ANTIRETROVIRAL THERAPY

What's New — September 2010 Update
Section III: *Deciding When to Initiate ART*
August 2010 Update
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I. INTRODUCTION

Antiretroviral therapy (ART) refers to the use of pharmacologic agents that have specific inhibitory effects on HIV replication. The commercially available antiretroviral drugs that are approved by the Food and Drug Administration (FDA) for the treatment of HIV/AIDS are listed in Appendix A. The use of less than three active agents is not recommended for initiating treatment in non-pregnant adults.

These agents belong to six distinct classes of drugs: the nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs, NtRTIs), the non-nucleoside reverse transcriptase inhibitors (NNRTIs), the protease inhibitors (PIs), the fusion inhibitors (FIs), the CCR-5 co-receptor antagonists, and the integrase inhibitors. The current standard for formulating a highly active ART regimen recommends the use of either a PI or an NNRTI in combination with two NRTIs. The combination of three NRTIs or two NRTIs and an NtRTI is not as potent as the recommended combinations and should not be used for initiation of ART.

II. GOALS, BENEFITS, AND RISKS OF ART

March 2006

RECOMMENDATIONS:
Clinicians should prescribe an ART regimen that is best able to delay disease progression, prolong survival, and maintain quality of life through maximal viral suppression (see Table 1)**.** (I)

The clinician should involve the patient in the decision-making process when determining whether to implement ART. The clinician should review the benefits and risks of treatment for each individual patient. (III)

TABLE 1
GOALS OF ANTIRETROVIRAL THERAPY

- Maximal and durable suppression of viral replication (measured by viral load assays)
- Restoration and/or preservation of immune function
- Reduced HIV-related morbidity and mortality
- Improved quality of life
- Limitation of the likelihood of viral resistance to preserve future treatment option

In typical clinical practice, durable suppression of viral replication to undetectable levels may be achieved in approximately 80% of cases. The maximal suppression of viral replication is generally associated with gradual increases in the CD4 count and clinical stabilization or improvement of HIV-associated symptoms. When maximal suppression is not attainable due to the inability to construct an effective regimen for the patient, partial viral suppression (≥0.5 log reduction, or 3-fold, from baseline viral load value) and stable CD4 counts are reasonable alternative goals. However, incomplete suppression of viral replication may be associated with continued immunologic and clinical deterioration and the evolution of additional resistance mutations. Patients who are unable to adhere strictly to complex medication regimens are those most likely to develop HIV-drug resistance and to face limited future ART options (see Section IV: *The Importance of Patient Adherence*). Most patients will benefit from ART, provided that they are able to take the medications reliably. It is the clinician's responsibility to involve the patient in the decision-making process when deciding whether to implement ART. The clinician needs to review the benefits and risks of treatment for each individual patient (see Table 2).

TABLE 2
BENEFITS AND RISKS OF ANTIRETROVIRAL THERAPY

The benefits of ART include:

- The preservation and/or restoration of immune function
- Improvement of overall health and the prolongation of life
- The suppression of viral replication
- The possible decrease in risk of viral transmission to others (including fetal transmission)

The risks of ART include:

- Adverse effects of the medications on quality of life
- Known, and as yet unknown, long-term drug toxicities, including potential fetal toxicity
- The development of HIV drug resistance to drugs currently available and possibly to those not yet available, which may limit future treatment options

III. Deciding When to Initiate ART

September 2010

General Recommendations:

The decision to initiate ART should be individualized for each patient and incorporate assessment of the following factors:

- **Risk of progression to illness or death if untreated**
- **Readiness and willingness to adhere to therapy; potential barriers to adherence**
- **Comorbidities and coexisting conditions**
- **Risk of HIV transmission to others if untreated**
- **Risk of toxicities and drug-drug interactions**

Clinicians should involve the patient when planning treatment, and the patient should make the final decision of whether and when to initiate ART.

Recommendations for Initiating ART

1. Initiation of ART is recommended for each of the following patient groups after modifiable barriers to adherence are minimized[a]:
Patients who:
• **are symptomatic from HIV, regardless of CD4 count, including any of the following conditions:**
  o **HIV-associated neurocognitive disorder (HAND)[b]** (see *Cognitive Disorders and HIV/AIDS*)
  o **Severe thrombocytopenia**
  o **HIV-associated nephropathy**
  o **HIV-related malignancies**
• **have an AIDS-defining condition**
• **are pregnant[c]**
• **have chronic active hepatitis B virus (see *Hepatitis B Virus* guidelines)**
• **have two successive measurements of CD4 counts ≤500 cells/mm^3**
• **have rapid decline in CD4 count, defined as >100 cells/mm^3 per year**
• **have two successive measurements of HIV RNA >100,000 copies/mL**

2. The following coexisting conditions should prompt consideration and discussion with patients about initiation of ART at CD4 counts >500 cells/mm^3.[a] Clinicians should consult with a provider who has extensive experience with management of ART: • **Chronic active hepatitis C virus infection** • **Non-HIV-related malignancies** • **Age >50 years** • **Acute HIV infection** (see *Diagnosis and Management of Acute Infection*) • **Partner serodiscordance**
3. There is no upper CD4 limit for initiating ART in patients who wish to receive it
[a] See Table 3 for evidence and ratings. [b] HAND is currently used to encompass a hierarchy of progressive patterns of central nervous system involvement ranging from asymptomatic neurocognitive impairment (ANI), to minor neurocognitive disorder (MND), to the more severe HIV-associated dementia (HAD). [c] For recommendations on initiating ART in HIV-infected pregnant women, refer to *Management of HIV-Infected Pregnant Women Including Prevention of Perinatal HIV Transmission.*

Discussion of antiretroviral therapy should occur at the start of care for all HIV-infected patients, regardless of CD4 count, with the anticipation that ART will be initiated at some time. The decision to initiate therapy depends on many individual factors for each patient and requires a lifelong commitment by the patient. The clinician and patient should discuss, usually over several visits, the risks and benefits of early ART and individual factors that may affect the decision to initiate, such as patient readiness and reluctance, adherence barriers, CD4 cell count and viral load, comorbidities, age, and partner serodiscordance. Misconceptions about treatment initiation should be addressed, including the implication that starting ART represents advanced HIV illness. Treatment is part of the natural history of living well with HIV. Initiating ART before symptoms occur allows patients to stay healthy and live longer.

Although data from randomized clinical trials are not available, a combination of data from observational cohort studies show that both morbidity and mortality are improved by initiation of therapy in patients with CD4 counts <500 cells/mm^3. Evidence shows that patients who initiate ART earlier are less likely to suffer a variety of complications, including cardiovascular disease, neurocognitive dysfunction, HIV-associated kidney disease, progression of hepatitis, and malignancies. **Based on accumulating evidence, this Committee now recommends treatment for patients with CD4 counts ≤500 cells/mm^3.**

In addition, clinicians should evaluate patients with CD4 counts >500 cells/mm^3 for comorbidities or coexisting conditions that may influence the decision to treat and favor earlier initiation when appropriate. In patients with CD4 counts >500 cells/mm^3, clinicians should focus on patient readiness for therapy and specific comorbidities rather than on the CD4 count or viral load. The NA-ACCORD study showed decreased risk of death in patients who initiated therapy at CD4 counts >500 cells/mm^3.[1] Consultation with a clinician who has extensive experience with management of ART is recommended. Randomized controlled trials are in progress that are designed to determine the ideal CD4 count and viral load parameters at which to initiate treatment.

The New York State Department of Health AIDS Institute follows the Centers for Disease Control and Prevention (CDC) definition of HIV/AIDS and list of AIDS-defining conditions.

See Appendix B for a comparison of the recommendations from the New York State Department of Health AIDS Institute, the Department of Health and Human Services, and the International AIDS Society – USA Panel.

TABLE 3 EVIDENCE BASE FOR RECOMMENDATIONS TO INITIATE ART	
Recommend Initiation of ART	**(Rating) and References**
Patients who are symptomatic	(AI) Refs 2-4
Patients with HIV-related conditions	
o HIV-related dementia	(AII) Ref 5
o Severe thrombocytopenia	(AII) Refs 6-8
o HIV-associated nephropathy	(AII) Refs 2,3,9-12
o HIV-related malignancies	(AII) Refs 13-18
Patients with chronic HBV	(AII) Refs 2,3,11,19, 20
Patients with CD4 count ≤500 cells/mm^3	(AII) Refs 1-3,19,21,22
Patients with rapid decline in CD4 count, defined as >100 cells/mm^3 per year	(AIII) Ref 3
Patients with HIV RNA >100,000 copies	(AII) Refs 3,4,23,24
Should prompt discussion with patient about initiation of ART at CD4 counts >500 cells/mm^3. Consult with a clinician who has extensive experience with management of ART	**(Rating) and References**
Chronic hepatitis C virus	(AII) Refs 3,4,11,20,25-27
Non-HIV-related malignancies	(BIII)
Patients aged >50 years	(AII) Refs 1,4,19,28,29
Acute HIV infection	(AIII) Refs 3,30-32
Partner serodiscordance	(AII) Refs 3,33-35

A. Benefits and Risks of Initiating ART

Table 4 outlines the benefits and risks to consider when deciding when to initiate ART.

TABLE 4
BENEFITS AND RISKS OF EARLY THERAPY IN THE ASYMPTOMATIC HIV-INFECTED PATIENT
(early therapy = initiation at CD4 counts >500 cells/mm^3)

Benefits of early therapy

- Earlier treatment may reduce both HIV-related and non-HIV-related morbidity and mortality[1,15,16, 21-24, 27,36-38]
- Control of viral replication is easier to achieve and maintain
- CD4 counts in the normal range are more likely to be achieved and maintained
- Delay or prevention of immune system compromise[22]
- Possible lower risk of antiretroviral resistance[39]
- Decreased risk of HIV transmission*[33-35]

Risks of early therapy

- Drug-related reduction in quality of life
- Greater cumulative side effects from ART
- Earlier development of drug resistance if viral suppression is suboptimal
- Limitation in future antiretroviral treatment options if viral suppression is suboptimal
- Greater chance of treatment fatigue

* The risk of viral transmission still exists even when the plasma viral load is undetectable; ART is not a substitute for primary HIV prevention measures (e.g., avoiding sharing needles, practicing safer sex).

B. Potential Barriers to Adherence

RECOMMENDATION:
Except when initiation of treatment is clinically urgent, clinicians should use more than one visit for education and counseling before committing a patient to a specific therapy. Counseling and education should include the following:

- **Available treatment options and potential benefits and risks of therapy** (see Table 4)
- **The need for strict adherence and the risk of viral drug resistance when adherence is suboptimal** (see Section IV: *The Importance of Patient Adherence*)
- **Use of safer-sex practices and avoidance of needle-sharing activity, regardless of viral load, to prevent HIV transmission or superinfection**

Except when initiation of treatment is clinically urgent, more than one visit before initiating ART is advisable to ensure adequate understanding of the importance of adherence to address potential barriers to therapy. These barriers may include active alcohol or drug use, medication side effects, lack of insurance or transportation, depression, mistrust of medical providers, low health literacy, or a poor social support system.

