° to 77° F).	• GI intolerance, nausea, vomiting, diarrhea • Paresthesia (circumoral and extremities) • Hyperlipidemia (especially hypertriglyceridemia) • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Saquinavir (SQV) *Invirase*	500 mg tablet 200 mg capsule	SQV 1000 mg + RTV 100 mg BID Unboosted SQV is **not** recommended. Take with meals or within 2 hours after a meal.	CYP3A4 inhibitor and substrate	1–2 hours	Room temperature (15° to 30° C/59° to 86° F)	• GI intolerance, nausea, and diarrhea • Headache • Serum transaminase elevation • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • PR interval prolongation • QT interval prolongation, torsades de pointes have been reported. Patients with pre-SQV QT interval >450 msec should not receive SQV.

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs) (Last updated February 12, 2013; last reviewed May 1, 2014) (page 5 of 5)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Tipranavir (TPV) *Aptivus*	250 mg capsule 100 mg/mL oral solution	TPV 500 mg + RTV 200 mg BID Unboosted TPV is **not** recommended. With RTV Tablets: • Take with meals. With RTV Capsules or Solution: • Take without regard to meals.	CYP P450 3A4 inducer and substrate Net effect when combined with RTV (CYP3A4, 2D6 inhibitor)	6 hours after single dose of TPV/r	Refrigerate capsules. Capsules can be stored at room temperature (25º C or 77º F) for up to 60 days. Oral solution should **not** be refrigerated or frozen and should be used within 60 days after bottle is opened.	• Hepatotoxicity: Clinical hepatitis (including hepatic decompensation and hepatitis-associated fatalities) has been reported; monitor patients closely, especially those with underlying liver diseases. • Skin rash (3% to 21%): TPV has a sulfonamide moiety; use with caution in patients with known sulfonamide allergy. • Rare cases of fatal and nonfatal intracranial hemorrhages have been reported. Risks include brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism, use of anti-coagulant or anti-platelet agents (including vitamin E). • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

[a] For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

Key to Acronyms: APV = amprenavir; ARV = antiretroviral; ATV = atazanavir; AV = atrioventricular; BID = twice daily; CYP = cytochrome P; DRV = darunavir; EFV = efavirenz; FPV = fosamprenavir; GI = gastrointestinal; IDV = indinavir; LPV = lopinavir; LPV/r = ritonavir-boosted lopinavir; msec = millisecond; NFV = nelfinavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RTV = ritonavir; SQV = saquinavir; TDF = tenofovir disoproxil fumarate; TID = three times a day; TPV = tipranavir

Appendix B, Table 4. Characteristics of Integrase Inhibitors (Last updated May 1, 2014; last reviewed May 1, 2014)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Dolutegravir (DTG) *Tivicay*	50 mg tablet	ARV-Naive or ARV-Experienced, INSTI-Naive Patients: • 50 mg once daily ARV-Naive or ARV-Experienced, INSTI-Naive Patients when Co-Administered with EFV, FPV/r, TPV/r, or Rifampin: • 50 mg BID INSTI-Experienced Patients with Certain INSTI Mutations (See Product Label) or with Clinically Suspected INSTI Resistance: • 50 mg BID Take without regard to meals	UGT1A1 mediated glucuronidation Minor contribution from CYP3A4	~14 hours	• HSRs including rash, constitutional symptoms, and organ dysfunction (including liver injury) have been reported. • Insomnia • Headache
Elvitegravir (EVG) *Stribild* (only available as a co-formulated product **with** cobi/TDF/FTC)	EVG 150 mg + cobi 150 mg + TDF 300 mg + FTC 200 mg tablet	1 tablet once daily with food **Not recommended** for patients with baseline CrCl< 70 mL/min (see Appendix B Table 7 for the equation for calculating CrCl). **Not recommended for use with other antiretroviral drugs.**	EVG: CYP3A, UGT1A1/3 cobi: CYP3A, CYP2D6 (minor)	~13 hours	• Nausea • Diarrhea • New onset or worsening renal impairment • Potential decrease in bone mineral density • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue FTC and TDF.
Raltegravir (RAL) *Isentress*	400 mg tablet 25 and 100 mg chewable tablets 100 mg single-pack for oral suspension	400 mg BID With Rifampin: • 800 mg BID Take without regard to meals.	UGT1A1-mediated glucuronidation	~9 hours	• Rash, including Stevens-Johnson syndrome, HSR, and toxic epidermal necrolysis • Nausea • Headache • Diarrhea • Pyrexia • CPK elevation, muscle weakness, and rhabdomyolysis

