DHHS Panel on Adult and Adolescent Antiretroviral Treatment Guidelines

Tables and Figure

November 3, 2008 release

The in-text and appendix tables from the November 3, 2008, release of the DHHS ***Adult and Adolescent Antiretroviral Treatment Guidelines*** have been compiled in this document to facilitate downloading. Each table is identical in numbering and content to those found in the guidelines document. References within these tables may be found in the appropriate section of the guidelines document, when applicable.

Appendix A: Financial Disclosure for Members of the DHHS Panel on Antiretroviral Guidelines for Adult and Adolescents (A Working Group of OARAC) – February 2008

Name	Panel Status*	Company	Relationship
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Name	Panel Status*	Company	Relationship
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		Glaxo Smith Kline	• Advisory Board
		Merck	• Advisory Board; Research support
		Monogram	• Advisory Board
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		Tibotec	• Advisory Board, Research support; Honoraria
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Name	Panel Status*	Company	Relationship
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Name	Panel Status*	Company	Relationship
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- C = Co-Chair; E.S. = Executive Secretary; M = Member; N/A = not applicable
- Note: The financial disclosure for Panel Members is updated annually. An updated list will be available at **http://aidsinfo.nih.gov** after February 2009.

Please refer to the **Introduction** section of the Adult Guidelines for more detailed discussions.

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 agents for the treatment of HIV infection in adults and adolescents in the United States.
Panel members	The Panel is composed of approximately 30 voting members who have expertise in HIV care and research. The U.S. government representatives include at least one representative from each of the following DHHS agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resource Services Administration (HRSA), and National Institutes of Health (NIH). These members are appointed by their respective agencies. Approximately 2/3 of the Panel are nongovernmental scientific members. There are 4–5 community members. Members who do not represent U.S. government agencies are selected after an open announcement to call for nominations. Each member serves on the Panel for a 4-year term, with an option to be reappointed for an additional term. A list of the current members can be found on Page vi of this document.
Financial Disclosure	All members of the Panel submit a written financial disclosure annually. A list of the latest disclosures can be found in Appendix A of this document.
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 generally are 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 with expertise in the area of interest. The members synthesize the available data and propose a recommendation to the Panel. All proposals are discussed at monthly teleconferences and then are voted on by the Panel members before being endorsed as official recommendations.
Other guidelines	These guidelines focus on treatment for adults and adolescents. Separate guidelines outline the use of antiretroviral therapy for such populations as pregnant women, children, and those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available at the **http://www.aidsinfo.nih.gov** Web site. There is a brief discussion of the management of women of reproductive age and pregnant women in this document. However, for more detailed and up-to-date discussion on this and other special populations, the Panel defers to the designated expertise offered by panels that have developed those guidelines.
Public comments	After release of an update in the AIDS*Info* Web site, the public is given a 2-week period to submit comments to the Panel. These comments are reviewed, and a determination is made as to whether or not revisions are indicated. The public is also able to submit comments to the Panel at **aidsinfowebmaster@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), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. For cases in which significant new data become available that may affect patient safety, a warning announcement with the Panel's recommendations may be made on the Web site until appropriate changes can be made in the guidelines document. Updated guidelines are available at the **http://www.aidsinfo.nih.gov** Web site.

Please refer to the **Introduction** section of the Adult Guidelines for more detailed discussions.

Table 2. Rating Scheme for Recommendations

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

Please refer to the **Initial Assessment and Monitoring** section of the Adult Guidelines for more detailed discussions.

Table 3. Laboratory Monitoring for Patients Prior to and After Initiation of Antiretroviral Therapy

Note: The following is a schedule for baseline and follow-up laboratory parameters to monitor prior to and after antiretroviral therapy initiation, for assessment of treatment response and detection of laboratory abnormalities. Some laboratory testing may require more frequent monitoring as clinically indicated.

	Entry into care	Follow-up before ART	ART initiation or switch[1]	2-8 weeks post–ART initiation	Every 3 -6 months	Every 6 months	Every 12 months	Treatment Failure	Clinically indicated
CD4 T-cell count	√	Every 3-6 months	√		√[2]			√	√
HIV RNA	√	Every 3-6 months	√	√	√[2]			√	√
Resistance testing	√		√[3]					√	√
HLA-B*5701 testing			√ (if considering ABC)						
Tropism testing								√ (if considering CCR5 antagonist)	√
Basic chemistry[4]	√	Every 6-12 months	√	√	√				√
ALT, AST, T. bili, D. bili,	√	Every 6-12 months	√	√	√				√
CBC w/ differential	√	Every 3-6 months	√	√ (if on ZDV)	√				√
Fasting lipid profile	√	If normal, annually	√	√ (consider after starting new ART)		√ (borderline or abnormal at last measurement)	√ (normal at last measurement)		√
Fasting glucose	√	If normal, annually	√		√ (borderline or abnormal at last measurement)	√ (normal at last measurement)			√
Urinalysis[5]	√		√			√ (patients with HIVAN)	√ (if on TDF)		√
Pregnancy test			√ (if starting EFV)						√

[1]Antiretroviral switch may be for treatment failure, adverse effects, or simplification.
[2]For adherent patients with suppressed viral load and stable clinical and immunologic status for >2-3 years, some experts may extend the interval for CD4 count and HIV RNA monitoring to every 6 months
[3]For treatment-naïve patients, if resistance testing was performed at entry into care, repeat testing is optional; for patients with viral suppression who are switching therapy for toxicity or convenience, resistance testing will not be possible and therefore, is not necessary.
[4]Serum Na, K, HCO_3, Cl, BUN, creatinine, glucose (preferably fasting); some experts suggest monitoring phosphorus while on tenofovir; determination of renal function should include estimation of creatinine clearance using Cockroft & Gault equation or estimation of glomerular filtration rate based on MDRD equation.
[5]For patients with renal disease, consult "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" (*Clin Infect Dis* 2005; 40: 1559-85).
Abbreviations: ART = antiretroviral therapy; HIVAN = HIV-associated nephropathy; ABC = abacavir; TDF = tenofovir.

Please refer to the **Drug Resistance Testing** section of the Adult Guidelines for more detailed discussions.

Table 4. Recommendations for Using Drug Resistance Assays
(Updated November 3, 2008)

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
In acute HIV infection: Drug resistance testing is recommended, regardless of whether treatment will be initiated immediately **(AIII)**. A genotypic assay is generally preferred **(AIII)**.	If treatment is to be initiated, drug resistance testing will determine whether drug-resistant virus was transmitted and will help in the design of initial or changed (if therapy was initiated prior to test results) regimens.
If therapy is deferred, repeat resistance testing should be considered at the time ART is initiated **(CIII)**.	If treatment is deferred, testing still should be performed because of the potentially greater likelihood that transmitted resistance-associated mutations will be detected earlier in the course of HIV infection; results of testing may be important when treatment is eventually initiated. Repeat testing at the time ART is initiated should be considered because of the possibility that the patient may have acquired drug-resistant virus.
In chronic HIV infection: Drug resistance testing is recommended at the time of entry into HIV care, regardless of whether therapy will be initiated **(AIII)**. A genotypic assay is generally preferred **(AIII)**.	Transmitted HIV with baseline resistance to at least one drug may be seen in 6%–16% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations.
If therapy is deferred, repeat resistance testing should be considered at the time ART is initiated **(CIII)**.	Repeat testing at the time ART is initiated should be considered because of the possibility that the patient may have acquired drug-resistant virus.
With virologic failure during combination antiretroviral therapy with HIV RNA levels >1,000 copies/mL **(AII)**. In persons with >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**.	Testing can help determine the role of resistance in drug failure and thus maximize the number of active drugs in the new regimen, if indicated. Drug resistance testing should be performed while the patient is taking his/her antiretroviral drugs or immediately (i.e., within 4 weeks) after discontinuing therapy.
With suboptimal suppression of viral load after antiretroviral therapy initiation **(AIII)**.	Testing can help determine the role of resistance and thus maximize the number of active drugs in the new regimen, if indicated.
In HIV-Infected Pregnant Women: Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AII)**.	The goals of antiretroviral therapy in HIV-infected pregnant women are to achieve maximal viral suppression for treatment of maternal HIV infection as well as for prevention of perinatal HIV transmission. Genotypic resistance testing will assist the clinician in selecting the optimal regimen for the patient.
Drug resistance assay not usually recommended	
After discontinuation (>4 weeks) of drugs **(BIII)**.	Drug resistance mutations might become minor species in the absence of selective drug pressure, and available assays might not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value, but its absence does not rule out the presence of minor drug-resistant species.
When plasma viral load <500 copies/mL **(AIII)**.	Resistance assays cannot be consistently performed because of low HIV RNA levels.

Please refer to the **When to Start** section of the Adult Guidelines for more detailed discussions.

Table 5a. Indications for Initiating Antiretroviral Therapy for the Chronically HIV-1 Infected Patient (Updated December 1, 2007)

Clinical Condition and/or CD4 Count	Recommendations
• History of AIDS-defining illness **(AI)** • CD4 count <200 cells/mm^3 **(AI)** • CD4 count 200-350 cells/mm^3 **(AII)** • Pregnant women* **(AI)** • Persons with HIV-associated nephropathy **(AI)** • Persons coinfected with hepatitis B virus (HBV), when HBV treatment is indicated (Treatment with fully suppressive antiviral drugs active against both HIV and HBV is recommended.) **(BIII)**	Antiretroviral therapy should be initiated.
• Patients with CD4 count >350 cells/mm^3 who do not meet any of the specific conditions listed above.	The optimal time to initiate therapy in asymptomatic patients with CD4 count >350 cells/mm^3 is not well defined. Patient scenarios and comorbidities should be taken into consideration. (See **Table 5b** and text regarding risks and benefits of therapy in patients with CD4 count >350 cells/mm^3).

* For women who do not require antiretroviral therapy for their own health, consideration can be given to discontinuing antiretroviral drugs postpartum. For more detailed discussion, please refer to the ***Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*** and the HIV-Infected Women section.

Table 5b. Benefits and Risks of Initiating Antiretroviral Therapy in Asymptomatic Patients with CD4 T-Cell Count >350 cells/mm^3 (Updated December 1, 2007)

Benefits and Risks of Treatment

In addition to the risks of disease progression, the decision to initiate antiretroviral therapy should also be influenced by an assessment of other potential risks and benefits associated with treatment. Potential benefits and risks of early (CD4 counts >350 cells/mm^3) or deferred (CD4 count <350 cells/mm^3) therapy initiation for the asymptomatic patient are outlined below.

Potential Benefits of Early Therapy Include:

- Maintenance of a higher CD4 count and prevention of potentially irreversible damage to the immune system
- Decreased risk for HIV-associated complications that can sometimes occur at CD4 counts >350 cells/mm3, including tuberculosis, non-Hodgkin's lymphoma, Kaposi's sarcoma, peripheral neuropathy, HPV-associated malignancies, and HIV-associated cognitive impairment
- Decreased risk of nonopportunistic conditions, including cardiovascular disease, renal disease, liver disease, and non–AIDS-associated malignancies and infections
- Decreased risk of HIV transmission to others, which will have positive public health implications

Potential Risks of Early Therapy Include:

- Development of treatment-related side effects and toxicities
- Development of drug resistance because of incomplete viral suppression, resulting in loss of future treatment options
- Less time for the patient to learn about HIV and its treatment and less time to prepare for the need for adherence to therapy
- Increased total time on medication, with greater chance of treatment fatigue
- Premature use of therapy before the development of more effective, less toxic, and/or better studied combinations of antiretroviral drugs
- Transmission of drug-resistant virus in patients who do not maintain full virologic suppression

Please refer to the **What to Start** section of the Adult Guidelines for more detailed discussions.

Table 6. Antiretroviral Therapy for Treatment-Naïve Patients (Updated November 3, 2008)

Patients naïve to antiretroviral therapy should be started on a combination regimen that consists of either:

- **1-NNRTI + 2 NRTI or**
- **PI (preferably boosted with ritonavir) + 2NRTI**

Listed below are antiretroviral component options for constructing a regimen for a treatment-naïve patient. Selection of a regimen should be individualized based on virologic efficacy, toxicities, pill burden, dosing frequency, drug-drug interaction potential, and comorbid conditions. Components are designated as preferred when clinical trial data suggest optimal and durable efficacy with acceptable tolerability and ease of use. Alternative components are those that clinical trial data show efficacy but that have disadvantages, such as antiviral activity or toxicities, compared with the preferred agent. In some cases, for an individual patient, a component listed as alternative may actually be the preferred component. When there is more than one component for a preferred or alternative option, the components are listed in alphabetical order. For management of an HIV-infected pregnant patient, please refer to ***"Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,"*** at **http://aidsinfo.nih.gov/guidelines/**.

NNRTI Options:

Recommendation	NNRTI	Population in which to avoid or use with caution
Preferred NNRTI	**Efavirenz (AI)**	Do not use during 1st trimester of pregnancy or in those with high pregnancy potential. Use with caution in patients with unstable psychiatric disease.
Alternative NNRTI	Nevirapine **(BI)**	Do not use in patients with moderate to severe hepatic impairment (Child-Pugh score B or C). Do not use in women with pre-ARV CD4 >250 cells/mm^3 or in men with pre-ARV CD4 >400 cells/ mm^3 Use with caution in patients on tenofovir/emtricitabine (or lamivudine)—early virologic failure has been reported with this combination **(CIII)**.

PI Options:

Recommendation	PI	Population in which to avoid or use with caution
Preferred PIs	**Atazanavir + ritonavir—once daily (AI)**	Do not use in patients who require high-dose (>20 mg omeprazole equivalent/day) proton pump inhibitors (PPIs). Use with caution in patients on PPIs (any dose), H2 blockers, or antacids.
	Darunavir + ritonavir—once daily (AI)	
	Fosamprenavir + ritonavir—twice daily (BI)	
	Lopinavir/ritonavir—once or twice daily (AI)	Do not use once-daily lopinavir/ritonavir in pregnant women.
Alternative PIs	Atazanavir (unboosted)—once daily **(BI)**	Do not use in combination with tenofovir or didanosine/lamivudine.
	Fosamprenavir + ritonavir—once daily— or fosamprenavir (unboosted)—twice daily **(BI)**	
	Saquinavir + ritonavir (twice daily) **(BI)**	

Dual-NRTI Options:

Recommendation	2-NRTI	Population in which to avoid or use with caution
Preferred Dual NRTI	**Tenofovir + emtricitabine (AI)**	Do not use in combination with unboosted atazanavir. Use with caution: • with nevirapine due to reports of early virologic failure • in patients with underlying renal insufficiency
Alternative Dual NRTI	Abacavir + lamivudine **(BI)**	Do not use in patients who test positive for HLA-B*5701. Use with caution in the presence of the following: • HIV RNA >100,000 copies/mL—higher rate of virologic failure reported in ACTG 5202; or • High risk for cardiovascular disease.
	Didanosine + lamivudine (or emtricitabine) **(BI)**	Do not use in combination with unboosted atazanavir. Do not use in patients with a history of pancreatitis or peripheral neuropathy.
	Zidovudine + lamivudine **(BI)**	Use with caution in the presence of pretreatment anemia and/or neutropenia (may improve or worsen with zidovudine).

Please refer to the **What to Start** section of the Adult Guidelines for more detailed discussions.

Table 7. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Updated November 3, 2008)

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

Please refer to the **What to Start** section of the Adult Guidelines for more detailed discussions.

Table 7. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Updated November 3, 2008)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PI (in alphabetical order)	**Fosamprenavir/ ritonavir (FPV/r)**	• Twice-daily dosing resulted in efficacy comparable to LPV/r • RTV-boosting: higher trough amprenavir concentration and greater antiviral effect • Once-daily dosing possible with RTV 100mg or 200mg daily • No food effect	• Skin rash • Hyperlipidemia • Once-daily dosing results in lower amprenavir concentrations than twice-daily dosing • Virologic failure with presence of amprenavir-resistant mutations may lead to suboptimal response to darunavir as salvage PI
	Lopinavir/ ritonavir (LPV/r)	• Coformulated • Once or twice-daily dosing in treatment-naïve patients • No food restriction • Recommended PI in pregnant women (twice daily only) • Greater CD4 T-cell count increase than with EFV-based regimens (ACTG 5142 and Mexican study	• Lower drug exposure in pregnant women – may need dose increase in third trimester; • Once-daily dosing not recommended in pregnant women • Once-daily dosing: lower trough concentration than twice-daily dosing
	Saquinavir + ritonavir (SQV/r)	• Efficacy similar to LPV/r with less hyperlipidemia • Alternative PI in pregnant women	• Highest pill burden among available PI regimens (6/day) • Food requirement
Dual NRTIs		**Dual NRTI Class Advantage:** Established backbone of combination antiretroviral therapy	**Dual NRTI Class Disadvantage:** Rare but serious cases of lactic acidosis with hepatic steatosis reported (d4T>ddI=ZDV>TDF=ABC=3TC=FTC)
Dual-NRTI pairs (in alphabetical order)	**Abacavir + lamivudine (ABC/3TC)**	• Non-inferior to ZDV+ 3TC with regard to virologic responses with better CD4 T-cell count response than with ZDV/3TC • Once-daily dosing • Coformulation • No food effect • No cumulative TAM-mediated resistance	• Potential for abacavir hypersensitivity reaction (HSR) in patients with HLA-B*5701 • Potential for increased cardiovascular events, especially in patients with cardiovascular risk factors • Inferior virologic responses when compared with TDF/FTC in patients with baseline HIV RNA >100,000 copies/mL in ACTG 5202 study
	Didanosine + lamivudine (ddI + 3TC) *or* Didanosine + emtricitabine (ddI + FTC)	• Once-daily dosing • No cumulative TAM-mediated resistance	• Peripheral neuropathy, pancreatitis • Food effect: must be taken on an empty stomach • Requires dosing separation from some PIs • Increase in toxicities when used with ribavirin, tenofovir, stavudine, or hydroxyurea • Preliminary data showed inferior virologic responses of ATV/ddI/FTC when compared with EFV/ZDV/3TC or EFV/TDF/FTC—combination of ATV/ddI/FTC should be avoided
	Tenofovir/ emtricitabine (or lamivudine) (TDF/FTC or TDF + 3TC)	• Better virologic responses than ZDV/3TC • Better virologic responses when compared with ABC/3TC in pts w/ baseline HIV RNA >100,000 copies/mL in ACTG 5202 study • Once-daily dosing • No food effect • Coformulated (TDF/FTC) and (EFV/TDF/FTC) • No cumulative TAM-mediated resistance	• Potential for renal impairment • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials • Potential for decrease in bone mineral density
	Zidovudine/ lamivudine (ZDV/3TC)	• Coformulated (ZDV/3TC and ZDV/3TC/ABC) • No food effect (though better tolerated with food) • Preferred 2-NRTI in pregnant women	• Bone marrow suppression, especially anemia, with ZDV • Gastrointestinal intolerance • Mitochondrial toxicity, including lipoatrophy, lactic acidosis, hepatic steatosis • Inferior to TDF/FTC in combination with EFV • Diminished CD4 T-cell responses compared with ABC/3TC

Please refer to the **What to Start** section of the Adult Guidelines for more detailed discussions.