Patients who meet clinical criteria for initiation of ART but who are at high risk for poor adherence may benefit if long-term ART is temporarily deferred while further patient education efforts are undertaken (see Section IV: *The Importance of Patient Adherence*). In these patients, the risk of viral resistance and eventual treatment failure may outweigh any clinical benefit from earlier treatment before strict adherence can be expected. These patients should remain under particularly close observation for clinical and laboratory signs of disease progression. ART should be initiated as soon as the patient seems prepared to strictly adhere to a treatment regimen. In patients with advanced AIDS, it may be appropriate to initiate ART even if barriers to adherence are present. In these cases, referrals to specialized adherence programs should be made for intensified adherence support (see Appendix C: *New York State Adherence Services Contact List*).

C. Initiating ART Following Acute Opportunistic Infections

RECOMMENDATION:
Clinicians should strongly recommend that patients recovering from acute opportunistic infections initiate ART as soon as patient tolerability has been established and the potential for drug-drug interactions has been minimized.

Clinicians should strongly recommend that patients recovering from acute opportunistic infections initiate ART as soon as it is safe, based on patient tolerability and drug-drug interactions.[40] In some cases, determining the optimal timing for initiating therapy in these patients is complex and may require consultation from a clinician who has extensive experience with management of ART. After initiating ART, clinicians need to be alert to the possibility of immune reconstitution syndromes as CD4 cell counts are restored (see *Immune Reconstitution Inflammatory Syndrome*). Effective communication from the hospital to the out-patient provider is critical to ensure a successful transition for the patient.

IV. THE IMPORTANCE OF PATIENT ADHERENCE

July 2004

RECOMMENDATIONS:
A team approach to achieving adherence should be used. Nurses, pharmacists, peer counselors, caseworkers, and others who work in outreach, evaluation, and support of adherence should be involved. (III)

The clinician should assess treatment readiness prior to initiation of treatment, adherence readiness for subsequent regimens, and adherence at every clinical visit. (III)

Interventions should be intensified in times of decreased adherence.

Information about patients' beliefs and attitudes should be communicated with all members of the healthcare team so that each provider can consistently address treatment adherence issues within the context of the overall treatment plan. (II)

If the patient is not fully committed to adhering to therapy, treatment should be delayed, and the clinician should continue to work on abating the patient's concerns. Appropriate referrals should be provided for support groups, mental health, and drug treatment. (III)

Potential barriers to adherence include:

- Communication difficulties that arise when the patient's attitude about disease and therapy is different from that of the provider's. Without open and nonjudgmental communication from the healthcare team, patients may not trust or may misunderstand the prescribed regimen.
- Language or literacy barriers.
- Unstable living situations (including limited or absent social support).
- Discomfort with disclosure of HIV status, which may become known when medications are taken.
- Inability to set long-term goals.
- Inadequate knowledge about disease and effectiveness of medications or healthy living, including a patient's lack of belief in his/her ability to take medications regularly.
- Difficulty accessing adequate health care.
- Housing, food, lack of childcare, or other immediate life needs, which are viewed as more pressing than taking the medications regularly.

Strict adherence to ART is essential for maintaining treatment benefit and preventing the development of HIV resistance. Study results are clear on the importance of a high level of adherence for good virologic control. Adherence to >95% of PI doses has been correlated with sustained viral suppression in several studies. Good adherence frequently wanes over time, and patients may need significant support the longer the duration of therapy.

Evidence from several studies suggests that patients who are confident about the efficacy of their treatment are more likely to adhere to their medication regimen and their healthcare visits. Confidence contains two significant components: understanding and belief.

Helping the patient understand the importance of treatment may be accomplished through a wide range of patient education activities, and especially through participation in peer education programs (see Section C: *Educating the Patient About Adherence*).

Encouraging belief in the efficacy of the regimen may be more challenging for the clinician and entails asking the patient what they believe about the causes of their disease and how it may be treated. Similarly, their opinions about what has contributed to the success or failure of their adherence to treatment should be sought (see Section D: *Patients' Beliefs and Attitudes*).

For further guidance on assessing and promoting adherence, refer to *Promoting Adherence to HIV Antiretroviral Therapy: Best Practices from New York State*.

A. The Patient-Healthcare Team Relationship: Involving the Patient
The quality of the relationship between the patient and the clinician greatly influences adherence. A trusting, open, and nonjudgmental relationship will improve the likelihood of strict adherence.

Strategies:

- *The healthcare team should promote active patient involvement in decision-making about initiating and managing ART regimens.* The patient's opinion of successes and challenges in maintaining adherence should be sought at routine visits.
- *A treatment plan should be negotiated, and active patient participation in the development of the treatment plan should be encouraged.* Patient concerns and questions regarding the regimen should be elicited, and an individualized schedule should be made based on the patient's lifestyle. A plan should be made for changes in routine (e.g., weekends, holidays, travel).
- *Patient trust should be established* and a strong working relationship should be developed.
- *Questions regarding adherence should be open-ended and should be asked in a nonjudgmental manner* with an understanding of the difficulty patients will have in admitting to adherence problems.
- *Members of the healthcare team should be open and accessible.* Ways for patients to reach medical team members 24 hours/day when questions or concerns arise should be made available.
- *Intensive support should be provided to patients beginning medication regimens.* Team members should meet with the patients frequently (or speak by phone) to provide encouragement, assess tolerability, assess adherence, and answer questions.

B. Barriers to and Predictors of Adherence
The factors involved in adherence are complex. Age, race, sex, education level, and socio-economic status are not independent predictors of adherence. Although active substance use may affect adherence, a past history of substance use does not correlate with poor adherence (see Section E: *Substance Use and Adherence*). There is also a poor correlation between medical clinicians' prediction of adherence and actual levels of adherence.

Strategies:

- *The healthcare team should be familiar with predictors of poor adherence and should address these issues in a caring and nonjudgmental manner.*
- Possible psychosocial factors and barriers to adherence, such as inadequate housing, active substance use, depression, or other mental health issues, should be addressed. Identifying patient-specific barriers to adherence will help determine which interventions are most appropriate.

C. Educating the Patient About Adherence

Strategies:

- *To foster understanding of the importance of adherence, the healthcare team should present information in language that is easily understood by the patient, consistent with the patient's level of education, and free of medical jargon.*
- *Sufficient time should be taken to fully educate the patient about the goals of treatment and the need for adherence*, both before beginning treatment and frequently during therapy.
- *Literature should be provided and, if available, peer counselors should be enlisted to reinforce education efforts*. Attention to language and use of culturally sensitive education materials are essential.
- *Adherence tools should be provided*. Written schedules, pictures of medications, pillboxes, alarms, and pagers may help patients understand and remember medication schedules. The need for greater adherence support (e.g., support groups, home visits, day treatment programs) should be assessed.
- *Reviewing the viral load response to ART in graphic form with the patient assists in reinforcing the efficacy of therapy*.
- *The clinician should advise the patient regarding events that may interrupt treatment and interfere with patient access to medications* (e.g., travel, pharmacy delays in restocking medications, manufacturer shortages, loss of medication, or incarceration). The patient should be counseled to notify his/her clinician for discussion of alternative options as soon as the patient foresees the occurrence of an interruption. Patients should be cautioned that if one (or more) drug in their ART regimen is not available for more than several days, all antiretroviral agents should be stopped until the entire ART regimen is again available to avoid the emergence of resistance while using a less suppressive regimen. This issue is of greatest concern when the antiretroviral agent in question is one to which a single point mutation confers a great degree of resistance (e.g., lamivudine and NNRTIs), which appears rapidly in the absence of a fully suppressive regimen.

D. Patients' Beliefs and Attitudes

When patients indicate that they do not believe that their medications will treat their infection, they are less likely to adhere to their regimens and need further preparation and guidance to successfully adhere to treatment.

Strategies:

- *If patients express beliefs that their medications work but also that diet, exercise, or prayer are particularly important in helping them fight their illness, then all of these modalities should be supported and integrated into the overall treatment plan,* provided that they pose no harm to the patient.
- *Information about patients' beliefs and attitudes should be communicated with all members of the healthcare team* so that each provider can consistently address treatment issues within the context of the overall treatment plan.

E. Substance Use and Adherence

Strategies:

- *Clinicians should help active substance users plan to decrease or stabilize their use in preparation for initiating ART.*
- *The healthcare team should discuss with their patients how patterns of substance use may affect adherence and should work with other providers who possess experience with treating this group to encourage reduction in substance use.* The link between reducing drug use and engaging in successful HIV treatment should be encouraged.

F. How the Regimen Affects Adherence

Studies demonstrate the difficulty of maintaining strict adherence to complex ART regimens and show significant levels of poor adherence in the "real world" of HIV care. Improved pharmacokinetics may produce ART regimens that simplify dosing and that may be more forgiving of missed dosages; however, until then, it is imperative that the clinician devotes sufficient time at each patient visit to assess the degree of adherence to prescribed therapies.

The largest obstacle in achieving strict adherence is the dosing schedule. There is a significant difference in adherence between regimens that are truly bid compared with tid or qid. The relationship of dosing with or without meals can add more complexity to the schedule. The concern about potential side effects prompts some patients to diminish adherence, often without confiding in the healthcare team.

Strategies:

- The entire medication list should be reviewed at every clinical visit to limit the concomitant use of unnecessary, ineffective, or contraindicated medications.
- Patients should be educated about the risks and benefits of ART and preservation of future treatment options to allow them to develop realistic long-term expectations.
- The side effects and toxicities associated with ART should be anticipated and explained. The patient should be informed that many side effects abate after the first weeks of treatment. Efforts should be made to plan for and to manage side effects at times when a new drug or regimen is being started.
- The regimen should be simplified to the furthest extent possible. Attention should be paid to the pill count, frequency of dosing, meal requirements, potential side effects, and drug interactions when planning a regimen.
- The regimen should be individualized. Each regimen should be planned on the basis of a given patient's unique circumstances (e.g., difficulty swallowing pills; complex work schedule; irregular meals; need for privacy; preexisting symptoms, such as diarrhea, neuropathy, depression).
- Regimens can be designed to "spare" a particular class or classes of antiretroviral drugs (see Table 5).

Class-sparing regimens may simplify dosing, delay certain side effects or drug interactions, and preserve the spared medications for later use in the event of failure of the initial regimen. Sequencing strategies should be individualized to address each patient’s concurrent morbidities and medications, ability to adhere to complex regimens, and personal tolerance for adverse medication effects.