[a] For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

Key to Abbreviations: BID = twice daily; cobi = cobicistat; CPK = creatine phosphokinase; CrCl = creatinine clearance; CYP = cytochrome P; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; FPV/r = ritonavir-boosted fosamprenavir; HBV = hepatitis B virus; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; RAL = raltegravir; TDF = tenofovir disoproxil fumerate; TPV/r = ritonavir-boosted tipranavir ; UGT = uridine diphosphate gluconyltransferase

Appendix B, Table 5. Characteristics of Fusion Inhibitor (Last updated January 29, 2008; last reviewed May 1, 2014)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendation	Serum Half-Life	Elimination	Storage	Adverse Events[a]
Enfuvirtide (T20) *Fuzeon*	• Injectable; supplied as lyophilized powder • Each vial contains 108 mg of T20; reconstitute with 1.1mL of sterile water for injection for delivery of approximately 90 mg/1 mL.	90 mg (1 mL) subcutaneously BID	3.8 hours	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool	Store at room temperature (up to 25° C or 77° F). Re-constituted solution should be refrigerated at 2° to 8°C (36° to 46° F) and used within 24 hours.	• Local injection site reactions (e.g., pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in almost 100% of patients • Increased incidence of bacterial pneumonia • HSR (<1% of patients): Symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Re-challenge is not recommended.

[a] Also see Table 14.

Key to Abbreviations: BID = twice daily, HSR = hypersensitivity reaction, T20 = enfuvirtide

Appendix B, Table 6. Characteristics of CCR5 Antagonist (Last updated March 27, 2012; last reviewed May 1, 2014)

Generic Name (Abbreviation)/ *Trade Name*	Formulation	Dosing Recommendations[a]	Serum Half-Life	Elimination/ Metabolic Pathway	Adverse Events[b]
Maraviroc (MVC) *Selzentry*	150 and 300 mg tablets	**150 mg BID** when given with drugs that are strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except TPV/r) **300 mg BID** when given with NRTIs, T20, TPV/r, NVP, RAL, and other drugs that are not strong CYP3A inhibitors or inducers **600 mg BID** when given with drugs that are CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) Take without regard to meals	14–18 hours	CYP3A4 substrate	• Abdominal pain • Cough • Dizziness • Musculoskeletal symptoms • Pyrexia • Rash • Upper respiratory tract infections • Hepatotoxicity, which may be preceded by severe rash or other signs of systemic allergic reactions • Orthostatic hypotension, especially in patients with severe renal insufficiency

[a] (For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.)

[b] Also see Table 14.

Key to Abbreviations: BID = twice daily, CYP = cytochrome P, EFV = efavirenz, ETR = etravirine, MVC = maraviroc, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, T20 = enfuvirtide, TPV/r = ritonavir-boosted tipranavir

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 6)

See the reference section at the end of this table for creatinine clearance (CrCl) calculation formulas and criteria for Child-Pugh classification.