Table 8. Antiretroviral Components Not Recommended as Initial Therapy
(Updated November 3, 2008)

Antiretroviral drugs or components (in alphabetical order)	**Reasons for not recommending as initial therapy**
Abacavir/lamivudine/zidovudine (coformulated) as triple-NRTI combination regimen **(BI)**	• Inferior virologic efficacy
Abacavir + didanosine **(BIII)**	• Insufficient data in treatment-naïve patients
Abacavir + tenofovir **(BIII)**	• Insufficient data in treatment-naïve patients
Darunavir (unboosted)	• Usage without ritonavir has not been studied
Delavirdine **(BII)**	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
Didanosine + tenofovir **(BII)**	• High rate of early virologic failure • Rapid selection of resistance mutations • Potential for immunologic nonresponse/CD4 decline
Enfuvirtide **(BIII)**	• No clinical trial experience in treatment-naïve patients • Requires twice-daily subcutaneous injections
Etravirine **(BIII)**	• Insufficient data in treatment-naïve patients
Indinavir (unboosted) **(BIII)**	• Inconvenient dosing (three times daily with meal restrictions) • Fluid requirement
Indinavir (ritonavir-boosted) **(BIII)**	• High incidence of nephrolithiasis
Maraviroc **(BIII)**	• Insufficient data in treatment-naïve patients
Nelfinavir **(BI)**	• Inferior virologic efficacy
Raltegravir **(BIII)**	• Insufficient data in treatment-naïve patients
Ritonavir as sole PI **(BIII)**	• High pill burden • Gastrointestinal intolerance
Saquinavir (unboosted) **(BI)**	• Inferior virologic efficacy
Stavudine + lamivudine **(BI)**	• Significant toxicities including lipoatrophy, peripheral neuropathy, and hyperlactatemia, including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis
Tipranavir (ritonavir-boosted) **(BI)**	• Inferior virologic efficacy

Please refer to the **What Not to Use** section of the Adult Guidelines for more detailed discussions.

Table 9. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time

(Updated January 29, 2008)

	Rationale	Exception
Antiretroviral Regimens Not Recommended		
Monotherapy with NRTI (AII)	• Rapid development of resistance • Inferior antiretroviral activity when compared with combination of three or more antiretrovirals	• No exception (see footnote below regarding the pregnant patient)
Dual-NRTI regimens (AI)	• Rapid development of resistance • Inferior antiretroviral activity when compared with combination of three or more antiretrovirals	• No exception (see footnotes below regarding the pregnant patient and postexposure prophylaxis)
Triple-NRTI regimens (AIII) except for abacavir/zidovudine/lamivudine (BI) or possibly tenofovir + zidovudine/lamivudine (BII)	• High rate of early virologic nonresponse seen when triple-NRTI combinations, including ABC/TDF/3TC or TDF/ddI/3TC, were used as initial regimen in treatment-naïve patients • Other triple-NRTI regimens have not been evaluated	• Abacavir/zidovudine/lamivudine **(BII)**; and possibly tenofovir + zidovudine/lamivudine **(BII)** in selected patients in whom other combinations are not desirable
Antiretroviral Components Not Recommended as Part of an Antiretroviral Regimen		
Atazanavir + indinavir (AIII)	• Potential additive hyperbilirubinemia	• No exception
Didanosine + stavudine (AIII)	• 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	• When no other antiretroviral options are available and potential benefits outweigh the risks **(BIII)**
2-NNRTI combination (AII)	• When EFV combined with NVP, higher incidence of clinical adverse events seen when compared to either EFV- or NVP-based regimen • Both EFV and NVP may induce metabolism and may lead to reductions in etravirine (ETV) exposure; thus, they should not be used in combination	• No exception
Efavirenz in first trimester of pregnancy or in women with significant child-bearing potential (AIII)	• Teratogenic in nonhuman primates	• When no other antiretroviral options are available and potential benefits outweigh the risks **(BIII)** (see footnote below regarding the pregnant patient)
Emtricitabine + lamivudine (AIII)	• Similar resistance profile • No potential benefit	• No exception
Etravirine + Unboosted PI (AII)	• Etravirine may induce metabolism of these PIs, appropriate doses not yet established.	• No exception
Etravirine + ritonavir-boosted atazanavir, fosamprenavir, or tipranavir (AII)	• Etravirine may induce metabolism of these PIs, appropriate doses not yet established.	• No exception
Nevirapine in treament-naïve women with CD4 >250 or men with CD4 >400 (BI)	• High incidence of symptomatic hepatotoxicity	• If no other antiretroviral option available, if used patients should be closely monitored
Stavudine + zidovudine (AII)	• Antagonistic effect on HIV-1	• No exception
Unboosted darunavir, saquinavir, or tipranavir (AII)	• Inadequate bioavailability	• No exception

When constructing an antiretroviral regimen for an HIV-infected pregnant woman, please consult ***"Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States"*** at **http://www.aidsinfo.nih.gov/guidelines**.

When considering an antiretroviral regimen to use in post-exposure prophylaxis, please consult *"Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis"* in ***CDC MMWR Recommendations and Reports***. September 30, 2005/54 (RR 09); 1–17 and *"Management of Possible Sexual, Injection-Drug-Use, or Other Non-occupational Exposure to HIV, Including Considerations Related to Antiretroviral Therapy"* in ***CDC MMWR Recommendations and Reports***. January 21, 2005/54 (RR 02); 1–19.

Please refer to the **Exposure-Response Relationship and Therapeutic Drug Monitoring** section of the Adult Guidelines for more detailed discussions.

Table 10. Suggested Minimum Target Trough Concentrations *[2-9]*

(Updated November 3, 2008)

Drug	Concentration (ng/mL)
Fosamprenavir	400 (measured as amprenavir concentration)
Atazanavir	150
Indinavir	100
Lopinavir	1,000
Nelfinavir[a]	800
Saquinavir	100–250
Efavirenz	1,000
Nevirapine	3,000
Recommendations applicable only to treatment-experienced persons who have resistant HIV-1 strains	
Maraviroc	>50
Tipranavir	20,500

a. Measurable active (M8) metabolite.

Please refer to the **Antiretroviral Use in Special Patient Populations** section of the Adult Guidelines for more detailed discussions.

Table 11. Identifying, Diagnosing, and Managing Acute HIV-1 Infection (Updated January 29, 2008)

- **Suspecting acute HIV infection:** Signs or symptoms of acute HIV infection with recent (within 2-6 weeks) high HIV risk exposure*
  - 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 a person infected with HIV or at risk for HIV, sharing of injection drug use paraphernalia, or contact of potentially infectious blood with mucous membranes or breaks in skin*

- **Differential diagnosis:** EBV- and non-EBV (e.g., CMV)-related infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, syphilis

- **Evaluation/diagnosis of acute/primary HIV infection**
  - HIV antibody EIA (rapid test if available)
    - Reactive EIA must be followed by Western blot
    - Negative EIA or reactive EIA with negative or indeterminate Western blot should be followed by a virologic test**
  - Positive virologic test in this setting is consistent with acute HIV infection
  - Positive quantitative or qualitative HIV RNA test should be confirmed with subsequent documentation of seroconversion

- **Patient management:**
  - Treatment of acute HIV infection is considered optional **(CIII)**.
  - Enrollment in clinical trial should be considered.

* 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.

** p24 antigen or HIV RNA assay. P24 antigen is less sensitive but more specific than HIV RNA tests; HIV RNA tests are generally preferred. HIV RNA tests include quantitative bDNA or RT-PCR, or qualitative transcription-mediated amplification (APTIMA, GenProbe).

Please refer to the **Limitations to Treatment Safety and Efficacy** section of the Adult Guidelines for more detailed discussions.

Table 12. Strategies to Improve Adherence to Antiretroviral Therapy

Strategies	Examples
Utilize a multidisciplinary team approach Provide an accessible, trusting healthcare team	• Nurses, social workers, pharmacists, and medications managers
Establish a trusting relationship with the patient	
Establish readiness to start ART	
Identify potential barriers to adherence prior to starting ART	• Psychosocial issues • Active substance abuse or at high risk for relapse • Low literacy level • Busy daily schedule and/or travel away from home • Lack of disclosure of HIV diagnosis • Skepticism about ART • Lack of prescription drug coverage
Provide resources for the patient	• Referrals for mental health and/or substance abuse treatment • Resources to obtain prescription drug coverage • Pillboxes
Involve the patient in ARV regimen selection	For each option, review potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of nonadherence
Assess adherence at every clinic visit	• Simple checklist patient can complete in the waiting room • Assessment also by other members of the healthcare team • Ask the patient open-ended questions (e.g., *In the last three days, please tell me how you took your medicines?*)
Identify the type of nonadherence	• Failure to fill the prescription(s) • Failure to take the right dose(s) at the right time(s) • Nonadherence to food requirements
Identify reasons for nonadherence	• Adverse effects from medications • Complexity of regimen – pill burden, dosing frequency, etc. • Difficulty swallowing large pills • Forgetfulness • Failure to understand dosing instructions • Inadequate understanding of drug resistance and its relationship to adherence • Pill fatigue • Reassess other potential barriers listed above
Assess and simplify regimen, if possible	

Please refer to the **Adverse Effects of Antiretroviral Agents** section of the Adult Guidelines for more detailed discussions.

Table 13. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Bleeding events	TPV/r: reports of intracranial hemorrhage (ICH) PIs: ↑ bleeding in hemophiliac patients	Median time to ICH event: 525 days on TPV/r therapy Hemophiliac patients: ↑ spontaneous bleeding tendency – in joints, muscles, soft tissues, and hematuria	In 2006, 13 cases of ICH reported, w/ TPV/r use, including 8 fatalities *[18]* For hemophilia: frequency unknown	For ICH: • Patients with CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension, alcohol abuse, or receiving anticoagulant or anti-platelet agents including vitamin E For hemophiliac patients: • PI use	Avoid Vitamin E supplements, particularly with the oral solution formulation of tipranavir For ICH: • Avoid use of TPV/r in patients at risk for ICH For hemophiliac patients: • Consider using NNRTI-based regimen • Monitor for spontaneous bleeding	For ICH: • Discontinue TPV/r ; manage ICH with supportive care For hemophiliac patients: • May require increased use of Factor VIII products
Bone marrow suppression	ZDV	Onset: few weeks to months Laboratory abnormalities: • anemia (usually macrocytic) • neutropenia Symptoms: fatigue because of anemia; potential for increased bacterial infections because of neutropenia	Severe anemia (Hgb <7 g/dL): 1.1%–4% Severe neutropenia (ANC <500 cells/mm^3): 1.8%–8%	• Advanced HIV • High dose • Pre-existing anemia or neutropenia • Concomitant use of bone marrow suppressants (e.g., cotrimoxazole, ganciclovir, valganciclovir, etc.) or drugs that cause hemolytic anemia (e.g., ribavirin)	• Avoid use in patients at risk • Avoid other bone marrow suppressants if possible • Monitor CBC with differential after the 1st few weeks, then at least every 3 months (more frequently in patients at risk)	• Switch to another NRTI if there is an alternative option; • Discontinue concomitant bone marrow suppressant if there is an alternative option; otherwise: For neutropenia: • Identify and treat other causes • Consider treatment with filgrastim For anemia: • Identify and treat other causes of anemia (if present) • Blood transfusion if indicated • Consider erythropoietin therapy
Cardiovascular effects [including myocardial infarction (MI)] and cerebrovascular accidents (CVA)	MI & CVA: associated with PI use MI only: Observational cohort found possible association of recent ABC & ddI use, and MI in pts with high risk for cardio-vascular events *[19]*	Onset: months to years after beginning of therapy Presentation: premature coronary artery disease or CVA	3–6 per 1,000 patient-years CVA: ~ 1 per 1,000 patient-years	Other risk factors for cardiovascular disease, such as smoking, age, hyperlipidemia, hypertension, diabetes mellitus, family history of premature coronary artery disease, and personal history of coronary artery disease	• Assess cardiac disease risk factors • Monitor & identify patients with hyperlipidemia or hyperglycemia • Consider regimen with less adverse lipid effects • Life style modification: smoking cessation, diet, and exercise	• Early diagnosis, prevention, and pharmacologic management of other cardiovascular risk factors, such as hyperlipidemia, hypertension, and insulin resistance/diabetes mellitus • Lifestyle modifications: diet, exercise, and/or smoking cessation • Switch to agents with less propensity for increasing cardiovascular risk factors
Central nervous system effects	EFV	Onset: begin with first few doses Symptoms: may include one or more of the following: drowsiness, somnolence, insomnia, abnormal dreams, dizziness, impaired concentration & attention span, depression, hallucination, exacerbation of psychiatric disorders, psychosis, suicidal ideation Most symptoms subside or diminish after 2–4 weeks	>50% of patients may have some symptoms	• Pre-existing or unstable psychiatric illnesses • Use of concomitant drugs with CNS effects • Higher plasma EFV concentrations in people with G-->T polymorphism at position 516 (516G-->T) of CYP2B6 *[20]*	• Take at bedtime or 2–3 hours before bedtime • Take on an empty stomach to reduce drug concentration & CNS effects • Warn patients regarding restriction of risky activities, such as operating heavy machinery during the 1st 2–4 weeks of therapy	• Symptoms usually diminish or disappear within 2–4 weeks • Consider switching to alternative agent if symptoms persist and cause significant impairment in daily function or exacerbation of psychiatric illness

Please refer to the **Adverse Effects of Antiretroviral Agents** section of the Adult Guidelines for more detailed discussions.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Gastrointestinal (GI) intolerance	All PIs, ZDV, ddI	Onset: within first doses Symptoms: • nausea, vomiting, abdominal pain with all listed agents • Diarrhea, most commonly seen with NFV	Varies with different agents	• All patients	•Taking with food may reduce symptoms (not recommended for ddI or unboosted IDV) • Some patients may require antiemetics or antidiarrheals pre-emptively to reduce symptoms	May spontaneously resolve or become tolerable with time; if not: For nausea & vomiting, consider: •Antiemetic prior to dosing •Switch to less emetogenic ARV For diarrhea, consider: • Bulk-forming agents, such as psyllium products • Antimotility agents, such as loperamide, diphenoxylate/atropine •Calcium tablets •Pancreatic enzymes •L-glutamate: may ↓ diarrhea, esp. when assoc. w/ NFV or LPV/r In case of severe GI loss: •Rehydration & electrolyte replacement as indicated
Hepatic failure	NVP	Onset: Greatest risk within first 6 weeks of therapy; can occur through 18 weeks Symptoms: Abrupt onset of flu-like symptoms (nausea, vomiting, myalgia, fatigue), abdominal pain, jaundice, or fever with or without skin rash; may progress to fulminant hepatic failure particularly in those with rash Approximately 1/2 of the cases have accompanying skin rash, some of which may present as part of DRESS syndrome (drug rash with eosinophilia and systemic symptoms)	Symptomatic hepatic events: • 4% overall (2.5%–11% from different trials) • In women: 11% in those w/ pre-NVP CD4 >250 cells/mm^3 vs. 0.9% w/ CD4 <250 cells/mm^3 • In men: 6.3% w/ pre-NVP CD4 >400 cells/mm^3 vs. 2.3% w/ CD4 <400 cells/mm^3	•Treatment-naive patients with higher CD4 count at initiation (>250 cells/mm^3 in women & >400 cells/mm^3 in men) •Females 3-fold higher risk than males •HIV (-) individuals when NVP is used for post-exposure prophylaxis •Possibly, high NVP concentrations	•Avoid initiation of NVP in women w/ CD4 >250 cells/mm^3 or men w/ CD4 >400 cells/mm^3 unless the benefit clearly outweighs the risk •Do not use NVP in HIV(-) individuals for post-exposure prophylaxis •Counsel patients re: signs & symptoms of hepatitis; stop NVP & seek medical attention if signs & symptoms of hepatitis, severe skin rash, or hypersensitivity reactions appear •Monitoring of ALT & AST (every 2 weeks x first month, then monthly x 3 months, then every 3 months) •Obtain AST & ALT in patients with rash •2-week dose escalation may reduce incidence of hepatic events	•Discontinue ARVs, including NVP (caution should be taken in discontinuation of 3TC, FTC, or TDF in HBV-coinfected patients) •Discontinue all other hepatotoxic agents if possible • Rule out other causes of hepatitis • Aggressive supportive care as indicated **Note:** Hepatic injury may progress despite treatment discontinuation. Careful monitoring should continue until symptom resolution. **Do not rechallenge patient with NVP.** The safety of other NNRTIs (e.g., EFV, ETR, or DLV) in patients who experienced significant hepatic event from NVP is unknown; use with caution.
Hepatotoxicity (clinical hepatitis or asymptomatic serum transaminase elevation)	All NNRTIs; all PIs; most NRTIs; maraviroc	Onset: NNRTIs: for NVP, 2/3 within 1st 12 weeks NRTIs: over months to years PIs: generally after weeks to months Symptoms/findings: **NNRTIs:** •Asymptomatic to non-specific symptoms, such as anorexia, weight loss, or fatigue. Approximately 1/2 of patients with NVP-associated symptomatic hepatic events present with skin rash. **NRTIs:** •ZDV, ddI, d4T: may cause hepatotoxicity associated with lactic acidosis with microvesicular or macrovesicular hepatic steatosis because of mitochondrial toxicity	Varies with the different agents	•HBV or HCV coinfection •Alcoholism •Concomitant hepatotoxic drugs, particularly rifampin •Elevated ALT &/or AST at baseline •For NVP-associated hepatic events: female w/ pre-NVP CD4 >250 cells/mm^3 or male w/ pre-NVP CD4 >400 cells/mm^3 •Higher drug concentrations for PIs, particularly TPV	•NVP: monitor liver-associated enzymes at baseline, at 2 & 4 weeks, then monthly for 1st 3 months; then every 3 months •TPV/RTV: contraindicated in patients with moderate to severe hepatic insufficiency; for other patients follow frequently during treatment •Other agents: monitor liver-associated enzymes at least every 3–4 months or more frequently in patients at risk	•Rule out other causes of hepatotoxicity, such as alcoholism, viral hepatitis, chronic HBV w/ 3TC, FTC, or TDF withdrawal, HBV resistance, etc. For symptomatic patients: •Discontinue all ARVs and other potential hepatotoxic agents •After symptoms subside & serum transaminases return to normal, construct a new ARV regimen without the potential offending agent(s) For asymptomatic patients: •If ALT >5–10x ULN, some may consider discontinuing ARVs, others may continue therapy with close monitoring unless direct bilirubin iw also elevated •After serum transaminases return to