TABLE 5
ADVANTAGES AND DISADVANTAGES OF CLASS-SPARING REGIMENS

Regimen	Regimen Possible Advantages	Regimen Possible Disadvantages	Drug Interaction Complications	Impact on Future Options
PI-based ART regimen (NNTRI- and FI-sparing)	• Clinical, virologic, and immunologic efficacy well-documented • Continued benefits sometimes seen despite viral breakthrough • Resistance requires multiple mutations, except in the case of nelfinavir • Avoids NNRTI- and FI-associated side effects • Targets HIV at two steps of viral replication (RT and PR)	• May be difficult to use and adhere to because of complex dosing schedule and number of pills • Long-term side effects may include fat redistribution,* hyperlipidemia, and insulin resistance	• Mild to severe inhibition of cytochrome P450 pathway; ritonavir is most potent inhibitor, but this effect can be exploited to boost levels of other PIs	• Preserves NNRTIs and FIs for use in treatment failure • Protease resistance mutations prime the development of additional mutations that may confer cross-resistance to the other PIs
NNRTI-based ART regimen (PI-sparing)	• Avoids PI- and FI-related side effects • Generally easier to use and adhere to compared with PIs • Efavirenz-based regimens may be more potent than regimens containing a single PI	• Comparability to PI-containing regimens with regard to clinical endpoints unknown • Resistance conferred by a single or few mutations • Nevirapine-based regimens may be less effective in patients with high baseline viral loads or low CD4 counts	• Fewer drug-drug interactions compared with PIs	• Preserves PIs and FIs for later use • Resistance usually leads to cross-resistance across entire NNRTI class

Triple NRTI regimen (NNRTI- and PI-sparing)	• Generally easier to use and adhere to compared with PIs • Avoids PI, NNRTI, and FI side effects	• Not recommended for initial therapy due to inferior virologic efficacy	• No cytochrome P450 interaction	• Preserves PI, NNRTI, and FI classes for use in treatment failure

Adapted from the DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents* (2006).
* Some side effects being attributed to PI therapy, such as fat redistribution, have not been proven to be strictly associated with the use of PI-containing regimens. Fat redistribution also has been described uncommonly in patients receiving NRTIs alone and in patients not receiving ART.

V. Selecting an Initial Antiretroviral Regimen

August 2010

Recommendations:

Clinicians should obtain genotypic resistance testing at baseline and should consider repeating the test prior to initiating treatment in ART-naïve patients. (AIII)

Clinicians should involve their patients when deciding which antiretroviral regimen is most likely to result in patient adherence. (AIII)

For ART-naïve patients, the initial preferred antiretroviral regimen should include a combination of two nucleoside/nucleotide RTIs plus either a ritonavir-boosted PI, an NNRTI, or an integrase inhibitor. (AI)

For women considering pregnancy or not using effective contraception, efavirenz or combination pills containing efavirenz should be avoided. If there are no alternatives for efavirenz in women of childbearing potential, clinicians should strongly advise the use of effective contraception and should obtain a pregnancy test before initiating treatment. (AI)

Selection of antiretroviral agents should be individualized to address each patient's concurrent morbidities and medications, ability to adhere to complex regimens, and personal tolerance for adverse medication effects. (AIII)

Clinicians should follow up with patients by phone or visit within 2 weeks of initiating therapy to assess tolerance and adherence to the antiretroviral regimen. Adherence should be reinforced at regular intervals during the course of therapy. (AIII)

Key Point:
The goal of the initial antiretroviral regimen is to achieve durable and maximal viral suppression (i.e., undetectable plasma HIV RNA) with minimal adherence challenges and long-term tolerability.

ART should be designed to achieve the maximal viral suppression. Such suppression generally requires three or more active agents to which the virus is susceptible.

Preferred, alternative, and contraindicated combinations for initial treatment of HIV infection are listed in Tables 6A-C. Clinicians should consult with a provider who has extensive experience with ART when a patient's resistance profile indicates the need for a regimen not listed in Tables 6-A or -B.

These tables should be used in conjunction with Appendix A, which includes specific dosing recommendations, including dose adjustments due to renal or hepatic impairment, adverse events, drug-drug interactions, and FDA pregnancy categories for each antiretroviral agent. For detailed information regarding ART in pregnant women, see *Management of HIV-Infected Pregnant Women Including Prevention of Perinatal HIV Transmission*.

Preferred regimens are those with optimal efficacy, favorable tolerability and toxicity profile, and simplified dosing.

TABLE 6-A
PREFERRED ANTIRETROVIRAL REGIMENS FOR INITIAL TREATMENT OF HIV-1 INFECTION IN NON-PREGNANT ADULTS AND ADOLESCENTS*

Dual N(t)RTI		**NNRTI** *or*	**PI** *or*	**Integrase Inhibitor**
• **tenofovir** *plus* **emtricitabine** (co-formulated as Truvada†) • **tenofovir** *plus* **lamivudine**	+	• **efavirenz** [a,b]	• **atazanavir** *plus* **ritonavir**‡ • **darunavir** *plus* **ritonavir** (once-daily dosing) • **fosamprenavir** *plus* **ritonavir** (once-daily dosing)‡	• **raltegravir** [c]

***** Options are listed alphabetically. For recommendations for ART use during pregnancy, see *Management of HIV-Infected Pregnant Women Including Prevention of Perinatal HIV Transmission*.
† Fixed-dose combinations should not be used in patients who need dose adjustment due to renal failure.
‡ See Appendix A for dose adjustments with this antiretroviral combination.

[a] When efavirenz is used with tenofovir + emtricitabine, Atripla, a fixed-dose, three-drug combination pill, can be prescribed.
[b] For women considering pregnancy or likely to become pregnant, efavirenz, or combination pills containing efavirenz, should be avoided. If there are no alternatives for efavirenz in women of childbearing age, clinicians should strongly advise the use of effective contraception and should obtain a pregnancy test before initiation.
[c] Disadvantage to this regimen is bid dosing; however, the benefit of increased tolerability may outweigh the limitation of twice-daily dosing.

Alternative antiretroviral regimens are effective and tolerable but have potential disadvantages compared with the preferred regimens in Table 6-A. In some cases, an alternative regimen may be the preferred regimen based on the individual characteristics of the patient. Additional alternative agents that are not listed in Table 6-B may be effective but are unlikely to be necessary as components of initial regimens.

TABLE 6-B
ALTERNATIVE ANTIRETROVIRAL AGENTS FOR INITIAL TREATMENT OF HIV-1 INFECTION IN NON-PREGNANT TREATMENT-NAÏVE ADULTS AND ADOLESCENTS*

N(t)RTI backbone	**PI**
• Abacavir[a] + emtricitabine • Abacavir[a]/lamivudine[b] (co-formulated as Epzicom†) • Tenofovir + lamivudine‡ • Zidovudine + emtricitabine • Zidovudine/lamivudine (co-formulated as Combivir†)	• Darunavir + ritonavir (twice-daily dosing) • Fosamprenavir + ritonavir (twice-daily dosing)‡ • Lopinavir/ritonavir† (co-formulated as Kaletra) • Unboosted atazanavir[c] • Unboosted fosamprenavir *or* **CCR5 Inhibitor** • Maraviroc

* Options are listed alphabetically.
† Fixed-dose combinations should not be used in patients who need dose adjustment due to renal failure.
‡ See Appendix A for dose adjustments with this antiretroviral combination.

[a] To avoid hypersensitivity reaction, HLA-B*5701 testing should be performed before initiating abacavir-based therapy. Abacavir should be promptly discontinued when a hypersensitivity reaction is suspected and should never be re-started. Re-challenge may result in an anaphylactic reaction with associated hypotension or death. Use of abacavir is not recommended in patients with a Child-Pugh Score of 7-12. Risk for myocardial infarction may be increased in patients receiving abacavir.
[b] Preliminary evidence suggests that abacavir/lamivudine-containing combinations may not be as effective in reducing viral load in patients with viral loads >100,000 copies/mL. However, at this time, changes in practice are not recommended until these data are confirmed.
[c] This option is acceptable but may be less favored than the other alternative choices. If tenofovir is used as part of the NRTI backbone, atazanavir + ritonavir must be used.

TABLE 6-C REGIMENS NOT RECOMMENDED OR CONTRAINDICATED FOR INITIAL TREATMENT OF HIV INFECTION	
Therapies and Components Not Recommended for Initial Treatment	**Rationale**
• Abacavir + lamivudine + zidovudine (co-formulated as Trizivir) • All triple and quadruple NRTI therapies	Higher rates of virologic failure with triple NRTI therapies
• Didanosine + stavudine	There is high incidence of toxicities (peripheral neuropathy, pancreatitis, hyperlactatemia) associated with this combination
• Etravirine	At this time, there are insufficient data to support using this agent as initial therapy (see *New Antiretroviral Drugs: Maraviroc, Raltegravir, and Etravirine*)
• Indinavir	Inconvenient dosing and pill burden
• Saquinavir (without ritonavir-boosting)	Inferior efficacy unless boosted with ritonavir
• Stavudine	The toxicities associated with stavudine generally outweigh the benefits when used as initial therapy, particularly when used in combination with didanosine
• Tenofovir + didanosine + NNRTI	High risk of early failure, possibly due to a lower barrier to development of resistance; it is unknown whether combining tenofovir + didanosine + a PI is more efficacious
Contraindicated Therapies and Components for Initial Treatment (Do Not Use)	**Rationale**
Emtricitabine + lamivudine	These agents are interchangeable – do not use in combination
Fosamprenavir + lopinavir/ritonavir (co-formulated as Kaletra)	The use of fosamprenavir with lopinavir/ritonavir causes a bi-directional drug interaction that results in lower drug levels
Ritonavir + nelfinavir	Not easily tolerated and no additional boosting effect on nelfinavir
Stavudine + zidovudine	Pharmacologic antagonism between stavudine and zidovudine
Two-drug therapy	Insufficient data to recommend
Monotherapy	Inferior efficacy

Ritonavir Boosting

Therapeutic doses of ritonavir are poorly tolerated when used as the only PI in a regimen. However, when used at lower and better tolerated doses in combination with selected PIs, ritonavir may enhance the bioavailability and prolong the elimination half-life of these medications, thus improving therapeutic thresholds while reducing overall pill burden. This is often referred to as "boosting." Initial ART regimens containing fosamprenavir and atazanavir are often given with ritonavir as a booster; however, darunavir and lopinavir must be given with ritonavir to be effective (lopinavir is co-formulated with ritonavir; therefore, a separate dose is not necessary).

Because all PIs, especially ritonavir, can greatly alter the levels of non-antiretroviral medications, clinicians should evaluate potential interactions with all concurrent prescription and over-the-counter medications.