<table>
<tr><th>ARVs
Generic Name
(Abbreviation)
Trade Name</th><th>Usual Daily Dose
(Refer to Appendix B, Tables 1–6 for additional dosing information.)</th><th>Dosing in Renal Insufficiency[a]</th><th>Dosing in Hepatic Impairment</th></tr>
<tr><td colspan="4">Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
Stribild should not be initiated in patients with CrCl <70 mL/min. Use of the following fixed-dose combinations is not recommended in patients with CrCl <50 mL/min: Atripla, Combivir, Complera, Stribild, Trizivir, or Epzicom. Use of Truvada is not recommended in patients with CrCl <30 mL/min.</td></tr>
<tr><td>Abacavir
(ABC)
Ziagen</td><td>300 mg PO BID</td><td>No dosage adjustment necessary</td><td>Child-Pugh Score 5–6:
• 200 mg PO BID (use oral solution)
Child-Pugh Score >6:
• Contraindicated</td></tr>
<tr><td>Didanosine EC
(ddI)
Videx EC</td><td>Body weight ≥60 kg:
• 400 mg PO once daily
Body weight <60 kg:
• 250 mg PO once daily</td><td><table><tr><th colspan="3">Dose (Once Daily)</th></tr><tr><th>CrCl (mL/min)</th><th>≥60 kg</th><th><60 kg</th></tr><tr><td>30–59</td><td>200 mg</td><td>125 mg</td></tr><tr><td>10–29</td><td>125 mg</td><td>125 mg</td></tr><tr><td><10, HD, CAPD</td><td>125 mg</td><td>Use ddI oral solution</td></tr></table></td><td>No dosage adjustment necessary</td></tr>
<tr><td>Didanosine oral solution
(ddI)
Videx</td><td>Body weight ≥60 kg:
• 200 mg PO BID, or
• 400 mg PO once daily
Body weight <60 kg:
• 250 mg PO once daily, or
• 125 mg PO BID</td><td><table><tr><th colspan="3">Dose (Once Daily)</th></tr><tr><th>CrCl (mL/min)</th><th>≥60 kg</th><th><60 kg</th></tr><tr><td>30–59</td><td>200 mg</td><td>150 mg</td></tr><tr><td>10–29</td><td>150 mg</td><td>100 mg</td></tr><tr><td><10, HD, CAPD</td><td>100 mg</td><td>75 mg</td></tr></table></td><td>No dosage adjustment necessary</td></tr>
<tr><td>Emtricitabine
(FTC)
Emtriva</td><td>200 mg oral capsule once daily
or
240 mg (24 mL) oral solution once daily</td><td><table><tr><th colspan="3">Dose</th></tr><tr><th>CrCl (mL/min)</th><th>Capsule</th><th>Solution</th></tr><tr><td>30–49</td><td>200 mg q48h</td><td>120 mg q24h</td></tr><tr><td>15–29</td><td>200 mg q72h</td><td>80 mg q24h</td></tr><tr><td><15 or on HD*</td><td>200 mg q96h</td><td>60 mg q24h</td></tr></table>* On dialysis days, take dose after HD session.</td><td>No dosage recommendation</td></tr>
<tr><td>Lamivudine
(3TC)
Epivir</td><td>300 mg PO once daily
or
150 mg PO BID</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td>30–49</td><td>150 mg q24h</td></tr><tr><td>15–29</td><td>1 x 150 mg, then 100 mg q24h</td></tr><tr><td>5–14</td><td>1 x 150 mg, then 50 mg q24h</td></tr><tr><td><5 or on HD*</td><td>1 x 50 mg, then 25 mg q24h</td></tr></table>* On dialysis days, take dose after HD session.</td><td>No dosage adjustment necessary</td></tr>
</table>

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 6)

<table>
<tr><th>ARVs
Generic Name
(Abbreviation)
Trade Name</th><th>Usual Daily Dose
(Refer to Appendix B, Tables 1–6 for additional dosing information.)</th><th>Dosing in Renal Insufficiency[a]</th><th>Dosing in Hepatic Impairment</th></tr>
<tr><td colspan="4">NRTIs, continued</td></tr>
<tr><td>Stavudine
(d4T)
Zerit</td><td>Body Weight ≥60 kg:
• 40 mg PO BID

Body Weight <60 kg:
• 30 mg PO BID</td><td><table><tr><th colspan="3">Dose</th></tr><tr><th>CrCl (mL/min)</th><th>≥60 kg</th><th><60 kg</th></tr><tr><td>26–50</td><td>20 mg q12h</td><td>15 mg q12h</td></tr><tr><td>10–25 or on HD*</td><td>20 mg q24h</td><td>15 mg q24h</td></tr></table>* On dialysis days, take dose after HD session.</td><td>No dosage recommendation</td></tr>
<tr><td>Tenofovir Disoproxil Fumarate
(TDF)
Viread</td><td>300 mg PO once daily</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td>30–49</td><td>300 mg q48h</td></tr><tr><td>10–29</td><td>300 mg twice weekly (every 72–96 hours)</td></tr><tr><td><10 and not on HD</td><td>No recommendation</td></tr><tr><td>On HD*</td><td>300 mg q7d</td></tr></table>*On dialysis days, take dose after HD session.</td><td>No dosage adjustment necessary</td></tr>
<tr><td>Emtricitabine
(FTC)
+
Tenofovir Disoproxil Fumarate
(TDF)
Truvada</td><td>1 tablet PO once daily</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td>30–49</td><td>1 tablet q48h</td></tr><tr><td><30 or on HD</td><td>Not recommended</td></tr></table></td><td>No dosage recommendation</td></tr>
<tr><td>Zidovudine
(AZT, ZDV)
Retrovir</td><td>300 mg PO BID</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td><15 or on HD*</td><td>100 mg TID or 300 mg once daily</td></tr></table>*On dialysis days, take dose after HD session.</td><td>No dosage recommendation</td></tr>
<tr><td colspan="4">Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</td></tr>
<tr><td>Delavirdine
(DLV)
Rescriptor</td><td>400 mg PO TID</td><td>No dosage adjustment necessary</td><td>No dosage recommendation; use with caution in patients with hepatic impairment.</td></tr>
</table>