Please refer to the **Adverse Effects of Antiretroviral Agents** section of the Adult Guidelines for more detailed discussions.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		• 3TC, FTC, or TDF: HBV-coinfected patients may develop severe hepatic flare when these drugs are withdrawn or when resistance develops. **PIs:** • Clinical hepatitis & hepatic decompensation have been reported with TPV/r and also with other PIs to varying degrees. Underlying liver disease increases risk. • Generally asymptomatic, some with anorexia, weight loss, jaundice, etc.				normal, construct a new ARV regimen without the potential offending agent(s) **Note:** Refer to information regarding NVP-associated symptomatic hepatic events & NRTI-associated lactic acidosis with hepatic steatosis in this table
Hyperlipidemia	All PIs (except unboosted ATV); d4T; EFV; NVP (to a less extent)	Onset: weeks to months after beginning of therapy Presentation: All PIs (except unboosted ATV): ↑ in LDL & total cholesterol (TC), & triglyceride (TG). Also: ↑ HDL seen w/ ATV,DRV, FPV, LPV, SQV when boosted w/ RTV LPV/r *[21]* & FPV/r *[22]*: disproportionate ↑ in TG EFV & NVP (to a lesser extent): ↑ in LDL & TC, and slight ↑ TG; also ↑ HDL d4T & ZDV: ↑ in LDL, TC, & TG	Varies with different agents Swiss Cohort: ↑TC & TG: 1.7–2.3x higher in patients receiving (non-ATV) PI	• Underlying hyperlipidemia • Risk based on ARV therapy PI: All RTV-boosted PI may ↑ LDL& TG; ATV/r may produce less of an ↑ in LDL & TG NNRTI: EFV >NVP *[23]* NRTI: d4T >ZDV>ABC>TDF *[24, 25]*	• Assess cardiac disease risk factors • Use PIs and NNRTIs with less adverse effect on lipids and non–d4T-based regimen • Fasting lipid profile at baseline, at 3–6 months after starting new regimen, then annually or more frequently if indicated (in high-risk patients or in patients with abnormal baseline levels)	• Lifestyle modification: diet, exercise, and/or smoking cessation • Switching to agents with less propensity for causing hyperlipidemia Pharmacologic Management: • Per HIVMA/ACTG guidelines *[26]* & National Cholesterol Education Program ATP III guidelines *[27]* • For potential interactions between ARV and lipid lowering agents, refer to **Table 15**
Hypersensitivity reaction (HSR)	ABC	Onset of 1st reaction: median onset , 9 days; approximately 90% within 1st 6 weeks Onset of rechallenge reactions: within hours of rechallenge dose Usually >2–3 acute symptoms seen with HSR, in descending frequency): high fever, diffuse skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms (pharyngitis, dyspnea/tachypnea) With continuation of ABC, symptoms may worsen to include hypotension, respiratory distress, vascular collapse Rechallenge reactions: generally greater intensity than 1st reaction, can mimic anaphylaxis	Clinically suspected ≈ 8% in clinical trial (2%–9%); 5% in retrospective analysis; significantly reduced with pre-treatment HLA-B*5701screening *[16]*	• HLA-B*5701, HLA-DR7, HLA-DQ3 • Higher incidence of grade 3 or 4 HSR with 600mg once-daily dose than 300mg twice-daily dose in one study (5% vs. 2%)	• HLA-B*5701 screening prior to initiation of ABC • Those patients tested (+) for HLA-B*5701 should be labelled as allergic to abacavir in medical records • Educate patients about potential signs and symptoms of HSR and need for reporting of symptoms promptly • Wallet card with warning information for patients • Note multiple names for products containing abacavir (ABC, ZIAGEN, EPZICOM or KIVEXA, TRIZIVIR)	• Discontinue ABC and switch to another NRTI • Rule out other causes of symptoms (e.g., intercurrent illnesses such as viral syndromes, and other causes of skin rash) • Most signs and symptoms resolve 48 hours after discontinuation of ABC *More severe cases:* • Symptomatic support: antipyretic, fluid resuscitation, pressure support (if necessary) • **Do not rechallenge patients with ABC after suspected HSR, even in patients who are (-) for HLA-B*5701. There are cases of hypersensitivity in HLA-B*5701 (-) patients.**
Insulin resistance/ diabetes mellitus (DM)	Combination ART, thymidine analogs (ZDV, d4T), some PIs linked to insulin resistance and diabetes mellitus (but this may not be a class effect)	Onset: weeks to months after beginning of therapy Presentation: Polyuria, polydipsia, polyphagia, fatigue, weakness; exacerbation of hyperglycemia in patients with underlying DM	Up to 3%–5% of patients developed diabetes in some series; D:A:D cohort incidence rate of 5.72 per 1,000 pt-yr f/up (95% CI: 5.31-6.13) *[28]* Incidence of DM in HIV (+) women in WHIS (2.5–2.9 pt- yrs) not different	• Family history of DM	• Use non-–thymidine analog–containing regimens or NNRTIs • Fasting blood glucose 1–3 months after starting new regimen, then at least every 3–6 months	• Diet and exercise • Consider switching to non–thymidine analog–containing ART • Consider switching PI to an alternative PI and/or NNRTI • Pharmacotherapeutic management per American Diabetic Association and American Association of Clinical Endocrinologists guidelines *[30, 31]*

Please refer to the **Adverse Effects of Antiretroviral Agents** section of the Adult Guidelines for more detailed discussions.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
			from HIV(-) pts *[29]* and associated with NRTIs			
Lactic acidosis/ hepatic steatosis +/- pancreatitis (severe mitochondrial toxicities)	NRTIs, esp. d4T, ddI, ZDV	Onset: months after initiation of NRTIs Symptoms: • Insidious onset with nonspecific GI prodrome (nausea, anorexia, abdominal pain, vomiting), weight loss, and fatigue; • Subsequent symptoms may be rapidly progressive, with tachycardia, tachypnea, hyperventilation, jaundice, muscular weakness, mental status changes, or respiratory distress • Some may present with multi-organ failure (e.g., hepatic failure, acute pancreatitis, encephalopathy, and respiratory failure) Laboratory findings: • Increased lactate (often >5 mmol/L) • Low arterial pH (some as low as <7.0) • Low serum bicarbonate • Increased anion gap • Elevated serum transaminases, prothrombin time, bilirubin • Low serum albumin • Increase serum amylase & lipase in patients with pancreatitis • Histologic findings of the liver: microvesicular or macrovesicular steatosis Mortality up to 50% in some case series, esp. in patients with serum lactate >10 mmol/L	Rare Depends on regimen and patient sex: U.S.: 0.85 cases per 1,000 pt-yrs *[32]* South Africa: 16.1 per 1,000 pt-yrs in female & 1.2 cases per 1,000 pt-yrs in male patients[7]	• d4T + ddI • d4T, ZDV, ddI use (d4T most frequently implicated) • Long duration of NRTI use • Female gender • Obesity • Pregnancy (esp. with d4T + ddI) • ddI + hydroxyurea or ribavirin	• Routine monitoring of lactic acid not recommended • Consider obtaining lactate levels in patients with low serum bicarbonate or high anion gap and with complaints consistent with lactic acidosis • Appropriate phlebotomy technique for obtaining lactate level should be employed	• For mild cases, consider switching off offending drugs to safe alternatives • For severe lactic acidosis, discontinue all ARVs if this syndrome is highly suspected (diagnosis is established by clinical correlations, drug history, and lactate level) • Symptomatic support with fluid hydration • Some patients may require IV bicarbonate infusion, hemodialysis or hemofiltration, parenteral nutrition, or mechanical ventilation • IV thiamine and/or riboflavin, which resulted in rapid resolution of hyperlactatemia in some case reports **Note:** • Interpretation of high lactate level should be done in the context of clinical findings • The implication of asymptomatic hyperlactatemia is unknown at this point **ARV treatment options**: • Use NRTIs with less propensity for mitochondrial toxicity (e.g., ABC, TDF, 3TC, FTC) • Recommend close monitoring of serum lactate after restarting NRTIs • Consider NRTI-sparing regimens
Lipodystrophy	Lipo-atrophy: NRTIs (d4T > ZDV > TDF, ABC, 3TC, FTC), especially when combined with EFV *[33]* Lipo-hypertrophy: Abdominal fat gain seen with PI- or NNRTI-based regimens & with thymidine analogs (e.g., d4T, ZDV)	Onset: gradual: months after initiation of therapy Symptoms: • Lipoatrophy: peripheral fat loss manifested as facial thinning and as thinning of extremities and buttocks (d4T) • Lipohypertrophy: increase in abdominal girth, breast size, and dorsocervical fat pad (buffalo hump)	High: exact frequency uncertain and dependent on regimen; increases with duration on offending agents	• Both lipoatrophy & lipohypertrophy: low baseline body mass index	• Lipoatrophy: avoid thymidine analogs (esp. when combined with EFV), or switch from ZDV or d4T to ABC or TDF • Lipohypertrophy: pretreatment diet/exercise program may reduce incidence and extent	Lipoatrophy: • Switch from thymidine analogs to TDF or ABC: may slow or halt progression; however, may not fully reverse effects • Injectable poly-L-lactic acid or other injectable fillers for treatment of facial lipoatrophy Lipohypertrophy: • Liposuction for dorsocervical fat pad enlargement (recurrence common) • Diet/exercise • Recombinant human growth hormone, under investigation
Nephrolithiasis/ urolithiasis/ crystalluria	IDV, ATV	Onset: any time after beginning of therapy, especially at times of reduced fluid intake Laboratory abnormalities: pyuria, hematuria, crystalluria; rarely, rise	IDV: 12.4% of nephrolithiasis reported in clinical trials (4.7%–34.4%	• History of nephrolithiasis • Patients unable to maintain adequate fluid intake	• Drink at least 1.5–2 liters of non-caffeinated fluid (preferably water) per day	• Increase hydration • Pain control • May consider switching to alternative agent or therapeutic drug monitoring (IDV) if treatment option is limited

Please refer to the **Adverse Effects of Antiretroviral Agents** section of the Adult Guidelines for more detailed discussions.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		in serum creatinine & acute renal failure Symptoms: flank pain and/or abdominal pain (can be severe), dysuria, frequency	in different trials) ATV: rare; case reports only	• High peak IDV concentration (↑ATV levels not found to correlate with risk) • ↑duration of exposure • warmer climate	• Increase fluid intake at first sign of darkened urine • Monitor urinalysis and serum creatinine every 3–6 months	• Stent placement may be required
Nephrotoxicity	IDV, TDF	Onset: IDV: months after therapy TDF: weeks to months after therapy Laboratory and other findings: IDV: ↑ serum creatinine, pyuria; hydronephrosis or renal atrophy TDF: ↑ serum creatinine, proteinuria, hypophosphatemia, glycosuria, hypokalemia, non-anion gap metabolic acidosis Symptoms: IDV: asymptomatic; rarely progresses to end-stage renal disease TDF: asymptomatic to signs of nephrogenic diabetes insipidus, Fanconi syndrome with weakness and myalgias	Severe toxicity is rare	IDV and TDF: • History of renal disease; elevated creatinine at baseline • Concomitant use of nephrotoxic drugs • TDF: advanced age, low body weight, low CD4 count	• Avoid use of other nephrotoxic drugs • Adequate hydration if on IDV therapy • Monitor serum creatinine, urinalysis, serum potassium and phosphorus in patients at risk	• Stop offending agent, generally reversible • Supportive care • Electrolyte replacement as indicated
Neuro-muscular weakness syndrome (ascending)	Most frequently implicated ARV: d4T	Onset: months after initiation of ARV; then dramatic motor weakness occurring within days to weeks Symptoms: very rapidly progressive ascending demyelinating polyneuropathy, may mimic Guillain-Barré syndrome; some patients may develop respiratory paralysis requiring mechanical ventilation; has resulted in deaths in some patients Laboratory findings may include: • lactic acidosis reported in some cases • Markedly increased creatine phosphokinase	Rare	• Prolonged d4T use (found in 61 of 69 [88%] cases in one report) *[34]*	• Early recognition and discontinuation of ARVs may avoid further progression	• Discontinuation of ARVs • Supportive care, including mechanical ventilation if needed (as in cases of lactic acidosis listed previously) • Other measures attempted with variable success: plasmapheresis, high-dose corticosteroid, intravenous immunoglobulin, carnitine, acetylcarnitine • Recovery often takes months and ranges from complete recovery to substantial residual deficits • Symptoms may be irreversible in some patients **Do not rechallenge patient with offending agent.**
Osteonecrosis	Link to older PIs, but unclear whether it is caused by ARVs or by HIV	Clinical presentation (generally similar to non–HIV-infected population): • Insidious in onset, with subtle symptoms of mild to moderate periarticular pain • 85% of cases involving one or both femoral heads, but other bones may also be affected • Pain may be triggered by weight bearing or movement	Symptomatic osteonecrosis: 0.08%–1.33%Asymptomatic osteonecrosis: 4% from MRI reports	• Diabetes • Advanced HIV disease • Prior steroid use • Old age • Alcohol use • Hyperlipidemia • Role of ARVs and osteonecrosis is still controversial	• Risk reduction (e.g., limit steroid and alcohol use) • Asymptomatic cases w/ <15% bony head involvement: follow with MRI every 3–6 months x 1 yr, then every 6 months x 1 yr, then annually to assess for disease progression	Conservative management: • ↓ weight bearing on affected joint; • Remove or reduce risk factors • Analgesics as needed Surgical Intervention: • Core decompression +/- bone grafting for early stages of disease • For more severe and debilitating disease. total joint arthroplasty
Osteopenia (defined as DEXA scan t-score of 1–2.5 SD from normal) or osteoporosis (t-score >2.5 SD from normal)	Some evidence for early but not progressive bone loss after starting variety of ARVs; Assoc/ with TDF or d4T; ↓ bone density and	Onset: months to years after starting ART Symptoms: generally asymptomatic, bone pain, increased risk of fractures	Wide range depending on methodology & patient population;rate appears much higher than seen in the general population: osteopenia: 20%–54%	General: low body weight, female, white, southeast Asian, older age, alcohol use, smoking, caffeine, hypogonadism, hyperthyroidism, corticosteroids, vitamin D deficiency, history of significant weight loss, TDF	• Consider assessment of bone mineral density with DEXA scan (baseline and f/u if abnormal; proper interval in setting of HIV(+) not determined) *[36]* • Weight-bearing exercise • Calcium & vitamin D	• Switch from potentially contributing ARVs (i.e., d4T or TDF) & stop other contributing drugs • Follow National Osteoporosis Foundation guidelines *[37]* • Increase exercise, improve diet, decrease alcohol & tobacco use, increase calcium & vitamin D supplementation • Bisphosphonate (e.g., once weekly

Please refer to the **Adverse Effects of Antiretroviral Agents** section of the Adult Guidelines for more detailed discussions.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
	markers of bone turnover with TDF observed in randomized clinical trials		*[35]*; osteoporosis: 2%–27% *[35]*	exposure HIV: low CD4 T-cell count, duration of HIV, lipoatrophy, increased lactic acid levels	supplementation • Hormone replacement	alendronate) • Judicious hormone replacement • Intranasal calcitonin
Pancreatitis	ddI alone; ddI + d4T, hydroxyurea (HU), ribavirin (RBV), or TDF	Onset: usually weeks to months Laboratory abnormalities: increased serum amylase and lipase Symptoms: postprandial abdominal pain, nausea, vomiting	ddI alone: 1%–7% ddI with HU: ↑ by 4–5-fold ↑ frequency if ddI use w/ d4T, TDF, or ribavirin	• High intraceullar and/or serum ddI concentrations • History of pancreatitis • Alcoholism • Hypertriglyceridemia • Concomitant use of ddI with d4T, HU, or RBV • Use of ddI + TDF without ddI dose reduction	• ddI should not be used in patients with history of pancreatitis • Avoid concomitant use of ddI with d4T, TDF, HU, or RBV • Reduce ddI dose when used with TDF • Monitoring of amylase/lipase in asymptomatic patients is generally not recommended • Treat hypertriglyceridemia	• Discontinue offending agent(s) • Symptomatic management of pancreatitis: bowel rest, IV hydration, pain control, then gradual resumption of oral intake • Parenteral nutrition may be necessary in patients with recurrent symptoms upon resumption of oral intake
Peripheral neuropathy	ddI, d4T, ddC	Onset: weeks to months after initiation of therapy (may be sooner in patients with pre-existing neuropathy) Symptoms: • Begins with numbness & paresthesia of toes and feet • May progress to painful neuropathy of feet and calf • Upper extremities less frequently involved • Can be debilitating for some patients • May be irreversible despite discontinuation of offending agent(s)	ddI: 12%–34% in clinical trials d4T: 52% in monotherapy trial ddC: 22%–35% in clinical trials Incidence increases with prolonged exposure	• Pre-existing peripheral neuropathy; • Combined use of these NRTIs or concomitant use of other drugs that may cause neuropathy • Advanced HIV disease • High dose or concomitant use of drugs that may increase ddI intracellular activities (e.g., HU or RBV)	• Avoid using these agents in patients at risk, if possible • Avoid combined use of these agents • Patient query at each encounter	• Discontinue offending agent if alternative is available; may halt further progression, but symptoms may be irreversible • Substitute alternative ART without potential for neuropathy Pharmacologic management (with variable successes): • Gabapentin (most experience), tricyclic antidepressants, lamotrigine, oxycarbamazepine (potential for CYP interactions), topiramate, tramadol • Narcotic analgesics • Topical capsaicin • Topical lidocaine
Stevens-Johnson syndrome (SJS)/ Toxic epidermal necrosis (TEN)	NVP > EFV, DLV, ETR Also reported with APV, FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV	Onset: first few days to weeks after initiation of therapy but can occur later Symptoms: • Skin eruption with mucosal ulcerations (may involve orogingival mucosa, conjunctiva, anogenital area) • Can rapidly evolve with blister or bullae formation • May eventually evolve to epidermal detachment and/or necrosis • For NVP, may occur with hepatic toxicity • Systemic symptoms (e.g., fever, tachycardia, malaise, myalgia, arthralgia) may be present Complications: ↓ oral intake; fluid depletion; bacterial or fungal superinfection; multiorgan failure	NVP: 0.3%–1%; DLV & EFV: 0.1%; ETR: <0.1% 1–2 case reports for ABC, FPV, ddI, ZDV, IDV, LPV/r, ATV, DRV	• NVP: Female, Black, Asian, Hispanic	• For NVP: 2-week lead-in period with 200mg once daily, then escalate to 200mg twice daily • Educate patients to report symptoms as soon as they appear • Avoid use of corticosteroid during NVP dose escalation: may increase incidence of rash	• Discontinue all ARVs and any other possible agent(s) (e.g., cotrimoxazole) Aggressive symptomatic support may include: • Intensive care support • Aggressive local wound care (e.g., in a burn unit) • Intravenous hydration • Parenteral nutrition, if needed • Pain management • Antipyretics • Empiric broad-spectrum antimicrobial therapy if superinfection is suspected Controversial management strategies: • Corticosteroid • Intravenous immunoglobulin **Do not rechallenge patient with offending agent.** • It is unknown whether patients who experienced SJS while on one NNRTI are more susceptible to SJS from another NNRTI. Most experts would suggest avoiding use of this class unless no other options are available.