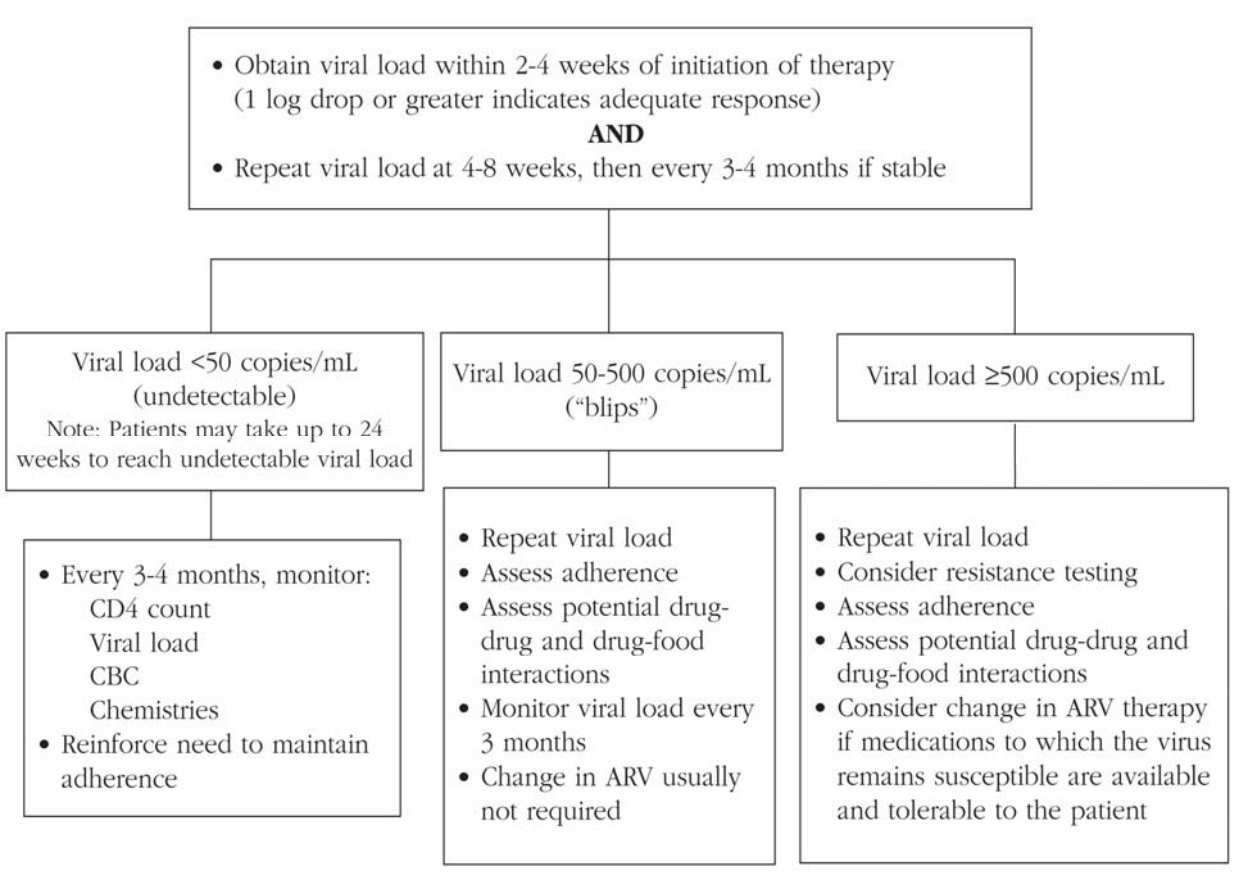
Rationale for Class-Sparing Regimens

Rational sequencing of antiretroviral agents may help to maximize the effect of each regimen and preserve future treatment options. Regimens can be designed to "spare" a particular class or classes of antiretroviral agents to simplify dosing regimens, delay certain side effects or drug interactions, and preserve the spared medications for later use in the event of failure of the initial regimen. Sequencing strategies should be individualized to address each patient's concurrent morbidities and medications, ability to adhere to complex regimens, and personal tolerance for adverse medication effects.

VI. MONITORING OF PATIENTS RECEIVING ART

The measurement of plasma viral load and of CD4 lymphocyte counts along with clinical assessment can provide an accurate picture of disease activity and response to ART. Periodic monitoring of viral load, CD4 counts, and other laboratory tests are necessary to evaluate the response to ART and its potential related side effects (see Figure 1). In the setting of ART failure, viral resistance assays should be used. Appendix D lists drugs with overlapping toxicities to guide frequency of monitoring.

Figure 1: Monitoring ART



A. Monitoring Markers of HIV Infection

1. Viral Load

March 2006

RECOMMENDATIONS:

In ART-naïve patients or patients who are on a successful regimen, plasma viral load should be measured at baseline and every 3 to 4 months thereafter. Patients with CD4 counts >500 cells/mm^3 may only require viral load monitoring every 6 months. (III)

Viral load should be measured immediately before initiation or change of ART and every 2 to 4 weeks after initiation or change until maximal suppression is documented. Once maximal suppression is attained, monitoring of viral load should occur every 3 to 4 months. (III)

If there is a significant increase (3-fold increase or more) in viral load without clear explanation, measurement should be repeated to confirm virologic failure. (III)

Virologic failure should prompt the clinician to assess the patient's adherence and to check for the presence of viral resistance. (I)

Plasma levels of viral RNA have been shown to correlate closely with clinical outcome. More than a dozen clinical trials involving thousands of patients have demonstrated this correlation at various stages of disease and with a wide variety of previous experience with antiretroviral treatment (see Appendix E and Appendix F). In addition, the level of viral RNA measured in this way provides the most precise means of establishing whether a response to ART has occurred. Typically, in patients beginning therapy or in those changing therapy as a result of virologic failure, viral load measured 2 to 4 weeks after therapy initiation decreases by at least 1 log (10-fold) in the presence of effective therapy (see Table 7). For patients who do not have background antiretroviral resistance, an undetectable viral load (<50 copies/mL) is usually achieved within a few months. Patients with resistance or a baseline viral load of >1 x 10^{5-6} copies/mL typically achieve an undetectable viral load after 6 months of effective treatment. An absent or incomplete response of the viral load to ART should raise concerns about poor patient adherence to therapy and/or viral resistance (see Section IV: *The Importance of Patient Adherence* and Section VIII: *Failure to Achieve Goals of Initial ART*).

Viral genetic diversity is characteristic of HIV-1. Furthermore, subtypes (clades) of the virus from various regions of the world are genetically distinct. Current polymerase chain reaction (PCR) viral load assays were developed primarily for clade B, which is the strain prevalent in Europe and North America. Non-clade B infections are present in approximately 2% of HIV-infected persons in the United States. Infection with a non-clade B strain should be suspected in the presence of 1) a low viral load and a low CD4 cell count in a patient not yet receiving ART, or 2) a decreasing CD4 count despite a low or undetectable viral load. Occasionally, patients may be infected with other undetermined subtypes of HIV-1 or HIV-2. Currently, viral load assays are not available that quantify these subtypes; therefore, response to treatment should be monitored by CD4 counts and clinical parameters.

TABLE 7 INTERPRETATION OF VIRAL LOAD			
HIV-1 RNA Copy Number			
Copies/mm^3			**Log$_{10}$**
1,000,000 100,000 10,000 1,000 100			6.0 5.0 4.0 3.0 2.0
Reduction With Antiretroviral Therapy if Patient Has 100,000 copies/mm^3			
Log Change	**Percent Decrease**	**Fold Reduction**	**Resultant Copy Number**
0.5	66.00	3	33,000
1.0	90.00	10	10,000
2.0	99.00	100	1,000
3.0	99.90	1000	100

2. Lymphocyte Subsets

March 2006

RECOMMENDATIONS:
Clinicians should measure CD4 cell counts at the time of diagnosis of HIV infection and every 3 to 4 months thereafter. (III)

The absence of a significant CD4 cell count increase should not be interpreted as treatment failure if the viral load declines appropriately. (III)

CD4 lymphocyte count, expressed as cells/mm^3 of blood, is a less precise indicator of antiretroviral response than viral RNA but is an essential measure to evaluate immunologic staging, to predict the risk of clinical progression, and to make decisions regarding prophylaxis of opportunistic infections. CD4 percentages are useful for comparison to absolute numbers, particularly in settings in which unexpected increases or decreases in absolute counts are observed. A significant change in CD4 cell percentage is a difference of >3%.

The CD4 response to ART, however, can be unpredictable. Although a significant increase often occurs among patients treated with effective ART, the absence of such an increase should not be taken to mean treatment failure if the viral load declines appropriately. Such a lack of correlation between viral load and CD4 cell response is particularly common among patients with extremely low initial CD4 cell counts (<50 cells/mm^3). In addition, some patients have stable or increasing

CD4 counts, although their viral loads are not well suppressed. Patients with these discordant responses who are clinically stable need close monitoring but may not need to change therapy immediately if an effective alternative ART regimen cannot be constructed based on the results of resistance testing. Appendix E illustrates that both parameters in interaction are predictive of disease progression.

3. HIV Resistance Assays

October 2006

RECOMMENDATIONS:
Clinicians should perform resistance testing under the following circumstances:

- **At baseline in the setting of acute HIV infection, regardless of whether ARTis being initiated (genotypic testing)**
- **In ART-naïve patients before initiation of ART (genotypic testing)** (III)
- **In patients experiencing treatment failure or incomplete viral suppression while receiving ART (genotypic and/or phenotypic testing)** (I)

When resistance testing is indicated, it optimally should be performed while patients are either receiving therapy or have been off therapy for less than 1 year. (III)

Clinicians should consult with an expert to interpret the results of resistance assays because the results of resistance assays are often complex (see Clinical Education Initiative sites available for phone consultation)**.** (I)

In vitro testing for resistance to antiretroviral agents is an essential means of rationally directing therapy in treatment-experienced patients with virologic failure. Several cohort studies have demonstrated that up to 10% of recently infected ART-naïve patients harbor drug-resistant HIV. A recently reported resistance survey completed in New York State used genotypic testing to examine the prevalence of drug resistance in treatment-naïve persons and treatment-experienced persons off therapy for ≥6 months. This study found several important findings. First, 8.8% of ART-naïve patients harbored significant drug-resistance mutations. Resistance mutations were seen in 4.8% of those infected prior to 1999 compared with 11% of those infected in 2000-2001. The second important finding was that 28.6% of patients off therapy for ≥6 months had significant drug-resistance mutations. The prevalence of drug-resistance mutations was greater in patients with more extensive antiretroviral experience. Based on this, genotypic resistance testing of all patients before the initiation of ART is recommended. However, current techniques of assessing resistance have limitations, and treatment failure has been documented in the absence of resistance. In many cases, such failure may be attributable to either poor patient adherence or inadequate drug levels. The role of resistance testing has been best established in treatment-experienced patients in whom viral resistance often correlates closely with subsequent response to ART (see Table 8). Currently available resistance assays have been tested and are considered reliable only for clade B strains of HIV-1.

Key Point:
Resistance testing more reliably indicates drugs that are not likely to be effective rather than identifying those drugs that may suppress viral replication.

TABLE 8
RECOMMENDATIONS FOR THE USE OF DRUG RESISTANCE ASSAYS

Clinical Setting/Recommendation	Rationale
Prior to initiating treatment in ART-naïve patients, including in the setting of acute HIV infection	Determine if drug-resistant virus was acquired so that an appropriate regimen may be chosen.
Virologic failure during ART	Determine the role of resistance in drug failure, and maximize the number of active drugs in the new regimen.
Suboptimal suppression of viral load after initiation of ART[a]	Determine the role of resistance, and maximize the number of active drugs in the new regimen if indicated.
Not generally recommended	
More than 1 year after discontinuation of drugs	Drug-resistance mutations may become minority species in the absence of selective drug pressure and may not be detectable. Current assays may not detect minority drug-resistant species.
Plasma viral load <500 to 1000 HIV RNA copies/mL[b]	Resistance assays cannot be reliably performed because of the low copy number of HIV RNA.

Adapted from the DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents* (2006).
[a] In pregnant women initiating therapy, the clinician may not have as much time to monitor for suboptimal suppression.
[b] The cutoff will vary according to the manufacturer of the kit.

Third-party reimbursement programs provide reimbursement for three assays (either genotype or phenotype) per year (within 12 months following date of first use).