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated May 1, 2014; last reviewed May 1, 2014) (page 3 of 6)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose (Refer to Appendix B, Tables 1–6 for additional dosing information.)	Dosing in Renal Insufficiency[a]	Dosing in Hepatic Impairment
NNRTIs, continued			
Efavirenz (EFV) *Sustiva*	600 mg PO once daily, at or before bedtime	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment.
Efavirenz (EFV) + **Tenofovir Disoproxil Fumarate** (TDF) + **Emtricitabine** (FTC) *Atripla*	1 tablet PO once daily	Not recommended for use in patients with CrCl <50 mL/min. Instead use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses according to CrCl level.	
Etravirine (ETR) *Intelence*	200 mg PO BID	No dosage adjustment necessary	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
Nevirapine (NVP) *Viramune* or *Viramune XR*	200 mg PO BID or 400 mg PO once daily (using Viramune XR formulation)	Patients on HD: Limited data; no dosage recommendation	Child-Pugh Class A: • No dosage adjustment Child-Pugh Class B or C: • Contraindicated
Rilpivirine (RPV) *Edurant*	25 mg PO once daily	No dosage adjustment necessary	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
Rilpivirine (RPV) + **Tenofovir Disoproxil Fumarate** (TDF) + **Emtricitabine** (FTC) *Complera*	1 tablet PO once daily	Not recommended for use in patients with CrCl <50 mL/min. Instead use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses levels according to CrCl level.	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated May 1, 2014; last reviewed May 1, 2014) (page 4 of 6)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose (Refer to Appendix B, Tables 1–6 for additional dosing information.)	Dosing in Renal Insufficiency[a]	Dosing in Hepatic Impairment
Protease Inhibitors (PIs)			
Atazanavir (ATV) *Reyataz*	400 mg PO once daily or ATV 300 mg + RTV 100 mg PO once daily	No dosage adjustment for patients with renal dysfunction who do not require HD ARV-Naive Patients on HD: • ATV 300 mg + RTV 100 mg once daily ARV-Experienced Patients on HD: • ATV or ATV/r not recommended	Child-Pugh Class B: • 300 mg once daily Child-Pugh Class C: • Not recommended RTV boosting is **not** recommended in patients with hepatic impairment (Child-Pugh Class B or C).
Darunavir (DRV) *Prezista*	DRV 800 mg + RTV 100 mg PO once daily (ARV-naive patients only) otherwise DRV 600 mg + RTV 100 mg PO BID	No dosage adjustment necessary	Mild-to-Moderate Hepatic Impairment: • No dosage adjustment Severe Hepatic Impairment: • Not recommended
Fosamprenavir (FPV) *Lexiva*	1400 mg PO BID or FPV 1400 mg + RTV 100–200 mg PO once daily or FPV 700 mg + RTV 100 mg PO BID	No dosage adjustment necessary	PI-Naive Patients Only *Child-Pugh Score 5–9:* • 700 mg BID *Child-Pugh Score 10–15:* • 350 mg BID PI-Naive or PI-Experienced Patients: *Child-Pugh Score 5–6:* • 700 mg BID + RTV 100 mg once daily *Child-Pugh Score 7–9:* • 450 mg BID + RTV 100 mg once daily *Child-Pugh Score 10–15:* • 300 mg BID + RTV 100 mg once daily
Indinavir (IDV) *Crixivan*	800 mg PO q8h	No dosage adjustment necessary	Mild-to-Moderate Hepatic Insufficiency Because of Cirrhosis: • 600 mg q8h
Ritonavir-Boosted Lopinavir (LPV/r) *Kaletra*	LPV/r 400/100 mg PO BID or LPV/r 800/200 mg PO once daily	Avoid once-daily dosing in patients on HD.	No dosage recommendation; use with caution in patients with hepatic impairment.