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Table 14. Drugs That Should Not Be Used With PI, NNRTI, or CCR5 Antagonist Antiretrovirals
(Updated January 29, 2008)

Drug Category[#]	Calcium Channel Blockers	Cardiac Agents	Lipid Lowering Agents	*Anti mycobacterials*[‡]	Anti-histamines[∂]	Gastro-intestinal Drugs[∂]	Neuro-leptics	Psychotropics	Ergot Alkaloids (vasoconstrictors)	Herbs	Others
Atazanavir	Bepridil	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	fluticasone indinavir irinotecan proton pump inhibitor (not recommended for unboosted ATV)
Darunavir/ ritonavir	(none)	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	as above	St. John's wort	carbamazepine phenobarbital phenytoin fluticasone[⊗]
Fosamprenavir	Bepridil	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	as above	St. John's wort	Delavirdine fluticasone oral contraceptives
Indinavir	(none)	amiodarone	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	as above	St. John's wort	atazanavir
Lopinavir/ ritonavir	(none)	flecainide propafenone	simvastatin lovastatin	rifampin[ſ] rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	as above	St. John's wort	fluticasone[⊗]
Nelfinavir	(none)	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	as above	St. John's wort	
Ritonavir	Bepridil	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	as above	St. John's wort	voriconazole (with RTV ≥400mg BID) fluticasone[⊗] alfuzosin
Saquinavir/ ritonavir	(none)	(none)	simvastatin lovastatin	rifampin[ſ] rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	as above	St. John's wort garlic supplements	fluticasone[⊗]
Tipranavir/ ritonavir	Bepridil	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	as above	St. John's wort	fluticasone[⊗]
Delavirdine	(none)	(none)	simvastatin lovastatin	rifampin rifapentine[‡] rifabutin	astemizole terfenadine	cisapride	(none)	alprazolam midazolam[Σ] triazolam	as above	St. John's wort	fosamprenavir carbamazepine phenobarbital phenytoin
Efavirenz	(none)	(none)	(none)	rifapentine[‡]	astemizole terfenadine	cisapride	(none)	midazolam[Σ] triazolam	as above	St. John's wort	
Etravirine	(none)	(none)	(none)	rifampin rifapentine[‡]	(none)	(none)	(none)	(none)	(none)	St John's wort	Unboosted PIs, ritonavir-boosted atazanavir, fosamprenavir, or tipranavir, other NNRTIs, carbamazepine, phenobarbital, phenytoin
Nevirapine	(none)	(none)	(none)	rifapentine[‡]	(none)	(none)	(none)	(none)	(none)	St. John's wort	
Maraviroc	•	•	•	rifapentine[‡]	•	•	•	•	•	St. John's wort	•

Certain listed drugs are contraindicated based on 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 among patients.

‡ HIV patients treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens; an alternative agent is recommended.

ſ A high rate of grade 4 serum transaminase elevation was seen when a higher dose of ritonavir was added to lopinavir/ritonavir or saquinavir or when double-dose lopinavir/ritonavir was used with rifampin to compensate for rifampin's induction effect, so these dosing strategies should not be used.

Σ Contraindicated 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.

† This is likely a class effect.

∂ Astemizole and terfenadine are not marketed in the United States. The manufacturer of cisapride has a limited-access protocol for patients who meet specific clinical eligibility criteria.

⊗ Concomitant use of fluticasone and ritonavir results in significantly reduced serum cortisol concentrations. Coadministration of fluticasone and ritonavir or any ritonavir-boosted PI regimen is not recommended unless potential benefit outweighs risk of systemic corticosteroid adverse effects. Fluticasone should be used with caution, and alternatives should be considered, if given with an unboosted PI regimen.

Suggested Alternatives to:

Lovastatin, simvastatin: Pravastatin and fluvastatin have the least potential for drug-drug interactions (except for pravastatin with darunavir/ritonavir, see Table 15a); atorvastatin and rosuvastatin - use with caution, start with the lowest possible dose and titrate based on tolerance and lipid-lowering efficacy.

Rifampin: Rifabutin (with dosage adjustment – see Tables 15a and b)

Astemizole, terfenadine (no longer marketed in the United States): desloratadine, loratadine, fexofenadine, cetirizine

Midazolam, triazolam: temazepam, lorazepam

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Table 15a. Drug Interactions Between Protease Inhibitors (PIs) and Other Drugs

This table provides information relating to pharmacokinetic interactions between PIs and non-antiretroviral drugs. When information is available, interactions with boosted and unboosted PIs are listed separately. For interactions among antiretroviral agents and dosing recommendations, please refer to **Table 16a**.

Concomitant Drug Class/Name	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV ± RTV	No data	↓ ATV concentrations expected when given simultaneously. Give ATV at least 2 hrs before or 1 hr after antacids or buffered medications.
	FPV	APV AUC ↓ 18%; Cmin: no significant change	Can be given simultaneously or separated at least 2 hrs before or 1 hr after antacids.
	DRV/r, FPV/r, IDV ± RTV, LPV/r, NFV, SQV/r	No data	
	TPV/r	↓ TPV ~30%	Give TPV at least 2 hrs before or 1 hr after antacids.
H_2 Receptor Antagonists	**RTV-boosted PI**		
	ATV/r	↓ ATV	H_2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40mg BID in treatment-naïve patients or 20mg BID in treatment-experienced patients. ATV 300mg + RTV 100mg should be administered simultaneously with and/or ≥10 hours after the H_2 receptor antagonist. In treatment-experienced patients, if TDF is used with H_2 receptor antagonists, ATV 400mg + RTV 100mg should be used.
	DRV/r, LPV/r	No effect	
	FPV/r, SQV/r, TPV/r	No data	
	PIs without RTV:		
	ATV	↓ ATV	H_2 receptor antagonist single dose should not exceed a dose equivalent of famotidine 20mg or total daily dose equivalent of famotidine 20mg BID in treatment-naïve patients. ATV should be administered ≥2 hours before and/or ≥10 hours after the H_2 receptor antagonist.
	FPV	APV AUC ↓ 30%; Cmin: unchanged	Separate administration if coadministration is necessary. Consider boosting with RTV.
	IDV, NFV	No data	
Proton Pump Inhibitors (PPIs)	ATV	↓ ATV	**PPIs are not recommended in patients receiving unboosted ATV.** In these patients, consider alternative acid-reducing agents, ritonavir-boosting, or alternative PIs.
	ATV/r	↓ ATV	PPIs should not exceed a dose equivalent to omeprazole 20mg daily in treatment-naïve patients. PPIs should be administered ≥ 12 hrs prior to ATV/r. **PPIs are not recommended in treatment-experienced patients**.
	DRV/r, FPV ± RTV, LPV/r,	No effect	
	IDV ± RTV	No data	
	NFV	NFV AUC ↓ 36% M8 AUC ↓ 92%	**Do not coadminister PPIs and NFV.**
	SQV/r	SQV AUC ↑ 82%	Monitor for SQV toxicities.
	TPV/r	↓ omeprazole, TPV: no effect	May need to increase omeprazole dose.

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Concomitant Drug Class/Name	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	**RTV-boosted PI**		
	ATV/r	No effect	
	DRV/r, FPV/r, IDV/r, LPV/r	No data	
	SQV/r	No data with RTV-boosting; SQV AUC ↑ 50%, Cmax ↑ 56% with SQV 1200mg TID	
	TPV/r	TPV AUC ↑ 50%, Cmax ↑ 32%, Cmin ↑ 69%	Fluconazole >200mg daily not recommended.
	PIs without RTV		
	ATV, FPV, NFV	No data	
	IDV	No effect	
Itraconazole	**RTV-boosted PI**		
	ATV/r, DRV/r, FPV/r, IDV/r, TPV/r	No data	Potential for bi-directional inhibition between itraconazole and PIs. Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended.
	LPV/r	↑ itraconazole	Consider not exceeding 200mg itraconazole daily, or monitor itraconazole level.
	SQV/r	Bi-directional interaction has been observed.	Dose not established, but decreased itraconazole dosage may be warranted. Consider monitoring itraconazole level.
	PIs without RTV:		
	ATV, FPV, NFV	No data	Potential for bi-directional inhibition between itraconazole and PIs. Consider monitoring itraconazole level to guide dosage adjustments.
	IDV	↑ IDV IDV 600mg Q8H + itraconazole 200mg BID: AUC similar to IDV 800mg Q8H	Dose: IDV 600mg Q8H (without ritonavir); Do not exceed 200mg itraconazole BID. Dosing of IDV when used with ritonavir and itraconazole not established.
Ketoconazole	**RTV-boosted PI**:		
	ATV/r, FPV/r	↑ ketoconazole levels	Use with caution. Do not exceed 200mg ketoconazole daily. Potential for bidirectional interaction between ketoconazole & IDV/r, SQV/r, TPV/r.
	DRV/r	DRV AUC ↑ 42%, ketoconazole ↑ 3-fold	
	IDV/r	No data	
	LPV/r	May ↑ or ↓ LPV , ketoconazole ↑ 3-fold	
	SQV/r	SQV ↑ 3x (when ketoconazole used with unboosted SQV)	
	TPV/r	No data	
	PIs without RTV:		
	ATV, NFV		No dosage adjustment necessary.
	FPV	No data with FPV ↑ APV ↑ ketoconazole	Consider ketoconazole dose reduction if dose is >400mg/day. Presumably similar interaction as seen with APV: APV ↑ 31%; ketoconazole ↑ 44%
	IDV	↑ IDV	Dose: IDV 600mg Q8H. Levels: IDV ↑ 68% IDV dosage when used with ritonavir and ketoconazole has not been established.
Posaconazole	All PIs	No data	
Voriconazole	**RTV-boosted PI**		
	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	voriconazole AUC ↓ 82% with RTV 400mg BID and ↓ 39% with RTV 100mg BID	Administration of voriconazole and RTV 100mg once daily or BID is not recommended unless benefit outweighs risk. Consider monitoring voriconazole level. **Administration of voriconazole and RTV 400mg BID or higher is contraindicated.**
	PIs without RTV:		
	ATV FPV NFV	No data	Potential for bi-directional inhibition between voriconazole and PIs. Monitor for toxicities.
	IDV	No significant effect	No dose adjustment.

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Concomitant Drug Class/Name	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	**RTV-boosted PI**		
	ATV/r, DRV/r, IDV/r, LPV/r SQV/r, TPV/r	↑ carbamazepine ↓ PI level	Consider alternative anticonvulsant or monitor levels of both drugs.
	FPV/r	↓ phenytoin ↑ APV	Monitor anticonvulsant level, and adjust dose accordingly. No change in FPV/r dose recommended.
	LPV/r	↓ phenytoin ↓ phenobarbital ↓ LPV/r level May ↓ other PI levels	Consider alternative anticonvulsant or monitor levels of both drugs.
	PIs without RTV:		
	ATV FPV NFV	No data May ↓ PI levels substantially NFV ↓ phenytoin	Monitor anticonvulsant level and virologic response. Consider alternative anticonvulsant, RTV boosting for ATV and FPV, and/or monitoring PI level.
	IDV	↓ IDV	Consider alternative anticonvulsant, RTV boosting, and/or monitoring IDV level.
Anti-mycobacterials			
Clarithromycin	ATV ± RTV	clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy.
	DRV/r IDV ± RTV LPV/r SQV/r TPV/r	DRV/r ↑ Clar AUC 57%; IDV ↑ Clar AUC 53%; LPV/r ↑ Clar AUC 77%; RTV ↑ Clar 77%; SQV ↑ Clar 45%; Clar ↑ SQV 177%; TPV/r ↑ Clar 19% and ↓ active metabolite 97%; Clar ↑ TPV 66%	Reduce clarithromycin dose by 50% in patients with CrCl 30-60mL/min. Reduce clarithromycin dose by 75% in patients with CrCl <30mL/min.
	FPV	↑ APV	No dose adjustment.
	NFV	No data	
	RTV-boosted PI:		
Rifabutin	ATV ± RTV FPV/r DRV/r IDV/r LPV/r SQVr TPV/r	ATV ↑ rifabutin AUC 2.5-fold; FPV/r, DRV/r, IDV/r: no PK data, expect ↑ rifabutin; RTV (500mg bid) ↑ rifabutin 4X; LPV/r ↑ rifabutin AUC 3-fold, ↑ 25-O-desacetyl metabolite 47.5-fold; Rifabutin ↓ unboosted SQV 40%; TPV/r ↑ rifabutin AUC 2.9-fold, ↑ 25-O-desacetyl metabolite 20.7-fold	Rifabutin 150mg QOD or 3x/week. Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150mg twice weekly and RTV-boosted PIs. May consider therapeutic drug monitoring and adjust dose accordingly.
	PIs without RTV:		
	FPV	↑ rifabutin	Rifabutin 150mg daily or 300mg 3x/week
	IDV	↑ rifabutin ↓ IDV	Rifabutin 150mg daily or 300mg 3x/week + IDV 1,000mg q8h or consider RTV boosting. Levels: rifabutin ↑ 2X, IDV ↓ 32%
	NFV	↑ rifabutin 2X; ↓ NFV 750mg Q8H 32%	Rifabutin 150mg daily or 300mg 3x/week
Rifampin	All PIs	Approximately >75% ↓ in PI concentrations	**Do not coadminister rifampin and PIs.**
Benzodiazepines			
Alprazolam Diazepam	All PIs	May ↑ benzodiazepine levels RTV 200mg BID x 2 days ↑ alprazolam half-life 200% and AUC 248%	Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam
Lorazepam Oxazepam Temazepam	All PIs	No data	Metabolism of these benzodiazepines via non-CYP450 pathways decreases interaction potential compared with other benzodiazepines.

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Concomitant Drug Class/Name	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Midazolam	All PIs	↑ midazolam SQV/r ↑ midazolam (oral) AUC 1144%, ↑ Cmax 327%	**Do not coadminister oral midazolam and PIs.** Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	All PIs	RTV 200mg BID: ↑ triazolam AUC by 20x; Other PIs: No data; may significantly ↑ triazolam concentration	**Do not coadminister triazolam and PIs.**
Calcium Channel Blockers			
Dihydropyridine	ATV ± RTV	No data	Caution warranted with ATV. Dose titration should be considered as well as ECG monitoring.
	DRV/r, FPV ± RTV, NFV, TPV/r	No data	
	IDV/r	↑ amlodipine	Monitor closely.
	LPV/r SQV/r	↑ dihydropyridine	Caution is warranted and clinical monitoring of patients is recommended.
Diltiazem	ATV ± RTV	↑ diltiazem AUC 125%	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/r, FPV ± RTV, IDV ± RTV, LPV/r, NFV, TPV/r	No data	Potential for ↑ diltiazem level.
	SQV/r	↑ diltiazem	Caution is warranted, and clinical monitoring of patients is recommended.
Herbal Products			
St. John's wort	All PIs	↓ PI	Administration of St. John's wort with PIs is not recommended.
Hormonal Contraceptives			
Hormonal Contraceptives	**RTV-boosted PI:**		
	ATV/r	↓ ethinyl estradiol ↑ progestin	Oral contraceptive should contain at least 35mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.
	DRV/r, IDV/r	No data	Use alternative or additional method because of possible interaction.
	FPV/r	↓ ethinyl estradiol AUC 37%; ↓ norethindrone AUC 34%; APV: no change	Use alternative or additional method.
	LPV/r	↓ ethinyl estradiol 42%	Use alternative or additional method.
	SQV/r	↓ ethinyl estradiol	Use alternative or additional method.
	TPV/r	↓ ethinyl estradiol Cmax & AUC ↓ ~50%	Use alternative or additional method. Used as hormone replacement therapy, monitor clinically for signs of estrogen deficiency.
	PIs without RTV:		
	ATV	↑ ethinyl estradiol AUC 48%; ↑ norethindrone AUC 110%	Oral contraceptive should contain no more than 30mcg of ethinyl estradiol, or use alternate method. Oral contraceptives containing less than 25mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
	FPV	With APV: ↑ ethinyl estradiol, ↑ norethindrone, ↓ APV 20%	Use alternative method.
	IDV	↑ ethinyl estradiol; ↑ norethindrone	No dose adjustment.
	NFV	ethinyl estradiol ↓ 47%; norethindrone ↓ 18%	Use alternative or additional method.
HMG-CoA Reductase Inhibitors			
Atorvastatin	All PIs	↑ atorvastatin; DRV/r + atorvastatin 10mg similar to atorvastatin 40mg alone; FPV ↑ atorvastatin AUC 150%; LPV/r ↑ atorvastatin AUC 5.88-fold; NFV ↑ atorvastatin AUC 74%; SQV/r ↑ atorvastatin levels 450%; TPV/r ↑ atorvastatin AUC 9-fold	Use lowest possible starting dose with careful monitoring, or consider other HMG-CoA reductase inhibitors with less potential for interaction.