All resistance assays are limited because 1) they only detect the most prevalent viral populations (i.e., HIV strains that represent >20% of the total viral population); 2) they require that patients have a viral load of 500 to 1000 copies/mL or greater; and 3) testing yields best results when performed in patients receiving ART. Resistance testing performed in antiretroviral-experienced patients who are not receiving ART may not display all of the resistance mutations given lack of selective pressure; however, some mutations might persist for an indefinite period.

Demonstration of resistance mutations known to confer decreased susceptibility by genotypic testing or evidence of reduced susceptibility by phenotypic testing should be considered accurate. The absence of resistance by either genotypic or phenotypic testing may indicate poor adherence in the setting of virologic failure; the absence of resistance should not be interpreted to mean that all viral populations in an individual patient are sensitive or lack resistance mutations.

A particularly important concept in the interpretation of drug-resistance assay results is that less prevalent (minority) resistant strains tend to decrease to below the threshold of detection, whereas sensitive (wild-type) virus emerges after a sustained period of treatment interruption. This occurrence may follow interruptions as short as 2 weeks or as long as 1 year. This may lead clinicians to incorrectly assume that drug-resistance mutations are not present. Neither genotypic nor phenotypic resistance testing will detect these less prevalent strains, which, nevertheless, may become dominant when selective pressure is again applied with the introduction of ART. Thus, interpretation of resistance becomes complicated in patients who have failed multiple antiretroviral regimens and/or who have the test(s) performed after ART has been discontinued. Because the rules for interpretation of results may change as understanding of resistance increases, clinicians should consult with an expert when interpreting complicated results. Current information on relevant mutations by antiretroviral class can be found at the International AIDS Society-USA's website: www.iasusa.org/resistance_mutations/index.html

New resistance mutations and the emerging clinical significance of these mutations frequently change. Several resources are available for more information on drug resistance and resistance testing. These include:

- HIVresistanceWeb (www.hivresistanceweb.com)
- Stanford University HIV Drug Resistance Database (http://hivdb.stanford.edu)
- HIV Sequence Database (www.hiv.lanl.gov/content/hiv-db/mainpage.html)

The two types of resistance assays are described in the following sections. Each assay has advantages and disadvantages.

Genotypic Assays

Genotypic assays detect mutations in the genes of the reverse transcriptase and protease enzymes, as well as the gp41 domain for the currently available fusion inhibitors, that confer resistance to various antiretroviral drugs. The resistance mutation profile permits a prediction about the probability of resistance. Genotypic assays are less expensive, have a shorter reporting time (4-21 days) and have been more extensively studied. Disadvantages of the genotypic assays are that they may fail to identify important mutational changes that are not yet known to be associated with resistance, may be difficult to interpret, and may fail to detect interactions among mutations (e.g., M184V and zidovudine susceptibility).

One method of genotypic testing ("virtual phenotype type") establishes a patient's genotype and then predicts susceptibility by comparing a patient's viral genotype to those in a large data set of viral isolates with correlated genotypic and phenotypic data. Viruses with similar genotypes to that of the patient's virus are identified by searching the

database, which then allows for the probable phenotype of the patient's virus to be estimated. The advantages of this type of virtual phenotype testing are that the results are available quicker and the interpretation is similar to that of a conventional phenotype assay. A disadvantage is that the actual viral phenotype may be different as a result of limitations of the database.

For more information, refer to *Diagnostic, Monitoring, and Resistance Tests for HIV*.

Phenotypic Assays

Phenotypic assays directly measure susceptibility of the patient's HIV strain to specific individual drugs compared to sensitive HIV. The advantages of the phenotypic assays are that their results are easier to interpret than those of genotypic assays, they may also measure the effect of multiple mutations, and they may identify resistance as a result of mutations that may not yet be known. Disadvantages of phenotypic assays are that they are substantially more expensive, usually have a longer reporting time (21 to 28 days), and have thresholds for susceptibility that are undefined for some antiretroviral agents.

Of note, replicative capacity (RC) measurements may appear with the phenotypic testing results; however, there are no data regarding the utility of this measurement in therapeutic decision-making.

For more information, refer to *Diagnostic, Monitoring, and Resistance Tests for HIV*.

4. Antiretroviral Serum Levels (Therapeutic Drug Monitoring)

March 2006

RECOMMENDATION:
Monitoring blood levels of antiretroviral drugs is not currently recommended. (III)

Monitoring of plasma drug levels, particularly the PIs, has been valuable in clinical research protocols to assess patient adherence and drug absorption, correlate antiretroviral drug levels to virologic response, and evaluate drug-drug interactions. However, reliable drug level monitoring has not been conclusively proven to enhance patient management. At the current time, monitoring of antiretroviral drug levels is not recommended outside clinical trials.

B. Laboratory Monitoring of ART Side Effects

This section describes monitoring of the following ART side effects: bone marrow suppression, pancreatitis, lactic acidosis/hepatic steatosis, hepatotoxicity, and renal toxicity. Recommendations concerning long-term metabolic and musculoskeletal complications, including glucose metabolism, dyslipidemia, body fat changes, osteopenia, osteoporosis, and avascular necrosis, are included in *Long-Term Complications of Antiretroviral Therapy*.

1. Bone Marrow Suppression

March 2006

RECOMMENDATION:
Complete blood counts should be measured before initiation of ART and at least every 4 months thereafter. For patients at high risk for bone marrow toxicity (e.g., those with advanced HIV infection, those with pre-treatment cytopenias, or those who are receiving zidovudine), blood counts may have to be monitored more frequently because significant cytopenias may occur. (III)

Bone marrow suppression is most often associated with zidovudine therapy. Significant drug-induced cytopenias become more common in the later stages of symptomatic HIV infection but occasionally develop abruptly in patients at earlier stages.

2. Pancreatitis

March 2006

RECOMMENDATIONS:
When patients receiving ART present with signs or symptoms suggestive of pancreatitis, clinicians should obtain serum amylase and lipase levels. (III)

If signs or symptoms of pancreatitis occur in patients taking antiretroviral medications, the clinician should temporarily suspend the entire ART regimen. A new ART regimen may be initiated when enzymes are normalized but should not include antiretroviral medications that are most likely linked to pancreatitis, such as didanosine or stavudine.

An elevated serum amylase level should be confirmed with a serum lipase level. (III)

Clinicians should not prescribe didanosine for patients who have a history of pancreatitis. (III)

The incidence of pancreatitis is higher in patients infected with HIV and may be associated with opportunistic infections as well as ART. Didanosine has been the agent most often associated with this complication; however, cases of pancreatitis also have been reported with other antiretroviral agents since the advent of triple combination therapy. Tenofovir increases the levels of didanosine, thereby increasing the theoretical risk of pancreatitis. Thus, when these antiretroviral medications are used in combination, the dose of didanosine should be reduced (see Appendix A).

Pancreatitis should be considered in any patient receiving ART who presents with signs or symptoms of pancreatitis (e.g., abdominal pain, persistent nausea, and vomiting), and serum amylase and lipase should be obtained in this setting. Significant hypertriglyceridemia (>500 mg/dL) is associated with an increased risk of pancreatitis, particularly in patients with other risk factors for pancreatitis (e.g., alcohol or didanosine use). Other causes linked to pancreatitis in the general population should be included in the differential diagnosis.

Hyperamylasemia of non-pancreatic (e.g., parotid) origin may occur in HIV-infected patients. Serum lipase levels should be obtained to delineate the source of the increased amylase. Asymptomatic patients with modest elevations in amylase and lipase levels (<3-fold) may be monitored closely without change in therapy.

3. Lactic Acidosis/Hepatic Steatosis

March 2006

RECOMMENDATIONS:
When patients develop symptoms consistent with lactic acidosis syndrome in conjunction with an elevated lactate level (>2 mmol/L) and decreased serum bicarbonate (<20 mmol/L), the clinician should temporarily discontinue the entire ART regimen while an evaluation is conducted. (II)

Routine monitoring of serum lactate levels is not indicated in asymptomatic patients. (I)

Patients who are asymptomatic and have an unexplained decrease in serum bicarbonate level (<20 mmol/L) should be promptly re-evaluated with a repeat test and a venous or arterial lactate. (II) **If a venous lactate is mildly elevated (2.1 to 5.0 mmol/L), an arterial lactate should be obtained, and re-assessment for the presence of symptoms associated with lactic acidosis should be performed.** (I) **If the lactate is persistently elevated, the arterial pH is abnormal, or the patient has become symptomatic, ART should be discontinued.** (III)

The syndrome of lactic acidosis/hepatic steatosis is rare but associated with a high mortality rate and has been most often associated with the use of NRTIs. Groups at higher risk for this complication include African Americans, obese patients, female patients, and patients with chronic hepatitis C virus (HCV). The syndrome is marked by constitutional complaints, such as abdominal pain, anorexia, nausea/vomiting, hyperventilation, and/or myalgias associated with elevations in serum lactate levels and decreased serum bicarbonate levels. Blood sampling for venous lactate levels should avoid the use of prolonged tourniquetting, and samples should be transported on ice and processed promptly. Lactic acidosis is believed to manifest only at lactate levels >5 mmol/L with an accompanying decreased bicarbonate level.

Patients taking NRTIs who present with constitutional symptoms should be evaluated for lactic acidosis, including lactate (arterial or venous) and bicarbonate level, arterial blood gas determination, serum amylase and lipase, and serum liver enzymes. In conjunction with the evaluation, ART should be discontinued. If the evaluation does not support the diagnosis of lactic acidosis, ART may be restarted.

Patients with mildly elevated lactate levels (2.1 to 5.0 mmol/L) and a normal bicarbonate level are usually asymptomatic. The clinical significance of mildly elevated lactate levels is still unknown. In the absence of decreased bicarbonate levels, lactic acidosis is uncommon.

4. Hepatotoxicity

January 2007

RECOMMENDATIONS:
Clinicians should obtain serum liver enzyme levels at baseline and every 3 to 4 months thereafter in patients receiving ART. (III)

Clinicians should screen for alcohol use in patients with abnormal serum liver enzyme levels. (III)

Use of Nevirapine
Clinicians should not use nevirapine as part of the initial regimen in women with CD4 counts >250 cells/mm^3 or men with CD4 counts >400 cells/mm^3 because of an increased incidence of hepatotoxicity. (I)

When initiating an ART regimen that includes nevirapine, clinicians should obtain serum liver enzymes at baseline, at the time of dose escalation (14 days), and 2 weeks after dose escalation. (III)

Clinicians should counsel patients to seek medical evaluation when signs and symptoms of hepatitis, severe skin reactions, or hypersensitivity reactions related to nevirapine occur. Serum liver enzymes should be obtained whenever patients develop a rash during nevirapine therapy, particularly during the first 18 weeks of therapy. (II)

In the setting of hepatotoxicity related to nevirapine, patients should not be re-challenged with nevirapine. (I)

All antiretroviral agents have the potential to cause abnormalities in liver function, especially in patients with preexisting liver disease. Serum liver enzyme levels should be obtained at baseline and every 3 to 4 months in patients receiving ART. More frequent monitoring may be necessary for patients with preexisting liver disease or serum liver enzyme abnormalities. The use of full-dose ritonavir (600 mg twice daily) has been associated with worsening transaminases in patients with preexisting liver disease and should be avoided. Patients who develop serum liver enzyme abnormalities greater than five times the upper limit of normal should be promptly assessed. Any potentially hepatotoxic medication, including all antiretroviral agents, should be discontinued (see Section X: *Management of Treatment Interruption*).