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated May 1, 2014; last reviewed May 1, 2014) (page 5 of 6)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose (Refer to Appendix B, Tables 1–6 for additional dosing information.)	Dosing in Renal Insufficiency[a]	Dosing in Hepatic Impairment
PIs, continued			
Nelfinavir (NFV) *Viracept*	1250 mg PO BID	No dosage adjustment necessary	Mild hepatic impairment: • No dosage adjustment Moderate-to-severe hepatic impairment: • Do not use.
Ritonavir (RTV) *Norvir*	As a PI-Boosting Agent: • 100–400 mg per day	No dosage adjustment necessary	Refer to recommendations for the primary PI.
Saquinavir (SQV) *Invirase*	SQV 1000 mg + RTV 100 mg PO BID	No dosage adjustment necessary	Mild-to-Moderate Hepatic Impairment: • Use with caution. Severe Hepatic Impairment: • Contraindicated
Tipranavir (TPV) *Aptivus*	TPV 500 mg + RTV 200 mg PO BID	No dosage adjustment necessary	Child-Pugh Class A: • Use with caution Child-Pugh Class B or C: • Contraindicated
Integrase Inhibitors (INSTIs)			
Dolutegravir (DTG) *Tivicay*	50 mg once daily or 50 mg BID	No dosage adjustment necessary	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • Not recommended
Elvitegravir (EVG) + **Cobicistat** (cobi) + **Tenofovir Disoproxil Fumarate** (TDF) + **Emtricitabine** (FTC) *Stribild* (only available as a co-formulated product)	1 tablet once daily	EVG/cobi/TDF/FTC **should not be initiated** in patients with CrCl <70 mL/min. Discontinue EVG/cobi/TDF/FTC if CrCl declines to <50 mL/min while patient is on therapy.	Mild-to-Moderate Hepatic Insufficiency: • No dosage adjustment necessary Severe Hepatic Insufficiency: • Not recommended
Raltegravir (RAL) *Isentress*	400 mg BID	No dosage adjustment necessary	Mild-to-Moderate Hepatic Insufficiency: • No dosage adjustment necessary Severe Hepatic Insufficiency: • No recommendation

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated May 1, 2014; last reviewed May 1, 2014) (page 6 of 6)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose (Refer to Appendix B, Tables 1–6 for additional dosing information.)	Dosing in Renal Insufficiency[a]	Dosing in Hepatic Impairment
Fusion Inhibitor			
Enfuvirtide (T20) *Fuzeon*	90 mg subcutaneous BID	No dosage adjustment necessary	No dosage adjustment necessary
CCR5 Antagonist			
Maraviroc (MVC) *Selzentry*	The recommended dose differs based on concomitant medications and potential for drug-drug interactions. See Appendix B, Table 6 for detailed dosing information.	CrCl <30 mL/min or on HD *Without Potent CYP3A Inhibitors or Inducers:* • 300 mg BID; reduce to 150 mg BID if postural hypotension occurs *With Potent CYP3A Inducers or Inhibitors:* • Not recommended	No dosage recommendations. Concentrations will likely be increased in patients with hepatic impairment.

[a] Including with chronic ambulatory peritoneal dialysis and hemodialysis

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; AZT = zidovudine; BID = twice daily; CAPD = chronic ambulatory peritoneal dialysis; cobi = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; d4T = stavudine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; EC = enteric coated; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG= elvitegravir; FPV = fosamprenavir; FTC = emtricitabine; HD = hemodialysis; IDV = indinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PO = orally; q(n)d = every (n) days; q(n)h = every (n) hours; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; T20 = enfuvirtide; TDF = tenofovir disoproxil fumarate; TID = three times daily; TPV = tipranavir; XR = extended release; ZVD = zidovudine

Creatinine Clearance Calculation	
Male: $\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine})}$	Female: $\frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times (0.85)}{72 \times (\text{serum creatinine})}$

Child-Pugh Score			
Component	**Points Scored**		
	1	**2**	**3**
Encephalopathy[a]	None	Grade 1–2	Grade 3–4
Ascites	None	Mild or controlled by diuretics	Moderate or refractory despite diuretics
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
Total bilirubin or	<2 mg/dL (<34 µmol/L)	2–3 mg/dL (34 µmol/L to 50 µmol/L)	>3 mg/dL (>50 µmol/L)
Modified total bilirubin[b]	<4 mg/dL	4–7 mg/dL	>7 mg/dL
Prothrombin time (seconds prolonged) or	<4	4–6	>6
International normalized ratio (INR)	<1.7	1.7–2.3	>2.3

[a] Encephalopathy Grades

Grade 1: Mild confusion, anxiety, restlessness, fine tremor, slowed coordination

Grade 2: Drowsiness, disorientation, asterixis

Grade 3: Somnolent but rousable, marked confusion, incomprehensible speech, incontinence, hyperventilation

Grade 4: Coma, decerebrate posturing, flaccidity

[b] Modified total bilirubin used for patients who have Gilbert's syndrome or who are taking indinavir or atazanavir

Child-Pugh Classification	Total Child-Pugh Score[c]
Class A	5–6 points
Class B	7–9 points
Class C	>9 points

[c] Sum of points for each component