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Concomitant Drug Class/Name	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Lovastatin	All PIs	Significant ↑ lovastatin level	**Contraindicated – do not coadminister.**
Pravastatin	DRV/r	Mean ↑ in pravastatin AUC 81% & up to 5-fold in some patients	Use lowest possible starting dose with careful monitoring.
	LPV/r	↑ pravastatin	No dose adjustment necessary.
	NFV, SQV/r	↓ pravastatin	No dose adjustment necessary.
	TPV/r ATV, FPV, IDV	No data	
Rosuvastatin	ATV +/- RTV, DRV/r, FPV +/- RTV, IDV +/- RTV, NFV, SQV/r	No data Potential for ↑ rosuvastatin level.	Use lowest possible starting dose with careful monitoring, or consider other HMG-CoA reductase inhibitors with less potential for interaction.
	LPV/r	rosuvastatin AUC ↑ 2.1-fold and Cmax ↑ 4.7-fold	Use lowest possible starting dose with careful monitoring for rosuvastatin toxicities, or consider other HMG-CoA reductase inhibitors with less potential for interaction.
	TPV/r	rosuvastatin AUC ↑ 37% and Cmax ↑ 123%	Use lowest possible starting dose with monitoring for rosuvastatin toxicities, or consider other HMG-CoA reductase inhibitors with less potential for interaction.
Simvastatin	All PIs	Significant ↑ simvastatin level; NFV ↑ simvastatin AUC 505%	**Contraindicated – do not coadminister**.
Methadone			
	RTV-boosted PI:		
Methadone	ATV/r, FPV/r, DRV/r, IDV/r, LPV/r, SQV/r, TPV/r	↓ methadone levels: ATV/r ↓ R-methadone AUC 16%; DRV/r ↓ R-methadone AUC 16%; FPV/r ↓ R-methadone AUC 18% ; LPV/r ↓ methadone AUC 26%–53%; SQV/r 1,000/100mg BID ↓ methadone AUC 19%; TPV/r ↓ R-methadone AUC 48%	Opiate withdrawal unlikely but may occur. No adjustment in methadone usually required but monitor for opiate withdrawal and increase methadone dose as clinically indicated. R-methadone is the active form of methadone.
	PIs without RTV:		
	ATV, IDV	No effect	
	FPV	No data with FPV ; with APV, R-methadone levels ↓ 13%	Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
	NFV	NFV ↓ methadone AUC 40%	Opiate withdrawal rarely occurs. Monitor and titrate dose as clinically indicated. May require ↑ methadone dose.
Phosphodiesterase Type 5 Inhibitors			
Sildenafil	All PIs	↑ sildenafil; APV ↑ sildenafil AUC 2- to 11-fold; DRV/r + sildenafil 25mg similar to sildenafil 100mg alone; IDV ↑ sildenafil AUC 3-fold; LPV/r ↑ sildenafil 11-fold; NFV ↑ sildenafil 2- to 11-fold; RTV ↑ sildenafil AUC 11-fold	Sildenafil: start with 25mg every 48 hours and monitor for adverse effects of sildenafil.
Tadalafil	All PIs	LPV/r ↑ tadalafil AUC 124%	Tadalafil: start with 5mg dose and do not exceed a single dose of 10mg every 72 hours. Monitor for adverse effects of tadalafil.
Vardenafil	All PIs	↑ vardenafil; IDV ↑ vardenafil AUC 16-fold, ↓ IDV AUC 30%; RTV ↑ vardenafil AUC 49-fold, ↓ RTV AUC 20%	Vardenafil: start with 2.5mg every 72 hours and monitor for adverse effects of vardenafil.

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Drug-Specific Interactions

Protease Inhibitor (PI)	Concomitant Drug Class/Name	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
DRV/r	**Paroxetine** **Sertraline**	↓ paroxetine ↓ sertraline	Monitor closely for antidepressant response. Carefully titrate SSRI dose based on clinical assessment.
IDV	**Grapefruit juice** **Vitamin C >1 g/day**	↓ IDV ↓ IDV	Monitor for virologic responses.
RTV	**Desipramine**	RTV ↑ desipramine 145%	Reduce desipramine dose.
	Trazodone	RTV 200mg BID ↑ trazodone AUC 2.4-fold.	Use lowest dose of trazodone, and monitor for CNS and CV adverse effects.
	Theophylline	RTV ↓ theophylline 47%.	Monitor theophylline levels.
SQV	**Grapefruit juice**	↑ SQV	
	Dexamethasone	↓ SQV	

Abbreviations: APV = amprenavir, ATV = atazanavir, ATV/r = atazanavir + ritonavir, DRV/r = darunavir + ritonavir, FPV = fosamprenavir, FPV/r = fosamprenavir + ritonavir, IDV = indinavir, IDV/r = indinavir + ritonavir, LPV/r = lopinavir/ritonavir, NFV = nelfinavir, RTV = ritonavir, SQV/r = saquinavir + ritonavir, TPV/r = tipranavir + ritonavir.

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Table 15b. Drug Interactions Between NNRTIs and Other Drugs

This table provides information relating to pharmacokinetic interactions between NNRTIs and non-antiretroviral drugs. For interactions among antiretroviral agents and dosing recommendations, please refer to **Table 16b**.

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Antifungals			
Fluconazole	DLV, EFV	No significant effect	
	ETR	↑ ETR	No dosage adjustment necessary.
	NVP	NVP Cmax, AUC, and Cmin ↑ 100%	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity.
Itraconazole	DLV, NVP	No data, potential for bi-directional interactions	Consider monitoring NNRTI and itraconazole levels.
	EFV	itraconazole and OH-itraconazole AUC, Cmax, and Cmin ↓ 35%–44%	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level.
	ETR	↑ ETR ↓ itraconazole	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level.
Ketoconazole	DLV	↑ DLV	No dosage adjustment necessary.
	EFV	No data	
	ETR	↑ ETR ↓ ketoconazole	Dose adjustment for ketoconazole may be necessary depending on other coadministered drugs.
	NVP	ketoconazole ↓ 63%, NVP ↑ 15%–30%	**Coadministration not recommended.**
Posaconazole	DLV, NVP	No data	
	EFV	Posaconazole AUC ↓ 50%, Cmax ↓45% EFV Cmax ↑ 13%	Consider alternative antifungal if possible or consider monitoring posaconazole level if available
	ETR	↑ ETR	No dosage adjustment necessary.
Voriconazole	DLV	No data	Potential for bi-directional inhibition of metabolism. Monitor for toxicity.
	EFV	EFV ↑ 44% voriconazole ↓ 77%	**Contraindicated at standard doses**. Dose: voriconazole 400mg BID, EFV 300mg daily
	ETR	↑ ETR ↑ voriconazole	Dose adjustments for voriconazole may be necessary depending on other coadministered drugs. Monitor voriconazole level.
	NVP	No data	Potential for induction of voriconazole metabolism and inhibition of NVP metabolism. Monitor for toxicity and antifungal outcome.
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	DLV	DLV Cmin ↓ 90% by phenytoin, phenobarbital, and carbamazepine	**Contraindicated – do not coadminister.**
	EFV	carbamazepine + EFV: AUCs ↓ 27% and 36%, respectively, when combined. EFV + phenytoin: ↓EFV concentrations (case report)	Monitor anticonvulsant levels, or if possible, use alternative anticonvulsant.
	ETR	No data. Potential for ↓ ETR and anticonvulsant concentrations.	**Do not coadminister.** Consider alternative anticonvulsants.
	NVP	No data	

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Anti-mycobacterials			
Clarithromycin	DLV	clarithromycin ↑ 100% DLV ↑ 44%	Reduce clarithromycin dose by 50% in patients with CrCl 30–60mL/min and by 75% in patients with CrCl <30mL/min.
	EFV	clarithromycin ↓ 39%	Monitor for efficacy or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	ETR	ETR AUC ↑ 42%, clarithromycin AUC ↓ 39% and Cmin ↓ 53%, OH-clarithromycin AUC ↑ 21%	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	NVP	NVP ↑ 26%, clarithromycin ↓ 30%	Monitor for efficacy or use alternative agent.
Rifabutin	DLV	DLV ↓ 80% rifabutin ↑ 100%	**Coadministration not recommended**.
	EFV	rifabutin ↓ 35%	Dose: rifabutin 450–600mg once daily or 600mg 3x/week if EFV is not coadministered with a PI.
	ETR	ETR AUC ↓ 37% & Cmin ↓ 35% rifabutin AUC ↓ 17% & Cmin ↓ 24%, 25-O-desacetylrifabutin AUC ↓ 17% & Cmin ↓ 22%	Dose: rifabutin 300mg once daily if ETR is not coadministered with a RTV-boosted PI. If ETR is coadministered with DRV/r or SQV/r and rifabutin is needed, consider alternative ARV agent to ETR. If ETR is coadministered with LPV/r, use rifabutin 150mg QOD or 3x/week. Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150mg twice weekly and RTV-boosted PIs. Consider therapeutic drug monitoring and adjust dose accordingly.
	NVP	↓ NVP ↑ Rifabutin	No dosage adjustment necessary.
Rifampin	DLV	DLV ↓ 96%	**Contraindicated—do not coadminister.**
	EFV	↓ EFV 25%	Maintain efavirenz dose at 600mg once daily and monitor for viral response. Some clinicians suggest EFV 800mg dose in patients >60kg.
	ETR	Potential for significant ↓ ETR levels	**Do not coadminister.**
	NVP	↓ NVP 20%–58%	**Do not coadminister.**
Benzodiazepines			
Alprazolam	DLV	No data May ↑ alprazolam	**Do not coadminister.** Consider alternative benzodiazepines, such as lorazepam, oxazepam, or temazepam.
	EFV, NVP, ETR	No data	Monitor for therapeutic efficacy of alprazolam.
Diazepam	DLV	No data May ↑ diazepam	Consider alternative benzodiazepines, such as lorazepam, oxazepam, or temazepam.
	EFV, NVP	No data	
	ETR	↑ diazepam	Decreased dose of diazepam may be necessary.
Lorazepam	DLV, ETR, NVP	No data	
	EFV	Lorazepam Cmax ↑ 16%, no significant effect on lorazepam AUC	No dosage adjustment necessary.
Midazolam	DLV, EFV	No data May ↑ midazolam	**Do not coadminister 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.
	ETR, NVP	No data	

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Triazolam	DLV, EFV	No data May ↑ triazolam	**Do not coadminister.**
	ETR, NVP	No data	
Herbal Products			
St. John's wort	All NNRTIs	↓ NNRTI	Administration of St. John's wort with NNRTIs is not recommended.
Hormonal Contraceptives			
Hormonal Contraceptives	DLV	No data Potential for ↑ ethinyl estradiol levels.	Clinical significance unknown.
	EFV	↑ ethinyl estradiol	Use alternative or additional methods. No data on other components.
	ETR	↑ ethinyl estradiol No effect on norethindrone levels.	No dosage adjustment necessary.
	NVP	ethinyl estradiol ↓ 20%.	Use alternative or additional methods.
HMG-CoA Reductase Inhibitors			
Atorvastatin	DLV	No data Potential for inhibition of atorvastatin metabolism.	Use lowest possible dose and monitor for toxicity, or consider other HMG-CoA reductase inhibitors with less potential for interaction.
	EFV	atorvastatin AUC ↓ 37%–43%.	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
	ETR	↓ atorvastatin AUC 37%	Dose: standard, adjust dose according to response.
	NVP	No data Potential for induction of atorvastatin metabolism	Dose: standard, adjust dose according to response.
Fluvastatin	DLV, EFV, NVP	No data	
	ETR	↑ fluvastatin	Dose adjustments for fluvastatin may be necessary.
Lovastatin **Simvastatin**	DLV	No data Potential for large increase in statin levels.	**Avoid concomitant use.**
	EFV	simvastatin AUC ↓ 68%	Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	↓ lovastatin ↓ simvastatin	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
Pravastatin **Rosuvastatin**	DLV, NVP	No data	
	EFV	pravastatin AUC ↓ 44%.	Adjust pravastatin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	No effect	Dose: standard
Methadone			
Methadone	DLV	No effect on DLV Potential for ↑ methadone	Monitor for methadone toxicity and need for dose reduction
	EFV	Methadone ↓ 60%	Potential for opiate withdrawal; increased methadone dose often necessary.
	ETR	No effect	Dose: standard
	NVP	↓ methadone No effect on NVP	Opiate withdrawal common; increased methadone dose often necessary.

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Oral Anticoagulant			
Warfarin	DLV	No data	May increase warfarin levels. Monitor INR.
	EFV, NVP	No data	May increase or decrease warfarin levels. Monitor INR.
	ETR	↑ warfarin	Monitor INR and adjust warfarin dose accordingly.

Abbreviations: DLV = delavirdine, EFV = efavirenz, ETR = etravirine, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, CBZ = carbamazepine.

Drug-Specific Interactions

NNRTI	Concomitant Drug Class/Name	Effect on NNRTI or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comment
DLV	**Fluoxetine**	↑ DLV	No dosage adjustment necessary.
	Quinidine	No data May increase quinidine levels.	Monitor quinidine level and toxicities.
	Sildenafil **Vardenafil** **Tadalafil**	No data Potential for increased phosphodiesterase inhibitor levels.	Use cautiously. Start with reduced dose of sildenafil 25mg Q48H, vardenafil 2.5mg Q24H, and tadalafil 5mg Q72H.
ETR	**Antiarrhythmics**	↓ antiarrhythmics	Use with caution with antiarrhythmic level monitoring if available.
	Dexamethasone	↓ ETR	Use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use.
	Sildenafil	↓ sildenafil	May need to increase sildenafil dose based on clinical effect. Levels: sildenafil AUC ↓ 57%.

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Table 15c. Drug Interactions Between NRTIs and Other Drugs (including antiretroviral agents)

Concomitant Drug Class/Name	NRTI	Effect on NRTI or Concomitant Drug Concentrations	Clinical Comment
Antivirals			
Ganciclovir (GCV) **Valganciclovir**	ddI	↑ ddI AUC ↑ 50%–111% ↓ GCV AUC ↓ 21% when ddI administered 2 hours prior to oral GCV. No change in IV GCV concentrations.	Appropriate doses for combination of ddI and GCV have not been established. Monitor for ddI associated toxicities.
	TDF	No data	Serum concentrations of these drugs and/or TDF may be increased. Monitor for dose-related toxicities.
	ZDV	No significant pharmacokinetic effects	Potential increase in hematologic toxicities.
Ribavirin	ddI	↑ intracellular ddI	**Coadministration not recommended**. May cause ddI-related serious toxicities.
	ZDV	Ribavirin inhibits phosphorylation of ZDV.	Avoid coadministration if possible, or closely monitor virologic response and hematologic toxicities.
Methadone			
Methadone	ABC	↓ methadone	Monitor for opiate withdrawal and titrate methadone as clinically indicated. May require ↑ methadone dose.
	d4T	↓ d4T	No dosage adjustment necessary.
	ZDV	↑ ZDV AUC 43%	Monitor for ZDV-related adverse effects.
NRTIs			
Didanosine	d4T	No significant effect	Avoid coadministration if possible. Peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination.
	TDF	↑ ddI-EC AUC and Cmax 48%–60%	Dose if CrCl >60mL/min: ddI-EC 250mg/day if patient weighs >60kg and ddI-EC 200mg if patient weighs <60kg. Monitor for ddI-associated toxicity.
PIs			
Atazanavir (ATV)	ddI	Simultaneous ddI-EC + ATV (with food) ↓ ddI AUC 34%. ATV no change.	ATV with food should be administered 2 hours before or 1 hour after didanosine.
	TDF	↓ ATV AUC 25% and Cmin 23%–40% (higher Cmin with RTV than without) ↑ TDF AUC 24%–30%	Dose: ATV/r 300/100mg daily coadministered with TDF 300mg daily. Avoid concomitant use without ritonavir. Monitor for TDF-associated toxicity.
	ZDV	↓ ZDV Cmin 30%, no change in AUC	Clinical significance unknown.
Darunavir (DRV)	TDF	↑ TDF AUC 22%, Cmax 24%, Cmin 37%	Clinical significance unknown. Monitor for TDF toxicity.
Indinavir (IDV)	TDF	↑ IDV	No dosage adjustment necessary.
Lopinavir/ritonavir (LPV/r)	TDF	↓ LPV/r AUC 15% ↑ TDF AUC 34%	Clinical significance unknown. Monitor for TDF toxicity.
Tipranavir/ritonavir (TPV/r)	ABC	↓ ABC 35%–44% with TPV/r 1,250/100mg BID	Appropriate doses for this combination have not been established.
	ddI	↓ ddI-EC 10% and ↓ TPV Cmin 34% with TPV/r 1,250/100mg BID	Separate doses by at least 2 hours.
	TDF	↓ TPV AUC 9%–18% and Cmin 12%–21% with TPV/r 1,250/100mg BID	Clinical significance is unknown.
	ZDV	↓ ZDV AUC 31%–43% and Cmax 46%–51% with TPV/r 1,250/100mg BID	Appropriate doses for this combination have not been established.

Abbreviations: ABC = abacavir, ddI = didanosine, d4T = stavudine, TDF = tenofovir, ZDV = zidovudine.

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Table 15d. Drug Interactions Between CCR5 Antagonists and Other Drugs

This table provides information relating to pharmacokinetic interactions between maraviroc and non-antiretroviral drugs. For interactions among antiretroviral agents and dosing recommendations, please refer to **Table 16b.**

Concomitant Drug Class/Name	CCR5 Antagonist	Effect on CCR5 Antagonist or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Antifungals			
Fluconazole **Posaconazole**	MVC	No data	
Itraconazole	MVC	No data possible ↑ MVC levels	Dose: MVC 150mg BID
Ketoconazole	MVC	↑ MVC AUC 5x	Dose: MVC 150mg BID
Voriconazole	MVC	No data possible ↑ MVC levels	Consider dose reduction to MVC 150mg BID.
Anticonvulsants			
Carbamazepine **Phenobarbital** **Phenytoin**	MVC	No data possible ↓ MVC levels	If used without a strong CYP3A inhibitor: MVC 600mg BID or use alternative antiepileptic agent.
Anti-mycobacterials			
Clarithromycin	MVC	No data possible ↑ MVC levels	Dose: MVC 150mg BID
Rifabutin	MVC	No data possible ↓ MVC levels	If used without a strong CYP3A inducer or inhibitor: MVC 300mg BID. If used with a strong CYP3A inhibitor: MVC 150mg BID.
Rifampin	MVC	↓ MVC AUC 64%	If used without a strong CYP3A inhibitor: MVC 600mg BID. If used with a strong inhibitor: 300mg BID
Herbal Products			
St. John's wort	MVC	No data possible ↓ MVC levels	Administration of St. John's wort with MVC is not recommended.
Hormonal Contraceptives			
Hormonal Contraceptives	MVC	No significant effect.	Safe to use in combination.

Abbreviation: MVC = maraviroc.

Table 15e. Drug Interactions Between Antiretrovirals and Other Drugs: Integrase Inhibitors

Concomitant Drug Class/Name	Integrase Inhibitors	Effect on Integrase Inhibitor or Concomitant Drug Concentrations	Clinical Comment
Anti-mycobacterials			
Rifampin	RAL	↓ RAL AUC 40%, Cmin 61%	Clinical significance unknown. Should consider using rifabutin as alternative. If rifampin is to be used, monitor for antiretroviral efficacy.

Abbreviation: RAL = raltegravir.