A higher incidence of significant hepatotoxicity associated with nevirapine therapy has recently been reported, especially in women with CD4 counts >250 cells/mm^3, men with CD4 counts >400 cells/mm^3, and in the setting of HCV co-infection. The greatest risk of severe and potentially fatal hepatotoxicity occurs in the first 6 weeks of treatment; however, the FDA and the manufacturer strongly recommend intensive monitoring during the first 18 weeks of nevirapine therapy, with discontinuation of the drug if moderate or severe abnormalities occur. In the absence of definitive clinical evidence, monitoring serum liver enzymes every 2 weeks for the first month of nevirapine therapy, then monthly for the first 12 weeks, and every 1 to

3 months thereafter is a reasonable approach, given the potential severity of adverse events. It is essential that the 14-day lead-in period be strictly followed (see Appendix A for guidance on step-up dosing for nevirapine). In some cases, the hepatic injury progresses even after discontinuation of nevirapine. In the setting of hepatotoxicity related to nevirapine, the patient should not be re-challenged with nevirapine.

Some clinicians would avoid using efavirenz after severe nevirapine-related hepatotoxicity (LFTs >5x ULN) with or without Grade 4 rash (Stevens-Johnson syndrome); however, there is no clear evidence to support an association between nevirapine-related hepatotoxicity and efavirenz-related hepatotoxicity.[41] For mild to moderate nevirapine-related hepatotoxicity (LFTs >3-5 x ULN), switching to efavirenz after complete resolution of hepatotoxicity is an option if there are no other contraindications to efavirenz. Contraindications to efavirenz include known adverse reactions to efavirenz, first-trimester pregnancy, or strong likelihood of becoming pregnant.

For pregnant women with nevirapine-related hepatotoxicity, the clinician should switch the regimen to 2 NRTIs + PI. Efavirenz should only be considered for women in the second or third trimester if there are no other options and the benefits outweigh the risks. See *Management of HIV-Infected Pregnant Women Including Prevention of HIV Perinatal Transmission* for more details.

In the setting of severe nevirapine-related hepatotoxicity, all antiretroviral agents and any other possible offending agents should be discontinued. The risk of severe hepatotoxicity outweighs the risk of possible emergence of resistance. See Section X: *Management of Treatment Interruption*.

5. Renal Toxicity

November 2006

RECOMMENDATIONS:

For all HIV-infected patients receiving ART:
Clinicians should obtain urinalysis at baseline and annually thereafter.

Clinicians should measure serum creatinine levels and calculate glomerular filtration rates at baseline and every 3 to 4 months thereafter in HIV-infected patients. (III)

For patients receiving tenofovir:
For patients initiating a tenofovir-containing regimen, clinicians should calculate glomerular filtration rates at baseline, 1 month, and then at least every 3 to 4 months thereafter.

Clinicians should discontinue tenofovir when patients present with symptoms suggestive of Fanconi syndrome.

For patients receiving indinavir:
Clinicians should counsel patients receiving indinavir to drink at least 48 ounces of fluid per day.

HIV infection has been associated with several renal complications that may lead to renal insufficiency or failure.[42] Renal impairment necessitates dose adjustment or discontinuation of many antiretroviral agents (see Appendix A).

Clinicians should routinely obtain urinalysis and serum creatinine levels as well as calculate glomerular filtration rates (GFR) to assess renal function. When calculating GFR, the clinician should consistently use the same method. GFR can be calculated by using either of two equations:

1. Modification of diet in renal disease (MDRD): calculates creatinine clearance based on age, sex, height, serum creatinine, serum albumin, and serum blood urea nitrogen (BUN). An MDRD calculator can be accessed at http://mdrd.com
2. Cockroft-Gault: calculates creatinine clearance based on serum creatinine, age, weight, and sex. A Cockroft-Gault calculator can be accessed at: http://nephron.com/cgi-bin/CGSI.cgi

Renal impairment has been reported in patients receiving tenofovir.[43,44] The extent of this toxicity is unclear. Tenofovir is excreted by glomerular filtration and tubular secretion, and a preliminary study suggests that persons with low estimated GFR are at a higher risk for tenofovir-associated renal toxicity even when baseline serum creatinine is normal. Additional risk factors include low body weight, older age, use of boosted regimens, hypertension, diabetes, and use of other nephrotoxic drugs. Hypophosphatemia may be an early indicator of renal failure. Clinicians may want to use a lower threshold for dose adjustment in patients receiving tenofovir. Clinicians should discontinue tenofovir when patients present with symptoms suggestive of Fanconi syndrome, such as declining renal function with associated metabolic acidosis, hypophosphatemia, hypokalemia, glycosuria, and uricosuria. The decision to rechallenge with tenofovir should be made on a case-by-case basis.

Indinavir (especially when used with ritonavir) and agents used to prevent and/or treat opportunistic infections may cause hematuria, pyuria, or crystalluria. Patients receiving indinavir should be counseled to drink at least 48 ounces of fluid per day. Clinicians should consider urinalysis every 3 to 4 months for patients receiving indinavir-containing regimens.

6. Myopathy/Myositis

March 2006

RECOMMENDATION:
Measurement of serum creatinine phosphokinase (CPK) is not routinely indicated. If the patient becomes symptomatic (e.g., muscle pain or weakness), CPK should be measured. (II)

HIV infection may be associated with asymptomatic elevation of CPK. In this setting, serial monitoring is not indicated.

C. Monitoring for Allergic Reactions Associated With ART

June 2010

RECOMMENDATIONS:
When patients receive any new antiretroviral drugs, clinicians should educate them about the possibility of ART-associated allergic reactions, including a hypersensitivity reaction, and the range of possible symptoms (see Table 9)**.** (III)

Clinicians should discontinue offending drugs when there is a moderate to severe skin reaction, mucous membrane involvement, systemic toxicity, or fever. (I)

Clinicians should perform HLA-B*5701 testing before initiating abacavir-based therapy.

Clinicians should avoid re-challenging patients with a medication that has been associated with a hypersensitivity reaction, especially in the setting of abacavir reactions and severe NNRTI reactions. (I)

In patients who develop mild rash in response to nevirapine, clinicians should avoid escalating the nevirapine dose to twice daily until after the rash has resolved. For patients with moderate to severe cutaneous toxicity, nevirapine should be discontinued and should not be re-challenged. Use of an alternate NNRTI should be avoided. (III)

TABLE 9 ANTIRETROVIRAL DRUGS TYPICALLY ASSOCIATED WITH ALLERGIC REACTIONS		
Antiretroviral Drug (usual timing of symptoms)	**Most Frequent Symptoms**	**Action**
Abacavir* (First 4-6 weeks after initiation)	*Hypersensitivity reaction*: Fever, headache, gastrointestinal symptoms, malaise, arthralgias, myalgias, and respiratory problems. Skin involvement, with rash and pruritus may be mild or absent.	• Prompt discontinuation of abacavir • Do not re-challenge
Delavirdine (First 4 weeks after initiation)	Mild to moderate cutaneous allergy	• Consider systemic antihistamines while continuing delavirdine for mild rashes • Discontinue when there is a moderate to severe skin reaction, mucous membrane involvement, systemic toxicity, or fever
Efavirenz (First 4 weeks after initiation)	Mild to moderate cutaneous allergy	• Consider systemic antihistamines while continuing efavirenz for mild rashes • Discontinue when there is a moderate to severe skin reaction, mucous membrane involvement, systemic toxicity, or fever
Enfuvirtide	In the phase 3 trials of enfuvirtide, three cases of probable hypersensitivity were identified. These included, either individually or in combination, rash, fever, nausea and vomiting, chills, rigors, hypotension, and elevated LFTs.	
Etravirine (generally occurs in the 2nd week of treatment and is infrequent after week 4)	*Severe reaction*: cutaneous reaction involving the mucocutaneous surfaces (Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme)	*Severe reaction*: ▪ Discontinue etravirine promptly Discontinue if rash accompanied by fever, hepatitis, and other systemic symptoms. ▪ Obtain serum liver enzyme levels Grade 3 and 4 rashes reported in 1.3% of patients Rash more common in women

	Mild reaction: mild skin rash	*Mild reaction:* ▪ Manage with antihistamines and close monitoring
Fosamprenavir, tipranavir, and darunavir	Mild to moderate cutaneous allergy	• Patients with sulfa allergy may be at increased risk of developing an allergic reaction • For mild rashes, consider using systemic antihistamines while continuing protease inhibitors with sulfa moiety • Discontinue when there is a moderate to severe skin reaction, mucous membrane involvement, systemic toxicity, or fever
Nevirapine (First 2 to 18 weeks after initiation)	*Severe reaction*: cutaneous reaction involving the mucocutaneous surfaces (Stevens-Johnson syndrome), often accompanied by fever and severe hepatitis *Mild reaction*: mild skin rash	*Severe reaction*: ▪ Discontinue nevirapine promptly ▪ Obtain serum liver enzyme levels ▪ Do not re-challenge ▪ Do not use alternate NNRTI (however, patients with NNRTI rash did not have a higher incidence of rash when given etravirine) *Mild reaction*: ▪ Close monitoring recommended, but most clinicians would switch to an alternative antiretroviral ▪ Obtain serum liver enzyme levels ▪ Do not escalate dose to twice daily until the rash has resolved
* HLA-B*5701 is a pharmacogenetic test (HLA-B*5701) used to identify patients who are predisposed to abacavir hypersensitivity. Clinicians should perform HLA-B*5701 testing before initiating abacavir-based therapy.		

Many medications pose the risk of causing various types of allergic reactions, typically presenting as maculopapular rash, with or without fever. Occasionally, a more severe hypersensitivity reaction occurs, consisting of rash and fever, with a combination of other symptoms, such as headache, arthralgias, hepatitis, eosinophilia, and GI or respiratory symptoms. The hypersensitivity reaction usually occurs within 2 to 6 weeks after the drug is started.

Although trimethoprim/sulfamethoxazole is the drug most frequently implicated in common allergic reactions in HIV-infected patients, abacavir, darunavir, tipranavir, fosamprenavir, all of the NNRTIs (nevirapine, delavirdine, efavirenz, etravirine), and enfuvirtide (less commonly) have been associated with a hypersensitivity reaction or syndrome (see Table 9). These reactions are for the most part idiosyncratic and unanticipated. The reactions to darunavir, fosamprenavir, tipranavir (all have a sulfa moiety), delavirdine, and efavirenz are generally mild to moderate cutaneous allergy (drug rash). Patients may rarely develop severe mucous membrane involvement with systemic toxicity. Occasionally, patients will only have a fever. Clinicians should discuss the possibility of these reactions with patients initiating ART because they are most commonly seen in the first 4 weeks of treatment; clinicians should educate patients about the symptoms of hypersensitivity.

Systemic antihistamines may be useful in treating mild cases while patients continue to receive the offending drug. The offending drug should be discontinued when there is a moderate to severe skin reaction, mucous membrane involvement, systemic toxicity, or fever.