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Table 16a. Interactions Among Protease Inhibitors

Drug Affected	Fosamprenavir	Atazanavir	Lopinavir/ Ritonavir	Nelfinavir	Ritonavir	Saquinavir*	Tipranavir
Protease Inhibitors							
Darunavir (DRV)	No data.	Levels: ATV 300mg once daily + DRV/r -- similar to ATV/r 300/100mg once daily. DRV was unchanged. Dose: Administer ATV 300mg once daily with DRV/r for exposure similar to ATV/r 300/100mg once daily.	Levels: DRV AUC and Cmin ↓ 53% and 65%, respectively. LPV AUC and Cmin ↑ 37% and 72%, respectively. **Dose: Should not be coadministered, as doses are not established.**	No data.	Levels: 14-fold ↑ in DRV exposure in combination with RTV 100mg BID. Dose: DRV should only be used in combination with RTV 100mg BID to achieve sufficient DRV exposure.	Levels: DRV AUC and Cmin ↓ 26% and 42%, respectively. SQV exposure similar to when administered with RTV 1,000/100mg BID.‡ **Dose: Should not be coadministered, as doses are not established.**	No data.
Fosamprenavir (FPV)	•	Levels: With FPV/ATV 1,400/400 once daily, ATV AUC & Cmin ↓ 33% and 57%, resp. APV AUC & Cmin ↑ 78% and 283%, respectively. With FPV/r 700/100mg BID + ATV 300mg once daily, ATV AUC and Cmax ↓ 22% and 24%, resp; APV unchanged. Dose: Insufficient data.for dose recommendation.	Levels: With coadministration of FPV 700mg BID and LPV/r capsules 400/100mg BID, FPV Cmin ↓64% and LPV Cmin ↓53%. An increased rate of adverse events was seen with coadministration. **Dose: Should not be coadministered, as doses are not established.**	See FPV + NFV cell	Levels: APV AUC and Cmin ↑100% and 400%, respectively, with 200mg RTV. Dose: (FPV 1,400mg + RTV 200mg) once daily; or FPV 700mg + RTV 100mg BID.	Levels: APV AUC ↓ 32%. Dose: Insufficient data.for dose recommendation	Levels: APV AUC and Cmin ↓44% and 55%, respectively, when given as APV/r 600/100 BID with TPV/r. No data with FPV, but a ↓ in AUC is expected. **Dose: Should not be coadministered, as doses are not established.**
Indinavir (IDV)	Levels: APV AUC ↑33%. Dose: Not established.	Coadministration of these agents is not recommended because of potential for additive hyperbilirubinema.	Levels: IDV AUC and Cmin↑. Dose: IDV 600mg BID.	Levels: IDV ↑50%; NFV ↑80%. Dose: Limited data for IDV 1,200mg BID + NFV 1,250mg BID.	Levels: IDV ↑ 2–5 times. Dose: IDV/RTV 800/100mg, 800/200mg, or 400/400mg BID Caution: Renal events may ↑ with ↑ IDV concentrations.	Levels: IDV-No effect. SQV ↑ 4-7 times.† Dose: Insufficient data.	No data. **Should not be coadministered, as doses are not established.**
Lopinavir/ Ritonavir (LPV/r)	see LPV/r + FPV cell	Levels: With ATV 300 once daily + LPV/r 400/100 BID, ATV Cmin ↑45%; ATV AUC and Cmax were unchanged. LPV PK similar to historic data.	•	see LPV/r + NFV cell	Additional ritonavir is generally not recommended.	see LPV/r + SQV cell	Levels: LPV AUC and Cmin ↓ 55% & 70%, respectively. **Dose: Should not be coadministered, as doses are not established.**
Nelfinavir (NFV)	Levels: APV AUC ↑ 1.5-fold. Dose: Insufficient data.	No data	Levels: With LPV/r capsules, LPV ↓27%; NFV ↑ 25%. Dose: No data with LPV/r tablets. No dosing recommendation.	•	see NFV + RTV cell	see NFV+SQV cell	No data. **Should not be coadministered, as doses are not established.**
Ritonavir (RTV)	see RTV + FPV cell	Levels: ATV AUC ↑238%. Dose: ATV 300mg QD + RTV 100mg QD.	Lopinavir is coformulated with ritonavir as Kaletra®. Additional ritonavir is generally not recommended.	Levels: RTV - No effect. NFV ↑ 1.5 times. Dose: not established	•	Levels: RTV no effect SQV ↑ 20 times.†‡ Dose: 1,000/ 100mg SQV/RTV BID	Levels: TPV AUC ↑ 11-fold.
Saquinavir **(SQV)**	Levels: APV AUC ↓32%. Dose: Insufficient data.	Levels: SQV AUC ↑60% with SQV/ATV/RTV 1,600/300/100 once daily, compared with SQV/ RTV 1,600/100 once daily Dose: No dose recommendations can be made.	Levels: SQV† AUC and Cmin ↑ Dose: SQV 1,000mg BID; LPV/r standard.	Levels: SQV ↑ 3–5 times; NFV ↑ 20%.†	see SQV + RTV cell	•	Levels: SQV AUC & Cmin ↓ 76% & 82%, respectively, when given as SQV/r 600/100 BID with TPV/r. **Dose: Should not be coadministered, as doses are not established.**

* Several drug interaction studies have been completed with saquinavir given as Invirase (old hard-gel capsule formulation) or Fortovase (soft-gel capsule formulation. Currently, only Invirase (as 500mg tablet or 200mg hard-gel capsule) is available.

† Study conducted with Fortovase.

‡ Study conducted with Invirase

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Table 16b. Interactions between NNRTIs, Maraviroc, and PIs

Drug Affected	Delavirdine	Efavirenz	Etravirine	Nevirapine	Maraviroc
Atazanavir **(ATV)**	No data.	Levels: With unboosted ATV, ATV AUC ↓ 74%. EFV no change. ATV 300 + RTV 100mg QD with food - ATV concentrations similar to unboosted ATV Dose: in treatment-naïve patients, ATV 400mg + RTV 100mg: EFV dose = standard. Do not coadminister in treatment-experienced patients.	Levels: With unboosted ATV, ETR AUC, Cmax and Cmin ↑ 50%, 47% and 58%, respectively ATV AUC ↓ 17%, Cmin ↓ 47% With ATV/RTV, ETR AUC, Cmax and Cmin ↑ approx 30%: ATV AUC ↓ 14% and Cmin ↓ 38% **Do not coadminister with unboosted ATV or ATV/RTV**	Levels: ↓ ATV, ↑ NVP **Coadministration of NVP is not recommended with ATV + RTV.**	Levels: With unboosted ATV, MVC AUC ↑ 3.6x. With ATV/r, MVC AUC ↑ 5x. Dose: With unboosted ATV or ATV/r, 150mg BID.
Darunavir (DRV)	No data.	Levels: DRV AUC and Cmin ↓ 13% and 31%, respectively. EFV AUC and Cmin ↑ 21% and 17%, respectively. Dose: Clinical significance unknown. Use standard doses and monitor closely. Consider monitoring levels.	Levels: ETR AUC ↓ 37% Cmin ↓ 49% DRV no change Dose: Standard for ETR and DRV. Despite decrease in ETR, safety and efficacy established with this combination	Levels: NVP AUC and Cmin ↑ 27% and 47%, respectively. DRV unchanged.† Dose: Standard.	Levels: With DRV/r, MVC AUC ↑ 4x. Dose: 150mg BID.
Delavirdine (DLV)	•	no data	•	•	Levels: Unknown, possibly ↑ MVC conc. Dose: 150mg BID.
Efavirenz (EFV)	no data	•	Potential for ↓ ETR concentration. **Do not coadminister**	•	Levels: MVC AUC ↓ 45%. Dose: 600mg BID.
EFV + LPV/r or SQV/r	•	•	•	•	Levels: MVC AUC ↑ 2.5–5x. Dose: 150mg BID.
Etravirine (ETR)	•	•	•	•	Levels: MVC AUC ↓ 53%, Cmax ↓ 60% Dose: 600mg BID
ETR + DRV/r	•	•	•	•	Levels: MVC AUC ↑210%, Cmax ↑77% Dose: 150mg BID
Fosamprenavir (FPV)	Levels: Presumably, similar PK effects as APV: APV AUC ↑ 130%, and DLV AUC ↓ 61%. Dose: Coadministration not recommended.	Levels: APV Cmin ↓ 36% (when dosed at 1,400mg QD with 200mg RTV). Dose: FPV 1,400mg + RTV 300mg QD; or FPV 700mg + RTV 100mg BID.	Levels: APV AUC ↑ 69%, Cmin ↑ 77% **Dose: Do not coadminister with boosted or unboosted FPV**	No data.	Levels: Unknown, possibly ↑ MVC conc. Dose: 150mg BID
Indinavir **(IDV)**	Levels: IDV ↑ >40%; DLV-No effect. Dose: IDV 600mg q8h. DLV standard.	Levels: IDV ↓ 31%. Dose: IDV 1,000mg q8h; consider IDV/RTV. EFV standard.	Dose: No data. Do not coadminister	Levels: IDV ↓ 28%; NVP no effect. Dose: IDV 1,000mg q8h, or consider IDV/RTV. NVP standard.	Levels: Unknown, possibly ↑ MVC conc. Dose: 150mg BID.
Lopinavir/ Ritonavir (LPV/r)	Levels: LPV levels expected to increase. Dose: Insufficient data.	Levels: With LPV/r tablets 600/150mg BID + EFV 600mg QD, LPV Cmin and AUC ↑ 35% and 36%, respectively. No formal study of LPV/r tablets 400/100mg BID + EFV. EFV no change. Dose: LPV/r tablets 600/150mg BID, when used in with EFV in tx-experienced patients. EFV dose - standard.	Levels: ETR AUC ↑ 17% Cmin ↑ 23%: LPV AUC ↓ 20%, Cmin ↓ 8% Dose: standard for ETR and LPV/RTV The amount of safety data at ↑ ETR exposures is limited, therefore, use with caution	Levels: With LPV/r capsules, LPV Cmin dec. 55%. Dose: LPV/r tablets 600/150mg BID, when used in combination with NVP in tx-experienced patients. NVP standard.	Levels: MVC AUC ↑ 4x. Dose: 150mg BID.
Nelfinavir **(NFV)**	Levels: NFV ↑ 2 times. DLV ↓50%. Dose: No data.	Levels: NFV ↑ 20%. Dose: Standard.	Dose: no data. Do not coadminister	Levels: NFV ↑ 10%. NVP no effect. Dose: Standard.	Levels: Unknown, possibly ↑ MVC conc. Dose: 150mg BID.
***Nevirapine* (NVP)**	No data.	Levels: NVP-no effect. EFV AUC ↓ 22%.	Potential for ↓ ETR concentration, Do not coadminister	•	Levels: No significant change. Dose: 300mg BID if use without PI 150mg BID – if used with PI (except TPV/r).
Ritonavir **(RTV)**	Levels: RTV ↑ 70%. DLV no effect. Dose: Appropriate doses not established.	Levels: RTV ↑ 18%. EFV ↑ 21%. Dose: Standard.	Dose: No data. Do not coadminister ETR and RTV 600mg	Levels: RTV ↓ 11%. NVP no effect. Dose: Standard.	Levels: With RTV 100 mg BID, MVC AUC ↑ 2.6x. Dose: 150mg BID.

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

***Saquinavir* (SQV)**	Levels: SQV‡ ↑ 5 times; DLV no effect. Dose: SQV/RTV 1,000mg/100mg BID.	Levels: SQV‡ ↓ 62%. EFV ↓ 12%. Dose: SQV/RTV 1000mg/100mg BID.	Level: ETR AUC ↓ 33% Cmin ↓ 29% SQV unchanged Dose: SQV/RTV 1000/100mg BID. ETR reduced exposures similar to ETR reduced exposures with DRV/RTV; therefore no dose adjustment	Levels: SQV ↓ 25%. NVP no effect. Dose: SQV/RTV 1,000mg/100mg BID.	Levels: With SQV/r, MVC AUC ↑ 9.8x. Dose: 150mg BID.
Tipranavir (TPV)	No data.	Levels: With TPV/r 500/100mg BID, TPV AUC and Cmin ↓ 31% and 42%, respectively. EFV unchanged. With TPV/r 750/200mg BID, TPV PK unchanged. Dose: No dose adjustments necessary.	Level: ETR AUC ↓ 76%, Cmin ↓ 82%; TPV AUC ↑ 18%, Cmin ↑ 24% Dose: Do not coadminister	Levels: No data on the effect of NVP on TPV/r PK. NVP PK unchanged.[a]	Levels: With TPV/r, no significant change. Dose: 300mg BID.

‡ Study conducted with Invirase.
† Based on between-study comparison.
[a] Study conducted with TPV/r dose(s) other than FDA-approved dose of 500/200mg BID.

Please refer to the **When to Start** section of the Adult Guidelines for more detailed discussions.

Appendix B: Tables and Figure

Appendix Table 1a. Probability of Progressing to AIDS or Death According to CD4 Cell Count, Viral Load, and Sociodemographic Factors (Updated October 29, 2004)

	CD4 cell count (cells/μL)									
	< 50		50–99		100–199		200–349		≥ 350	
	Viral load ≥5*	Viral load <5*	Viral load ≥5*	Viral load <5*	Viral load ≥5*	Viral load <5*	Viral load ≥5*	Viral load <5*	Viral load ≥5*	Viral load <5*
CDC stage A/B and no history of IDU										
Age < 50 years										
Year 1	12 (11–14)	9.5 (8.0–11)	9.2 (7.7–11)	7.0 (5.8–8.5)	6.2 (5.2–7.3)	4.7 (4.0–5.6)	2.6 (2.1–3.2)	2.0 (1.6–2.5)	2.0 (1.6–2.5)	1.5 (1.2–1.9)
Year 2	17 (15–20)	13 (11–15)	13 (11–15)	10 (8.4–12)	9.5 (8.1–11)	7.3 (6.2–8.5)	4.5 (3.7–5.4)	3.3 (2.8–4.1)	3.3 (2.7–4.0)	2.5 (2.1–3.0)
Year 3	20 (18–23)	16 (13–19)	16 (14–19)	12 (10–15)	12 (10–14)	9.3 (7.9–11)	6.1 (5.0–7.4)	4.7 (3.9–5.6)	4.4 (3.6–5.4)	3.4 (2.8–4.1)
Age ≥ 50 years										
Year 1	17 (14–20)	13 (11–16)	12 (10–15)	9.6 (7.7–12)	8.5 (7.0–10)	6.5 (5.3–7.9)	3.6 (2.8–4.5)	2.7 (2.2–3.4)	2.8 (2.2–3.5)	2.1 (1.6–2.7)
Year 2	23 (19–27)	18 (15–21)	18 (15–21)	14 (11–17)	13 (10–15)	9.9 (8.2–12)	6.1 (5.0–7.6)	4.7 (3.8–5.8)	4.5 (3.6–5.7)	3.4 (2.8–4.3)
Year 3	27 (23–32)	21 (18–25)	22 (18–26)	17 (14–20)	16 (14–19)	13 (10–15)	8.3 (6.7–10)	6.4 (5.1–7.9)	6.0 (4.8–7.6)	4.6 (3.7–5.8)
CDC stage A/B and history of IDU										
Age < 50 years										
Year 1	17 (14–20)	13 (11–16)	12 (10–15)	9.5 (7.7–12)	8.4 (7.0–10)	6.5 (5.3–7.9)	3.6 (2.8–4.5)	2.7 (2.2–3.4)	2.7 (2.1–3.5)	2.1 (1.6–2.6)
Year 2	24 (21–28)	19 (16–23)	19 (16–22)	15 (12–18)	14 (12–16)	11 (8.8–13)	6.6 (5.4–8.1)	5.0 (4.1–6.1)	4.9 (3.9–6.1)	3.7 (3.0–4.6)
Year 3	30 (26–35)	24 (20–28)	24 (20–28)	19 (15–23)	18 (15–22)	14 (12–17)	9.4 (7.6–11)	7.2 (5.8–8.8)	6.8 (5.4–8.6)	5.2 (4.2–6.5)
Age ≥ 50 years										
Year 1	22 (18–27)	17 (14–22)	17 (13–21)	13 (10–16)	11 (9.1–14)	8.8 (6.9–11)	4.9 (3.7–6.4)	3.7 (2.8–4.9)	3.8 (2.8–5.0)	2.9 (2.2–3.8)
Year 2	32 (26–38)	25 (20–31)	25 (20–31)	20 (15–25)	18 (15–23)	14 (11–18)	9.0 (7.0–11)	6.9 (5.4–8.8)	6.7 (5.1–8.7)	5.1 (3.9–6.6)
Year 3	39 (32–46)	31 (25–38)	33 (26–38)	25 (20–31)	24 (20–30)	19 (15–24)	13 (9.9–16)	9.8 (7.6–12)	9.3 (7.1–12)	7.1 (5.4–9.2)
CDC stage C and no history of IDU										
Age < 50 years										
Year 1	17 (15–19)	13 (11–15)	13 (11–15)	9.8 (8.1–12)	8.7 (7.2–10)	6.6 (5.5–8.1)	3.7 (2.9–4.7)	2.8 (2.2–3.5)	2.8 (2.2–3.6)	2.1 (1.7–2.7)
Year 2	23 (21–26)	18 (16–21)	18 (15–21)	14 (12–17)	13 (11–16)	10 (8.4–12)	6.3 (5.1–7.8)	4.8 (3.9–5.9)	4.6 (3.7–5.9)	3.5 (2.8–4.4)
Year 3	28 (25–31)	22 (19–25)	22 (19–26)	17 (14–21)	17 (14–20)	13 (11–15)	8.5 (6.9–11)	6.5 (5.2–8.1)	6.2 (4.9–7.9)	4.7 (3.7–6.0)
Age ≥ 50 years										
Year 1	23 (20–26)	18 (15–21)	17 (14–20)	13 (11–16)	12 (9.7–14)	9.1 (7.3–11)	5.1 (3.9–6.5)	3.8 (3.0–5.0)	3.9 (3.0–5.1)	3.0 (2.3–3.9)
Year 2	31 (27–35)	24 (20–28)	24 (20–28)	19 (15–23)	18 (15–21)	14 (11–17)	8.6 (6.8–11)	6.6 (5.2–8.3)	6.4 (4.9–8.2)	4.9 (3.8–6.2)
Year 3	36 (32–41)	29 (24–34)	29 (25–34)	23 (19–28)	22 (18–27)	17 (14–21)	12 (9.2–15)	8.9 (7.0–11)	8.5 (6.5–11)	6.5 (5.0–8.3)
CDC stage C and history of IDU										
Age < 50 years										
Year 1	23 (20–26)	18 (15–21)	17 (14–21)	13 (11–16)	12 (9.5–14)	9.0 (7.2–11)	5.0 (3.9–6.5)	3.8 (2.9–5.0)	3.9 (2.9–5.1)	2.9 (2.2–3.9)
Year 2	33 (29–37)	26 (22–30)	26 (22–30)	20 (16–24)	19 (15–23)	15 (12–18)	9.2 (7.3–12)	7.0 (5.6–8.9)	6.8 (5.3–8.8)	5.2 (4.1–6.7)
Year 3	40 (35–45)	32 (27–37)	32 (27–38)	25 (21–31)	25 (22–30)	19 (16–24)	13 (10–16)	10 (7.9–13)	9.5 (7.3–12)	7.3 (5.6–9.4)
Age ≥ 50 years										
Year 1	30 (25–36)	24 (19–29)	23 (18–28)	18 (14–23)	16 (12–20)	12 (9.5–16)	6.9 (5.1–9.2)	5.3 (3.9–7.1)	5.3 (3.9–7.2)	4.0 (3.0–5.5)
Year 2	42 (36–49)	34 (28–41)	34 (27–41)	27 (21–33)	25 (20–31)	20 (15–25)	12 (9.6–16)	9.6 (7.3–13)	9.3 (7.0–12)	7.1 (5.3–9.5)
Year 3	50 (43–58)	41 (34–49)	42 (34–50)	33 (27–41)	33 (26–40)	26 (20–32)	17 (13–23)	14 (10–18)	13 (9.6–17)	9.9 (7.4–13)

IDU=injection-drug use. *Log copies/mL

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Please refer to the **When to Start** section of the Adult Guidelines for more detailed discussions.

Appendix Table 1b. Predicted 6-month Risk of AIDS According to Age and Current CD4 Cell Count and Viral Load, Based on a Poisson Regression Model (Updated October 29, 2004)

Viral load (copies/mL)	Predicted risk (%) at current CD4 cell count (x 10^6 cells/l)[a]									
	50	100	150	200	250	300	350	400	450	500
Age 25 years										
3,000	6.8	3.7	2.3	1.6	1.1	0.8	0.6	0.5	0.4	0.3
10,000	9.6	5.3	3.4	2.3	1.6	1.2	0.9	0.7	0.5	0.4
30,000	13.3	7.4	4.7	3.2	2.2	1.6	1.2	0.9	0.7	0.6
100,000	18.6	10.6	6.7	4.6	3.2	2.4	1.8	1.4	1.1	0.8
300,000	25.1	14.5	9.3	6.3	4.5	3.3	2.5	1.9	1.5	1.2
Age 35 years										
3,000	8.5	4.7	3.0	2.0	1.4	1.0	0.8	0.6	0.5	0.4
10,000	12.1	6.7	4.3	2.9	2.0	1.5	1.1	0.9	0.7	0.5
30,000	16.6	9.3	5.9	4.0	2.8	2.1	1.6	1.2	0.9	0.7
100,000	23.1	13.2	8.5	5.8	4.1	3.0	2.3	1.7	1.3	1.1
300,000	30.8	18.0	11.7	8.0	5.7	4.2	3.1	2.4	1.9	1.5
Age 45 years										
3,000	10.7	5.9	3.7	2.5	1.8	1.3	1.0	0.7	0.6	0.5
10,000	15.1	8.5	5.4	3.6	2.6	1.9	1.4	1.1	0.8	0.7
30,000	20.6	11.7	7.5	5.1	3.6	2.6	2.0	1.5	1.2	0.9
100,000	28.4	16.5	10.6	7.3	5.2	3.8	2.9	2.2	1.7	1.3
300,000	37.4	22.4	14.6	10.1	7.2	5.3	4.0	3.1	2.4	1.9
Age 55 years										
3,000	13.4	7.5	4.7	3.2	2.3	1.7	1.2	0.9	0.7	0.6
10,000	18.8	10.7	6.8	4.6	3.3	2.4	1.8	1.4	1.1	0.8
30,000	25.4	14.6	9.4	6.4	4.6	3.3	2.5	1.9	1.5	1.2
100,000	34.6	20.5	13.3	9.2	6.5	4.8	3.6	2.8	2.2	1.7
300,000	44.8	27.5	18.2	12.6	9.1	6.7	5.0	3.9	3.0	2.4

[a] Shading distinguishes risk: <2%, no shading; 2%–9.9%, light gray; 10%–19.9%, mid-gray; ≥ 20%, darkest gray.

Please refer to the **What to Start** section of the Adult Guidelines for more detailed discussions.

Appendix Table 2. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

 (Updated November 3, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Intracellular half-life	Elimination	Adverse Events
Abacavir (ABC) ZIAGEN **TRIZIVIR** - w/ ZDV+3TC **EPZICOM** - w/ 3TC	ZIAGEN 300mg tablets or 20mg/mL oral solution TRIZIVIR ABC 300mg + ZDV 300mg + 3TC 150mg EPZICOM ABC 600mg + 3TC 300mg	ZIAGEN 300mg BID or 600mg once daily TRIZIVIR 1 tablet BID EPZICOM 1 tablet once daily	Take without regard to meals; Alcohol increases abacavir levels 41%; abacavir has no effect on alcohol	83%	1.5 hours	12–26 hours	Metabolized by alcohol dehydrogenase and glucuronyl transferase. Renal excretion of metabolites 82% TRIZIVIR & EPZICOM not for patients with CrCl < 50 mL/min	• Hypersensitivity reaction that can be fatal, symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, respiratory symptoms such as sore throat, cough, shortness of breath • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NNRTIs)
Didanosine (ddI) VIDEX EC, Generic didanosine enteric coated (dose same as VIDEX EC)	VIDEX EC 125, 200, 250, 400mg capsules Buffered tablets (non-EC) are no longer available.	Body weight **≥ 60kg:** 400mg once daily with TDF: 250mg once daily **< 60 kg**: 250mg once daily with TDF: 200mg once daily	Levels decrease 55%; Take 1/2 hour before or 2 hours after meal	30–40%	1.5 hours	>20 hours	Renal excretion 50% Dosage adjustment in renal insufficiency (See **Appendix Table 8**)	• Pancreatitis • Peripheral neuropathy • Nausea • Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity associated with use of NRTIs.
Emtricitabine (FTC) EMTRIVA **ATRIPLA -** w/ EFV+TDF **TRUVADA** - w/ TDF	EMTRIVA 200mg hard gelatin capsule and 10mg/mL oral solution ATRIPLA EFV 600mg + FTC 200mg + TDF 300mg TRUVADA FTC 200mg + TDF 300mg	EMTRIVA 200mg capsule once daily or 240mg (24 mL) oral solution once daily ATRIPLA 1 tablet once daily TRUVADA 1 tablet once daily	Take without regard to meals	93%	10 hours	>20 hours	Renal excretion Dosage adjustment in renal insufficiency (See **Appendix Table 8**) ATRIPLA - not for patients with CrCl <50 mL/min TRUVADA - not for patients with CrCl < 30 mL/min	• Minimal toxicity • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs.) • Hyper-pigmentation/ skin discoloration
Lamivudine (3TC) EPIVIR **COMBIVIR-** w/ ZDV **EPZICOM** - w/ ABC **TRIZIVIR**- w/ ZDV+ABC	EPIVIR 150 or 300mg tablets or 10mg/mL oral solution COMBIVIR 3TC 150mg + ZDV 300mg EPZICOM 3TC 300mg + ABC 600mg TRIZIVIR 3TC 150mg + ZDV 300mg + ABC 300mg	EPIVIR 150mg BID or 300mg once daily COMBIVIR 1 tablet BID EPZICOM 1 tablet once daily TRIZIVIR 1 tablet BID	Take without regard to meals	86%	5–7 hours	18–22 hours	Renal excretion Dosage adjustment in renal insufficiency (See **Appendix Table 8**) COMBIVIR, TRIZIVIR & EPZICOM not for patients with CrCl < 50 mL/min	• Minimal toxicity • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs)

Please refer to the **What to Start** section of the Adult Guidelines for more detailed discussions.

Appendix Table 2. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

 (Updated November 3, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Intracellular half-life	Elimination	Adverse Events
Stavudine (d4T) ZERIT	ZERIT 15, 20, 30, 40mg capsules or 1mg/mL oral solution	Body weight >60 kg: 40mg BID Body weight <60 kg: 30mg BID Note: WHO recommends 30mg BID dosing regardless of body weight	Take without regard to meals	86%	1.0 hour	7.5 hours	Renal excretion 50% Dosage adjustment in renal insufficiency (See Appendix Table 8)	• Peripheral neuropathy • Lipodystrophy • Pancreatitis • Lactic acidosis with hepatic steatosis-higher incidence than w/ other NRTIs • Hyperlipidemia • Rapidly progressive ascending neuromuscular weakness (rare)
Tenofovir Disoproxil Fumarate (TDF) VIREAD **ATRIPLA** - w/ EFV+FTC **TRUVADA** - w/ FTC	VIREAD 300mg tablet ATRIPLA EFV 600mg + FTC 200mg + TDF 300mg TRUVADA TDF 300mg + FTC 200mg	VIREAD 1 tablet once daily ATRIPLA 1 tablet once daily TRUVADA 1 tablet once daily	Take without regard to meals	25% in fasting state; 39% with high-fat meal	17 hours	>60 hours	Renal excretion Dosage adjustment in renal insufficiency (See Appendix Table 8) ATRIPLA- not for patients with CrCl <50 mL/min TRUVADA - not for patients with CrCl < 30 mL/min	• Asthenia, headache, diarrhea, nausea, vomiting, and flatulence • Renal insufficiency,, Fanconi syndrome • Potential for osteopenia • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs)
Zidovudine (AZT, ZDV) RETROVIR **COMBIVIR** - w/ 3TC **TRIZIVIR- w/** 3TC+ABC	RETROVIR 100mg capsules, 300mg tablets, 10mg/mL intravenous solution, 10mg/mL oral solution COMBIVIR 3TC 150mg + ZDV 300mg TRIZIVIR 3TC 150mg + ZDV 300mg + ABC 300mg	RETROVIR 300mg BID or 200mg TID COMBIVIR 1 tablet BID TRIZIVIR 1 tablet BID	Take without regard to meals	60%	1.1 hours	7 hours	Metabolized to AZT glucuronide (GAZT). Renal excretion of GAZT Dosage adjustment in renal insufficiency (See Appendix Table 8) COMBIVIR & TRIZIVIR - not for patients with CrCl < 50 mL/min	• Bone marrow suppression: macrocytic anemia or neutropenia; • Gastrointestinal intolerance, headache, insomnia, asthenia; • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity associated with use of NRTIs)

Please refer to the **What to Start** section of the Adult Guidelines for more detailed discussions.

Appendix Table 3. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

(Updated November 3, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Elimination	Adverse Events
Delavirdine (DLV)/ RESCRIPTOR	100mg tablets or 200mg tablets	400mg 3 times/day; four 100mg tablets can be dispersed in ≥3 oz. of water to produce slurry; 200mg tablets should be taken as intact tablets; separate dose from antacids by 1 hour	Take without regard to meals	85%	5.8 hours	Metabolized by cytochrome P450 (3A inhibitor); 51% excreted in urine (<5% unchanged); 44% in feces	• Rash* • Increased transaminase levels • Headaches
Efavirenz (EFV)/ SUSTIVA Also available as **ATRIPLA** - with FTC + TDF	50, 100, 200mg capsules or 600mg tablets ATRIPLA - EFV 600mg + FTC 200mg + TDF 300mg	600mg daily on an empty stomach, at or before bedtime	High-fat/high-caloric meals increase peak plasma concentrations of capsules by 39% and tablets by 79%; take on an empty stomach	Data not available	40–55 hours	Metabolized by cytochrome P450 (3A mixed inducer/ inhibitor); No dosage adjustment in renal insufficiency if EFV is used alone; ATRIPLA - not for patients with CrCl <50 mL/min	• Rash* • Central nervous system symptoms† • Increased transaminase levels • False-positive cannabinoid test • Teratogenic in monkeys‡
Etravirine (ETR)/ INTELENCE	100mg tablets	200mg twice daily following a meal	Take following a meal. Fasting conditions reduce drug exposure by approximately 50%	Unknown	41 ± 20 hours	Metabolized by cytochrome P450 (3A4, 2C9, and 2C19 substrate, 3A4 inducer, 2C9 and 2C19 inhibitor)	• Rash* • Nausea
Nevirapine (NVP)/ VIRAMUNE	200mg tablets or 50mg/5 mL oral suspension	200mg daily for 14 days; thereafter, 200mg by mouth twice daily	Take without regard to meals	>90%	25–30 hours	Metabolized by cytochrome P450 (3A inducer); 80% excreted in urine (glucuronidated metabolites; <5% unchanged); 10% in feces Not recommended in patients with moderate-to-severe hepatic impairment (Child Pugh B or C) Dosage adjustment in hepatic insufficiency recommended (See **Appendix Table 8**)	• Rash including Stevens-Johnson syndrome* • Symptomatic hepatitis, including fatal hepatic necrosis, have been reported‡

* During clinical trials, NNRTI was discontinued because of rash among 7% of patients taking nevirapine, 4.3% of patients taking delavirdine, 1.7% of patients taking efavirenz, and 2% of patients taking etravirine. Rare cases of Stevens-Johnson syndrome have been reported with the use of all four NNRTIs, the highest incidence seen with nevirapine use.

† Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Overall frequency of any of these symptoms associated with use of efavirenz was 52%, as compared with 26% among controls subjects; 2.6% of those persons on efavirenz discontinued the drug because of these symptoms; symptoms usually subside spontaneously after 2–4 weeks.

‡ Symptomatic, sometimes serious, and even fatal hepatic events (accompanied by rash in approximately 50% of cases) occur with significantly higher frequency in treatment-naive female patients with prenevirapine CD4 counts >250 cells/mm3 or in treatment-naive male patients with prenevirapine CD4 counts >400 cells/mm3. Nevirapine should not be initiated in these patients unless the benefit clearly outweighs the risk. This toxicity has not been observed when nevirapine is given as single doses to mothers or infants for prevention of mother-to-child HIV transmission.

Please refer to the **What to Start** section of the Adult Guidelines for more detailed discussions.

Appendix Table 4. Characteristics of Protease Inhibitors (PIs) (Updated November 3, 2008)

Generic Name/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Atazanavir (ATV)/ REYATAZ	100mg, 150mg, 200mg, 300mg capsules	400mg once daily (unboosted ARV only recommended for PI-naïve pts) With efavirenz or tenofovir TDF, or for ARV-experienced pts: (ATV 300mg + RTV 100mg) once daily With EFV in treatment-naïve pts: (ATV 400mg + RTV 100mg) once daily (for dosing recommendations with H2 antagonists and PPIs, please refer to Table 15a)	Administration with food increases bioavailability. Take with food; avoid taking simultaneously with antacids	Not determined	7 hours	Cytochrome P450 3A4 inhibitor and substrate Dosage adjustment in hepatic insufficiency recommended (See Appendix Table 8)	Room temperature (up to 25ºC or 77ºF)	• Indirect hyperbilirubinemia • Prolonged PR interval— 1st degree symptomatic AV block in some pts • Use with caution in pts with underlying conduction defects or on concomitant medications that can cause PR prolongation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia • Nephrolithiasis
Darunavir (DRV)/ PREZISTA	300mg, 400mg, 600mg tablets	ARV-naïve pts: (DRV 800mg + RTV 100mg) once daily ARV- experienced pts: (DRV 600mg + RTV 100mg) BID Unboosted DRV is **not** recommended	Food ↑ Cmax & AUC by 30% - should be administered with food	Absolute bioavailability: DRV alone – 37%; w/ RTV – 82%;	15 hours (when combined with RTV)	Cytochrome P450 3A4 inhibitor and substrate	Room temperature (up to 25ºC or 77ºF)	• Skin rash (7%) – DRV has a sulfonamide moiety; Stevens-Johnson syndrome & erythrema multiforme have been reported. • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia • Transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia
Fosamprenavir (FPV)/ LEXIVA	700mg tablet or 50mg/mL oral suspension	ARV-naïve pts: • FPV 1,400mg BID or • (FPV 1,400mg + RTV 100-200mg) once daily or • (FPV 700mg + RTV 100mg) BID PI-experienced pts (once daily dosing not recommended): • (FPV 700mg + RTV 100mg) BID With EFV (FPV boosted only): • (FPV 700mg + RTV 100mg) BID or • (FPV 1,400mg + RTV 300mg) once daily	No significant change in amprenavir pharmacokinetics in fed or fasting state	Not established	7.7 hours (amprenavir)	Amprenavir is a cytochrome P450 3A4 inhibitor, inducer, and substrate Dosage adjustment in hepatic insufficiency recommended (See Appendix Table 8)	Room temperature (up to 25ºC or 77ºF)	• Skin rash (19%) • Diarrhea, nausea, vomiting • Headache • Hyperlipidemia • Transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Indinavir/ CRIXIVAN	200mg , 333mg, 400mg capsules	800mg every 8 hours; With RTV: (IDV 800mg + RTV 100-200mg) BID	Unboosted IDV Levels decrease by 77% Take 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal RTV-boosted IDV: Take with or without food	65%	1.5–2 hours	Cytochrome P450 3A4 inhibitor (less than ritonavir) Dosage adjustment in hepatic insufficiency recommended (See Appendix Table 8)	Room temperature 15º–30ºC (59º–86ºF), protect from moisture	• Nephrolithiasis • GI intolerance, nausea • Indirect hyperbilirubinemia • Hyperlipidemia • Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia

Please refer to the **What to Start** section of the Adult Guidelines for more detailed discussions.

Appendix Table 4. Characteristics of Protease Inhibitors (PIs) (Updated November 3, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Lopinavir + Ritonavir (LPV/r)/ KALETRA	Each tablet contains LPV 200mg + RTV 50mg Oral solution: Each 5 mL contains LPV 400mg + RTV 100mg Note: Oral solution contains 42% alcohol	LPV 400mg + RTV 100mg (2 tablets or 5 mL) BID or LPV 800mg + RTV 200mg (4 tablets or 10mL) once daily (**Note:** once-daily dosing only recommended for treatment-naïve pts; not for pregnant women or patients receiving EFV, NVP, FPV, or NFV) With EFV or NVP: For ARV-experienced pts: LPV 600mg + RTV 150mg (3 tablets) BID or LPV 533 mg + RTV 133 mg (6.7 mL oral solution) BID with food	Oral tablet -No food effect; take with or without food Oral solution - Moderately fatty meal ↑ LPV AUC & Cmin by 80% & 54%, respectively; take with food	Not determined in humans	5–6 hours	Cytochrome P450 (3A4 inhibitor and substrate)	Oral tablet is stable at room temperature Oral solution is stable at 2°–8°C until date on label; is stable when stored at room temperature (up to 25ºC or 77ºF) for 2 months	• GI intolerance, nausea, vomiting, diarrhea (higher incidence with once-daily than twice-daily dosing) • Asthenia • Hyperlipidemia (esp. hypertriglyceridemia) • Elevated serum transaminases • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Nelfinavir (NFV)/ VIRACEPT	250mg, 625mg tablets 50mg/g oral powder	1,250mg BID or 750mg TID	Levels increase 2–3 fold Take with meal or snack	20%–80%	3.5–5 hours	Cytochrome P450 3A4 inhibitor and substrate	Room temperature 15º–30ºC (59º–86ºF)	• Diarrhea • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes among patients with hemophilia • Serum transaminase elevation •
Ritonavir (RTV)/ NORVIR	100mg capsules or 80 mg/mL oral solution	As pharmacokinetic booster for other PIs: 100mg – 400mg per day in 1–2 divided doses (please refer to other PIs for specific dosing recommendations) 600mg every 12 hours* (when ritonavir is used as sole PI)	Levels increase 15% Take with food if possible; this may improve tolerability	Not determined	3–5 hours	Cytochrome P450 (3A4 > 2D6) substrate; Potent 3A4, 2D6 inhibitor	Refrigerate capsules Capsules can be left at room temperature (up to 25ºC or 77ºF) for ≤30 days; Oral solution should NOT be refrigerated	• GI intolerance, nausea, vomiting, diarrhea • Paresthesias – circumoral and extremities • Hyperlipidemia, esp. hypertriglyceridemia • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Saquinavir tablets and hard gel capsules (SQV)/ INVIRASE	200mg hard gel capsules, 500mg tablets	(SQV 1,000mg + RTV 100mg) PO BID Unboosted SQV is **not** recommended	Take within 2 hours of a meal	4% erratic (when taken as sole PI)	1–2 hours	Cytochrome P450 (3A4 inhibitor and substrate)	Room temperature 15º–30ºC (59º–86ºF)	• GI intolerance, nausea and diarrhea • Headache • Elevated transaminase enzymes • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

* Dose escalation for Ritonavir when used as sole PI: Days 1 and 2: 300mg two times; Days 3–5: 400mg two times; Days 6–13: 500mg two times; Day 14: 600mg two times/day.