Hypersensitivity to abacavir occurred in as many as 5% of patients before routine HLA-B*5701 testing was recommended. The reaction usually occurs within the first 10 to 14 days of therapy and rarely occurs after the first 6 weeks. Fever, headache, GI symptoms, malaise, arthralgias, myalgias, and respiratory problems are the most frequent manifestations of the abacavir hypersensitivity reaction. Skin involvement, with rash and pruritus, may be mild or absent. HLA-B*5701 is a pharmacogenetic test (HLA-B*5701) used to identify patients who are predisposed to abacavir hypersensitivity. Clinicians should perform HLA-B*5701 testing before initiating abacavir-based therapy.

Prompt discontinuation of abacavir when a hypersensitivity reaction is suspected is necessary because symptoms will worsen over time. Once abacavir has been discontinued because of a possible or definite hypersensitivity reaction, abacavir should never be administered again. Re-challenge may result in an anaphylactic reaction with associated hypotension or death.

Nevirapine, an NNRTI, has been associated with severe hypersensitivity reactions in the first 2 to 12 weeks of use. Graduated dosing of nevirapine at initiation with 200 mg daily for the first 2 weeks followed by 200 mg twice daily thereafter has reduced the incidence of hypersensitivity reactions. Systemic antihistamines or corticosteroids given at the time of nevirapine initiation have not been proven useful. Such reactions manifest as severe cutaneous reaction involving the mucocutaneous surfaces (Stevens-Johnson syndrome), often with accompanying fever and severe hepatitis. Deaths associated with these reactions have been reported. Patients who develop mild rashes without systemic toxicity may be managed with antihistamines and close monitoring. The nevirapine dose should not be escalated to twice daily until the rash has resolved. However, those with moderate to severe cutaneous toxicity should discontinue nevirapine promptly and should not be re-challenged with this drug. Because of potential cross-reactivity, use of an alternate NNRTI should be avoided in patients who have a severe reaction to nevirapine; however, the incidence of etravirine rash is not high in patients with a history of NNRTI rash.

Etravirine, an NNRTI, has been associated with hypersensitivity reaction. Up to 10% of patients in clinical trials reported rashes. Most reported mild to moderate rashes. Grade 3 and 4 rashes reported in 1.3% of patients, and up to 2.2% of patients required etravirine discontinuation. Rashes generally occur in the second week of treatment and are infrequent after week 4. Etravirine should be discontinued for severe rash or if rash is accompanied by fever, hepatitis, and other systemic symptoms.

In the phase 3 trials of enfuvirtide, three cases of probable hypersensitivity to the drug were identified. These have included, either individually or in combination, rash, fever, nausea and vomiting, chills, rigors, hypotension, and elevated serum liver enzymes.

VII. CHANGING A SUCCESSFUL INITIAL ART REGIMEN

March 2006

RECOMMENDATIONS:

Clinicians should change a successful initial ART regimen when the patient's adherence will be compromised by continuing the current regimen. (III)

When considering a change in the ART regimen due to drug toxicity, the clinician should confirm that the viral load is maximally suppressed. (III) **If maximal viral suppression has been achieved, the clinician should substitute the offending drug.** (I)

The clinician should review results from previous resistance testing before changing a successful regimen. (III)

Even when the goals of ART are achieved in a patient, clinicians may be faced with the challenge of making a change to a successful regimen. The reasons most often encountered are drug toxicity, quality-of-life issues, and/or fear of long-term adverse drug reactions. Changing therapy for quality-of-life issues or for fear of potential toxicity is appropriate if the patient's concerns will lead to reduction in adherence or discontinuation of therapy. Many patients adhere less successfully to their ART regimen if they associate side effects with one or more of the drug components. It is important to fully discuss the issues of drug toxicity with the patient so that his/her expectations remain realistic.

Many side effects will abate after the first weeks of treatment. For patients who experience persistent mild to moderate side effects that cannot be managed and that would be expected to improve by a change in the ART regimen, it is good practice to consider changing the regimen when there are viable options. Following are examples of side effects that may be resolved by substituting the offending drug:

- Peripheral neuropathy from stavudine or didanosine
- Gastrointestinal intolerance from PIs
- Insomnia, neuro-irritability, headaches, abnormal dreams from efavirenz or zidovudine
- Changes in the skin/appendages (recurrent paronychia, xerosis, pruritus, jaundice) from indinavir, atazanavir, or zidovudine, emtricitabine (discoloration of palms/soles)

- Renal lithiasis, renal colic from indinavir
- Lipoatrophy or fat redistribution syndrome
- Dyslipidemia, glucose intolerance from PIs
- Rash from NNRTIs
- Hypersensitivity from abacavir or nevirapine
- Hepatitis from nevirapine or PIs

If adherence is compromised and the offending agent can be identified with a reasonable degree of certainty, a substitution for that one agent is appropriate as long as the viral load is maximally suppressed. Before changing therapy, however, results from previous resistance testing should be reviewed to identify drugs that are not likely to be effective.

In some situations, such as intractable diarrhea, one PI may be substituted for another. In other situations, a drug from one class may be replaced with a drug from another class. Studies have demonstrated that substituting an NNRTI for a PI in the setting of maximal suppression is generally safe and effective in the majority of patients. Although hypertriglyceridemia, hypercholesterolemia, or glucose intolerance would be expected to improve promptly by replacing a PI with an NNRTI, fat redistribution may change slowly after replacement of stavudine.

The risks of altering therapy are as follows:

- The patient may experience toxicity with the new regimen
- The exposure of HIV to multiple antiretroviral agents may increase the risk of drug resistance and reduce the number of available treatment options in the future
- Maximal viral suppression may not be maintained
- Changing regimens may have an emotional impact on the patient

VIII. Failure to Achieve Goals of Initial ART

March 2006 – Currently under revision

Recommendations:

Clinicians should address adherence, obtain resistance assays, and consult with a provider with extensive experience in HIV treatment before changing ART regimens that have failed.

Clinicians should not change an ART regimen when there is incomplete but significant viral suppression (≥0.5 log reduction, or 3-fold, from baseline viral load value) compared with baseline and a more effective ART regimen cannot be constructed as a result of drug resistance or intolerance.

The goal of ART is to use a regimen that is well tolerated and that will promote maximal viral suppression and immune reconstitution. Failure to demonstrate a >1.5-log drop in viral load within 3 months of treatment and, more importantly, failure to achieve a viral load <50 copies/mL within 6 months (depending on baseline viral load) indicates unsuccessful ART.

The initial ART regimen affords the best opportunity to attain maximal viral suppression. Currently, in clinic practice, only 60% to 70% of patients receiving initial ART will achieve sustained viral loads below the limits of detection by ultrasensitive assays. The reasons for this are complex. Low levels of detectable viremia should not be the sole determinant of treatment failure.

Treatment failure is best defined by any one of the following:

- Failure of viral load to decrease from baseline
- Progressive increase in viral load after initial suppression
- Progressive decline of CD4 cell counts
- Progression of HIV disease

Failure of decline (1.5- to 2.5-log drop) in HIV RT-PCR levels 3 months after initiating ART is a poor prognostic sign and usually indicates that continuation of that particular regimen will fail. Possible reasons for failure are poor patient adherence, primary HIV resistance to the chosen drug regimen, pharmacokinetic issues, and drug-drug interactions. In such cases, it is advisable to obtain appropriate resistance testing to determine the best treatment options (see Section VI: *Monitoring of Patients Receiving ART*). Early discontinuation of the failing regimen is important to reduce the likelihood of the development of resistance mutations. A significant increase in viral load after an initial good response has a similar implication and should be handled in the same manner.

In contrast to the above situations, some patients will demonstrate a major reduction in HIV RT-PCR levels within several months of initiation of ART, but their viral loads will fail to become undetectable. Many of these patients will have had viral set points of >500,000 copies/mL prior to ART. In these cases, the nadir of viral load may not decrease to less than 5,000 to 10,000 copies/mL with the initial three-drug regimen. Over time, such patients have a higher risk of treatment failure because of the selection of resistance mutations. In these cases, some clinicians may enhance drug levels through the use of pharmacologic boosting (e.g., adding ritonavir) or may add a single agent for intensification. Although treatment intensification may produce good results in selected patients with relatively low viral loads, many clinicians view this as a suboptimal option or sequential monotherapy; therefore, the potential benefits of this strategy should be carefully weighed against the risk of introducing a single agent to a failing regimen that invariably would lead to resistance. A genotypic assay should be obtained to exclude the existence of primary drug resistance before intensifying the regimen.

Despite even maximal HIV suppression, CD4 cell counts may increase very slowly or not at all, especially for patients with baseline CD4 counts <100 cells/mm^3 at the time of initiation of ART. Such patients have been shown to benefit from ART (i.e., reduction in likelihood of clinical disease progression), and therapy should not be altered. However, a small percentage of patients with excellent viral suppression will continue to demonstrate decreasing CD4 cell counts. This discordant response has been reported in a number of studies, although the mechanism is poorly understood. Some experts suggest empirically changing regimens in this setting.

Patients with drug-resistant HIV infection may maintain increased CD4 counts, most likely from the decreased replicative capacity of the resistant virus. Ideally, resistance testing should be obtained to determine if a new ART regimen can be constructed using available antiretroviral agents to attempt to achieve maximal viral suppression. However, when this is not possible, maintenance of the current regimen is acceptable.[45]

IX. SECOND-LINE REGIMENS AND SALVAGE ART

March 2006 – Currently under revision

RECOMMENDATIONS:

Clinicians should consult with a provider with extensive experience in HIV treatment when constructing a second-line regimen and salvage therapy regimens.

Clinicians should review individual antiretroviral history and results from HIV drug resistance testing when constructing salvage therapy regimens. Clinicians should consult with an expert to interpret the results of resistance assays. (I)

Clinicians should use a drug from a class that was not used in the first regimen when constructing a second-line regimen. (I)

When treating patients with high levels of HIV drug resistance, clinicians should consider using agents in novel antiretroviral classes or with unique resistance profiles, such as the entry inhibitors or drugs available through clinical trials or expanded access.

Although the best chance for success is with the initial ART regimen, the expectations are still good for second-line regimens, especially with the availability of new antiretroviral drugs. Salvage therapy refers to antiretroviral regimens prescribed for patients who have failed serial ART regimens. Use of the term "salvage therapy" originates from the clinical observation that fewer than 40% to 50% of patients will respond optimally to new ART regimens after first and second ART regimens have failed.

Because of cross-resistance within antiretroviral classes, the clinician cannot assume that the patient's HIV strain(s) will be sensitive to a novel drug in the same class. Several studies examining the utility of HIV resistance testing in ART-experienced patients have shown that these tests are valuable when choosing subsequent successful ART regimens. However, when multiple regimens have failed in a patient, resistance testing is of limited value. In some cases, when multiple resistance mutations are found on genotypic resistance analysis, phenotypic resistance testing may be helpful in constructing an effective regimen. Expert interpretation of the resistance results in conjunction with a detailed antiretroviral history, including any previous resistance testing, is essential.