Please refer to the **What to Start** section of the Adult Guidelines for more detailed discussions.

Appendix Table 4. Characteristics of Protease Inhibitors (PIs) (Updated November 3, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Tipranavir (TPV)/ APTIVUS	250mg capsules	(TPV 500mg + RTV 200mg) PO BID Unboosted TPV is **not** recommended	No clinically significant change in TPV pharmacokinetics in fed or fasting state	Not determined	6 hours after single dose of TPV/ RTV	TPV – Cytochrome P450 (3A4 inducer and substrate) Net effect when combined with RTV – CYP 3A4 inhibitor and CYP 2D6 inhibitor	Refrigerated capsules are stable until date on label; if stored at room temperature (up to 25ºC or 77ºF) – must be used within 60 days	• Hepatotoxicity – clinical hepatitis including hepatic decompensation has been reported, monitor closely, esp. in patients with underlying liver diseases • Skin rash – 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. Most patients had underlying comorbidity such as brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism, or on medication with increase risk for bleeding • Hyperlipidemia (esp. hypertriglyceridemia) • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

Please refer to the **What to Start** section of the Adult Guidelines for more detailed discussions.

Appendix Table 5. Characteristics of Fusion Inhibitors (Updated January 29, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Enfuvirtide (T20)/ FUZEON	• Injectable – in lyophilized powder • Each vial contains 108 mg of enfuvirtide, reconstitute with 1.1 mL of Sterile Water for injection for delivery of approximatel y 90mg/1 mL	90mg (1 mL) subcutaneously BID	Not applicable	Not applicable	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 25ºC or 77ºF) Reconstitute d solution should be stored under refrigeration at 2ºC–8ºC (36ºF–46Fº) and used within 24 hours	• Local injection site reactions – almost 100% of patients (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) • Increased bacterial pneumonia • Hypersensitivity reaction (<1%) - symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases; rechallenge is not recommended

Appendix Table 6. Characteristics of CCR5 Antagonists (Updated January 29, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Maraviroc (MVC)/ SELZENTRY	150mg, 300mg tablets	• **150mg BID** when given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except tipranavir/ritonavir) • **300mg BID** when given with NRTIs, enfuvirtide, tipranavir/ritonavir, nevirapine, and other drugs that are not strong CYP3A inhibitors • **600mg BID** when given with CYP3A inducers, including efavirenz, rifampin, etc. (without a CYP3A inhibitor)	No food effect; take with or without food	23% for 100mg dose and 33% (predicted) for 300mg	14–18 hrs	Cytochrome P450 (CYP3A substrate)	Room temperature	Abdominal pain, cough, dizziness, musculoskeletal symptoms, pyrexia, rash, upper respiratory tract infections, hepatotoxicity, orthostatic hypotension.

Appendix Table 7. Characteristics of Integrase Inhibitors (Updated January 29, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Raltegravir (RAL)/ ISENTRESS	400mg tablets	400mg BID	Take with or without food	Not established	≈ 9 hrs	UGT1A1-mediated glucuronidati on	Room temperature	Nausea, headache, diarrhea, pyrexia, CPK elevation

Please refer to the **What to Start** section of the Adult Guidelines for more detailed discussions.

Appendix Table 8. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Updated November 3, 2008)

Antiretrovirals	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment
Nucleoside Reverse Transcriptase Inhibitors – Note: Use of fixed-dose combination NRTI (+/- NNRTI) of: ATRIPLA, COMBIVIR, TRIZIVIR, EPZICOM – not recommended in patients with CrCl <50 mL/min; use of TRUVADA – not recommended in patients with CrCl <30 mL/min			
Abacavir* (ZIAGEN)	300mg PO BID	No need for dosage adjustment	No dosage recommendation
Didanosine (VIDEX EC)	≥60 kg 400mg PO once daily <60 kg 250mg once daily	**Dose** **CrCl (mL/min) >60 kg <60 kg** 30-59 200mg 125 mg 10-29 125 mg 100mg < 10 125 mg 75 mg CAPD or HD patients: use same dose as CrCl < 10 ml/min	No dosage recommendation
Emtricitabine (EMTRIVA)	200mg oral capsule PO once daily or 240mg (24mL) oral solution PO once daily	**CrCl capsule solution** 30-49 200mg q48h 120mg q24h 15-29 200mg q72h 80mg q24h <15 200mg q96h 60mg q24h or HD*	No dosage recommendation
Lamivudine* (EPIVIR)	300mg PO once daily or 150mg PO BID	**CrCl (mL/min) Dose** 30-49 150mg q24h 15-29 150mg x 1, then 100mg q24h 5-14 150mg x 1, then 50mg q24h <5 50mg x 1, then 25 mg q24h or HD*	No dosage recommendation
Stavudine (ZERIT)	≥60 kg 40mg PO BID <60 kg 30mg PO BID	**Dose** **CrCl (mL/min) >60 kg <60 kg** 26-50 20mg q12h 15 mg q12h 10-25 20mg q24h 15 mg q24h or HD*	No dosage recommendation
Tenofovir (VIREAD)	300mg PO once daily	**CrCl (mL/min) Dose** 30-49 300mg q48h 10-29 300mg twice weekly ESRD 300mg q7d or HD*	No dosage recommendation
Tenofovir + Emtricitabine (TRUVADA)	1 tablet PO once daily	**CrCl (mL/min) Dose** 30-49 tablet q48h <30 not recommended	No dosage recommendation
Zidovudine* (RETROVIR)	300mg PO BID	"Severe" renal impairment (CrCl < 15 mL/min) or HD*: 100mg TID or 300mg once daily	No dosage recommendation
Non-Nucleoside Reverse Transcriptase Inhibitors			
Delavirdine (RESCRIPTOR)	400mg PO TID	No dosage adjustment necessary	No recommendation; use with caution in patients with hepatic impairment
Efavirenz (SUSTIVA) Efavirenz/tenofovir/ emtricitabine (ATRIPLA)	600mg PO once daily One tablet PO once daily	No dosage adjustment necessary ATRIPLA™ - not recommended if CrCl <50 ml/min	No recommendation; use with caution in patients with hepatic impairment
Etravirine (INTELENCE)	200mg PO BID following a meal	No dosage adjustment necessary	No dosage adjustment for Child-Pugh Class A or B. Has not been evaluated in patients with Child-Pugh Class C
Nevirapine (VIRAMUNE)	200mg PO BID	No dosage adjustment necessary	Contraindicated in patients with Child-Pugh Class B or C

HD* = dose after dialysis on dialysis days, HD = hemodialysis, CAPD = chronic ambulatory peritoneal dialysis, ESRD = End Stage Renal Disease

Please refer to the **What to Start** section of the Adult Guidelines for more detailed discussions.

Appendix Table 8. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Updated November 3, 2008)

Antiretrovirals	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment
Protease Inhibitors			
Atazanavir (REYATAZ, ATV)	400mg PO once daily or (ATV 300mg + RTV 100mg) once daily	No dosage adjustment for patients with renal dysfunction not requiring hemodialysis Treatment-naïve patients on hemodialysis: ATV 300mg + RTV 100mg once daily Treatment-experienced patients on hemodialysis: ATV or RTV-boosted ATV not recommended	**Child-Pugh Score** **Dose** 7-9 300mg once daily >9 not recommended RTV boosting is not recommended in patients with hepatic impairment
Darunavir (PREZISTA, DRV)	(DRV 800mg + RTV 100mg) PO once daily (ARV-naïve pts) (DRV 600mg + RTV 100mg) PO BID	No dosage adjustment necessary	No dosage adjustment in patients with mild to moderate hepatic impairment. DRV is not recommended in patients with severe hepatic impairment.
Fosamprenavir (LEXIVA, FPV)	1,400mg PO BID; or (FPV 1,400mg + 100-200mg RTV) PO once daily; or (FPV 700mg + RTV 100mg) PO BID	No dosage adjustment necessary	**Child-Pugh Score** **Dose** 5-8 700mg BID 9-12 not recommended Ritonavir boosting should not be used in patients with hepatic impairment
Indinavir (CRIXIVAN)	800mg PO q8h	No dosage adjustment necessary	Mild to moderate hepatic insufficiency because of cirrhosis: 600mg q8h
Lopinavir/ritonavir (KALETRA)	400/100mg PO BID or 800/200mg PO once daily (only for treatment-naïve patients)	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Nelfinavir (VIRACEPT)	1,250mg PO BID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Ritonavir (NORVIR)	600mg PO BID	No dosage adjustment necessary	No dosage adjustment in mild hepatic impairment; no data for moderate to severe impairment, use with caution
Saquinavir (INVIRASE, SQV)	(SQV 1,000mg + RTV 100mg) PO BID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Tipranavir (APTIVUS)	(TPV 500mg + RTV 200mg) PO BID	No dosage adjustment necessary	No dosage recommendation; use with caution in Child-Pugh Class A; TPV/RTV is contraindicated in pts with moderate to severe (Child-Pugh Class B & C) hepatic insufficiency
Fusion Inhibitors			
Enfuvirtide (FUZEON)	90mg SUB-Q q12h	No dosage adjustment necessary	No dosage recommendation
CCR5 Antagonists			
Maraviroc (SELZENTRY)	The recommended dose differs based on concomitant medications because of drug interactions. See **Appendix Table 6** for detailed dosing information.	No dosage recommendation; use with caution. Patients with CrCL <50 mL/min should receive MVC and CYP3A inhibitor only if potential benefits outweigh the risk.	No dosage recommendations. Concentrations will likely be increased in patients with hepatic impairment.
Integrase Inhibitors			
Raltegravir (ISENTRESS)	400mg twice daily	No dosage adjustment.	No dosage adjustment.

Creatinine Clearance calculation:

Male: $\frac{(140\text{-age in yr}) \times \text{weight (kg)}}{72 \times \text{S.Cr.}}$ Female: $\frac{(140\text{-age in yr}) \times \text{weight (kg)} \times 0.85}{72 \times \text{S.Cr.}}$

Child-Pugh Score

Component	Score Given		
	1	2	3
Encephalopathy*	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 to 3.5 g/dl	<2.8 g/dl
Total Bilirubin OR Modified Total Bilirubin**	<2 mg/dL (<34 μ mol/L) <4 mg/dL	2 to 3 mg/dL(34 μ mol/L to 50 μ mol/L) 4-7 mg/dL	>3 mg/dL(>50 μ mol/L) >7 mg/dL
Prothrombin time (sec prolonged) OR INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3

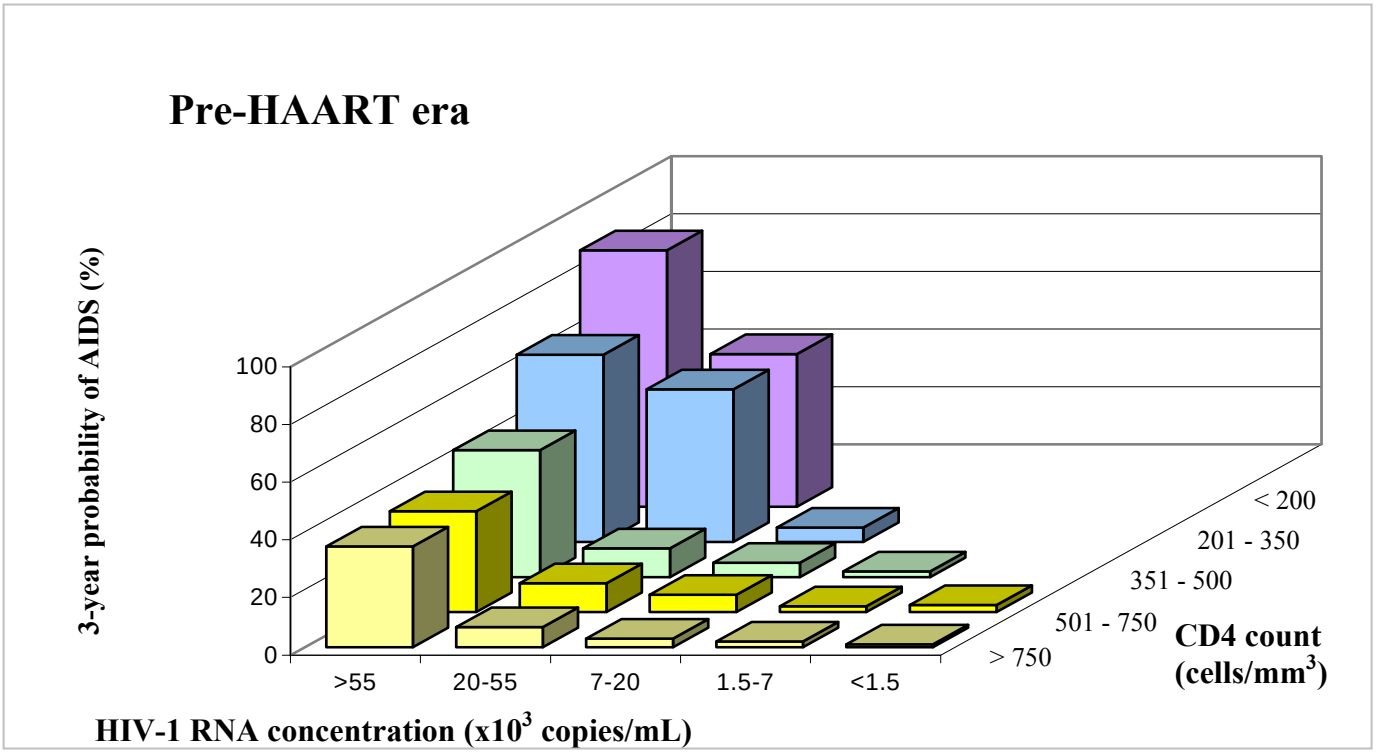
* NB: Encephalopathy Grades - Grade 1: Mild confusion, anxiety, restlessness, fine tremor, slowed coordination; Grade 2: Drowsiness, disorientation, asterixis; Grade 3: Somnolent but rousable, marked confusion, incomprehensible speech, incontinence, hyperventilation; Grade 4: Coma, decerebrate posturing, flaccidity

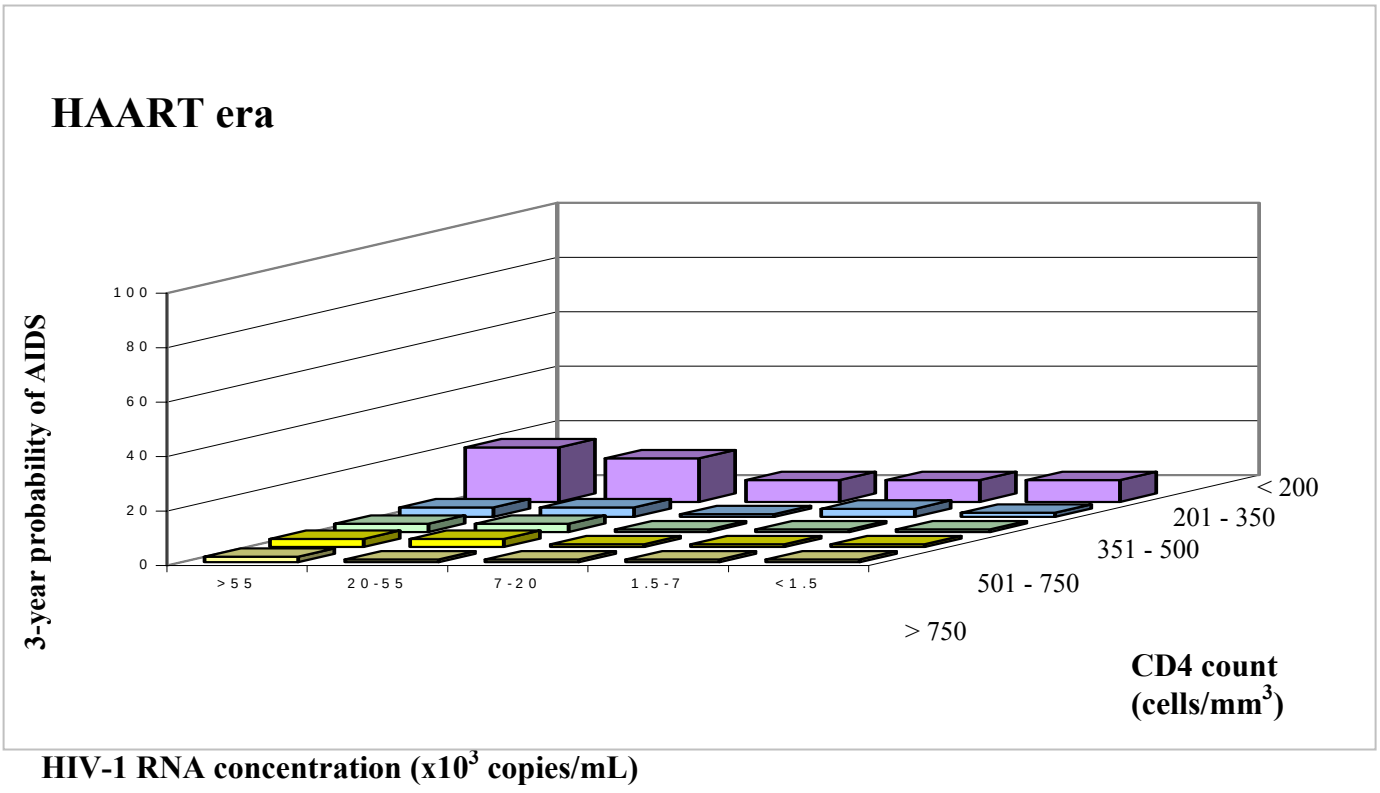
** Modified Total Bilirubin used to score patients who have Gilbert's syndrome or who are taking indinavir

Child-Pugh Classification - Child-Pugh Class A = score 5–6; Class B = score 7–9; Class C = score >9

Please refer to the **When to Start** section of the Adult Guidelines for more detailed discussions.

Figure A: Prognosis According to CD4 Cell Count and Viral Load in the Pre-HAART and HAART Eras (Updated October 29, 2004)





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