For a second-line regimen, drugs from a class that was not used in the first regimen should be used. Agents in new drug classes (e.g., an entry inhibitor) or with novel resistance profiles may lead to an improved antiviral response for patients with multi-drug resistant HIV. Clinical trials and "expanded access" therapies should be considered in this setting. Combinations of five or

more antiretroviral drugs, colloquially referred to as "mega-ART" or "multi-drug rescue therapy," may be attempted in patients who have a high level of drug resistance in all available antiretroviral classes. There are limited data on such an approach, with an unclear benefit in the context of the high pill burdens and significantly increased toxicity of such complex regimens.

When maximal suppression is not achievable due to inability to construct a fully effective regimen, partial viral suppression (<0.5 log or 3-fold reduction from baseline viral load value) and stable CD4 counts are reasonable alternative goals. When CD4 counts are decreased, prophylaxis for opportunistic infections should be initiated.

Several investigators have shown that individuals infected with HIV may become superinfected with a different strain of HIV in the setting of high-risk behavior. In some cases, superinfecting HIV strains may carry drug-resistance mutations. Therefore, sudden regimen failure in a patient who was virologically controlled should raise suspicion that HIV superinfection may be present. Resistance testing and safer-sex counseling are appropriate in these settings.

X. MANAGEMENT OF TREATMENT INTERRUPTION

June 2006

RECOMMENDATIONS:

Patients should be discouraged from stopping ART without first consulting with their clinician. (III)

When ART is interrupted, clinicians should inform patients of the potential increased risk of transmitting HIV. Risk-reduction counseling and prevention interventions should be intensified at this time.

Before interrupting ART in patients receiving antiretroviral medications with prolonged half-lives, such as NNRTIs, clinicians should consult with a provider with extensive experience in HIV treatment for guidance on how to avoid the emergence of resistance.

Clinicians should not interrupt lamivudine, emtricitabine, or tenofovir (or combination pills containing these drugs) in patients who are co-infected with chronic hepatitis B without implementing another HBV treatment option.

Strategic treatment interruption (STI) is not recommended in the management of the HIV-infected patient. (I)

There are several reasons why it may be necessary to interrupt ART. Following are some scenarios that may result in an interruption in treatment:

- Serious adverse drug reactions (e.g., rashes, neuropathy, severe lipoatrophy or fat redistribution, severe nephrolithiasis)
- Lack of access to drugs due to poverty, incarceration, or lack of medical benefits

- Medical/surgical conditions requiring patients to avoid eating or drinking for a specified time period (e.g., pancreatitis, appendicitis)
- Poor adherence—in some cases, lack of adherence may be sufficient cause for the clinician to stop treatment while further interventions and education attempts are undertaken
- Minor drug side effects that mimic disease progression, making it necessary to temporarily interrupt therapy for clinical evaluation of signs and symptoms
- Patient choice—patients may decide to stop therapy due to treatment fatigue, fear of toxicities (e.g., fat redistribution, cardiac disease), traveling overseas for an extended period, perceived ineffectiveness of medications, or pregnancy and fear of teratogenicity.

Discontinuation of ART by patient's choice is a complex issue regardless of whether viral suppression had been obtained with the regimen. In some instances, patients lack understanding of the benefits of the medications and fail to adhere to the prescribed regimen. The reasons for non-adherence are multiple (see Section IV: *The Importance of Patient Adherence*).

Treatment interruption, especially in established (>6 months) HIV infection, can be potentially dangerous. It could lead to dramatic increases in HIV viral load, which may exceed baseline viral load levels, and precipitous declines in CD4 cell counts, which may reach pre-treatment levels, with the risk of clinical events. The Strategies for Management of Antiretroviral Therapy (SMART) trial compared patients receiving continuous ART with patients who were given intermittent ART. The patients in the intermittent therapy group received ART whenever CD4 counts decreased to <250 cells/mm^3 then discontinued treatment when CD4 counts increased again to >350 cells/mm^3. Patients in the intermittent treatment group had more than twice the risk of progression to AIDS or death compared with the continuous therapy group.

During a treatment interruption, patients may present as if they have acute HIV syndrome or the initial HIV-related symptoms may return. Rebound in HIV-1 RNA plasma level may enhance horizontal and vertical transmission of HIV-1, which is of particular importance during pregnancy when a rebound in viral load may favor transplacental, peripartum, and breastfeeding-related transmission. CD4 cell counts may take longer to decrease after the discontinuation of ART; therefore, clinicians should inform patients that a stable CD4 count after discontinuation of therapy does not predict long-term immunologic stability.

Treatment interruption also may result in selection of resistance mutations. The increasing use of antiretroviral medications with prolonged half-lives and low resistance thresholds complicates discontinuation of treatment. Low plasma levels of antiretroviral medications with prolonged half-lives, such as nevirapine and efavirenz, can be detected many days after discontinuation of the medication. These low levels, although insufficient to suppress viral replication, may select for resistance mutations. Reports have documented the association between discontinuation of an NNRTI, lingering low plasma levels, and emergence of resistance mutations. The duration of these low detectable levels may vary widely from patient to patient. There is no consensus regarding how best to manage treatment discontinuation. Some experts would suggest replacing the NNRTI with a PI and continuing the two NRTIs and PI for approximately 1 week before interrupting therapy. Others would discontinue the NNRTI first and continue the NRTIs for several days (referred to as an "NRTI tail"). Resistant virus usually recedes and wild-type, susceptible virus predominates once treatment is interrupted; however, once antiretroviral

medications are re-started, if resistance develops, selective pressure is again established and resistant virus again emerges. These complex considerations coupled with the rapid changes in knowledge and treatment regimens make it advisable to consult with a provider who has extensive experience with management of ART when considering discontinuation of ART.

Structured or strategic treatment interruption is a theoretical approach aimed at reducing long-term toxicity and enhancing HIV-specific immune response while maintaining treatment options. To date, strategic treatment interruptions in patients receiving ART with an undetectable viral load have failed to consistently stimulate HIV-specific T-helper and cytotoxic T-lymphocyte responses. Ongoing clinical trials are trying to elucidate predictors of response. Several treatment interruption studies are basing re-initiation of treatment on CD4 threshold. Preliminary data from some of these trials indicate increased morbidity and mortality among patients in the treatment-interruption arm. At this time, structured treatment interruption cannot be recommended, and it should only be considered in the context of a clinical trial. To locate a clinical trial, refer to the AIDS Community Research Initiative of America clinical trials directory at: http://trialsearch.org/clinical_trials/index.html

XI. Referring Patients to Research Studies

March 2006

Recommendations:

Referral of patients to research protocols should be 1) to provide treatment or diagnostic options that may be otherwise unavailable and that may enhance treatment outcome, and 2) to attempt to answer a relevant research question. (III)

Patients should be fully informed of any financial benefit their referral to a research study might have for the referring clinician. (III)

Patients should be informed that research studies often require major commitments of time and effort in addition to potential unforeseeable risk. (III)

The clinician should provide assistance to patients who want to participate in research studies. (III)

The first priority in the care of any patient is to maximize the therapeutic benefit of treatment and to support the individual. Sometimes patients ask if they can help with any new research studies, and clinicians often realize that the patient might benefit from a therapy that is currently under study. In addition, many standard therapies are still being scrutinized in terms of timing and appropriateness. Because there are so many clinical uncertainties (e.g., when to initiate ART, what is the optimal initial therapy, whether there are occasions for interruption of therapy), the clinician should keep in mind that if a patient is willing to join a trial that will help to resolve these issues, then ultimately there may be a benefit to many others.

In considering referral to a clinical study, the clinician should review with the patient the risks and benefits of participating:

- If the agent is new, what toxicities have been shown in preliminary trials?
- What is the patient's current clinical status and what would be the risks of not using the new agent(s) (i.e., the natural history of the patient's current condition)?
- If the trial compares randomization to 1 of 2 standard therapies, are the current data insufficient to recommend one or the other to the patient?
- If the clinical trial is being held in a center other than the institution where the patient is receiving primary care, how much time and travel will the trial involve? Will the patient get any help with time/travel issues?
- Is the patient willing and able to meet the rigors that may be imposed on study participants?
- Is there a stipend for participation?

If the clinician is also an investigator on the study, it is important that he/she is scrupulous in avoiding any real or perceived conflict of interest in the referral. The informed consent that the patient signs should disclose any financial benefit to the clinician if the patient enrolls. Clinicians should be sensitive to some communities' continued distrust derived from a history of research that was tainted by racism or other prejudice, such as the Tuskegee study. Discussions about research studies should be culturally sensitive, and the voluntary nature of all enrollments must be made very clear.

Clinicians providing care to patients with HIV/AIDS have an obligation to keep abreast of trials that are available in their geographic area and in the field of HIV/AIDS in general.

A resource that may help with this process is the AIDS Clinical Trials Information Service (phone: 1-800-TRIALS-A; website: www.actis.org). Other resources are listed at AIDS Community Research Initiative of America (http://trialsearch.org/clinical_trials/index.html), www.aidsinfonyc.org, and the AIDS Treatment Data Network (www.atdn.org). Establishing a referral network with accessible study centers can be helpful. Centers involved in research should make an effort to be aware of HIV clinicians in their area and vice versa.

XII. Access to Expanded Access or Compassionate Use Therapies

March 2006

Obtaining drugs on compassionate use can be a time-consuming and cumbersome task, particularly for clinicians who are at institutions without any research support system, but it is often the patient with the fewest options who needs these drugs the most. Clinicians should consider making these expanded access or compassionate use therapies available if the need exists in their practice. If the infrastructure is not present to do so, referral to other sites should be made.

XIII. FUTURE DIRECTIONS OF ART

March 2006

Although ART has been successful in suppressing viral replication, treatment failures are common and most available antiretroviral agents have class-cross resistance problems. There are many new drugs in development in both existing and novel classes (e.g., entry inhibitors, integrase inhibitors) that may offer more solutions for these problems. As these agents are approved by the FDA, updates to these guidelines will be made available on the HIV Clinical Resource website at: www.hivguidelines.org

REFERENCES

1. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med* 2009;360:1897-1899. [PubMed] **Initiating ART at CD4 counts <500 cells/mm^3 and older age were independently associated with increased mortality.**

2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009. Available at: www.aidsinfo.nih.gov. **Recommends treatment for patients with any of the following: CD4 count <500 cells/mm^3, HIV-associated nephropathy, and HBV co-infection that requires treatment, AIDS-defining illness, pregnancy.**

3. Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society -- USA Panel. *JAMA* 2010;304:321-333. [PubMed] **Recommends treatment for patients with any of the following: symptomatic HIV disease, pregnancy, plasma HIV viral load >100,000 copies/mL, rapidly declining CD4 count (>100 cells/mm^3 per year), active HBV or HCV co-infection, active or high risk for cardiovascular disease, HIV-associated nephropathy, symptomatic primary HIV infection, risk for secondary HIV transmission is high, CD4 cell count ≤500 cells/mm^3.**

4. European AIDS Clinical Society (EACS). Guidelines for the clinical management and treatment of HIV-infected adults in Europe, version 5. November 2009. Available at: www.eacs.eu. **Recommends treatment for patients with any of the following: symptomatic HIV disease, CD4 ≤350, active HCV co-infection, HBV requiring treatment, HIV-associated nephropathy.**

5. Tozzi V, Balestra P, Bellagamba R, et al. Persistence of neuropsychologic deficits despite long-term highly active antiretroviral therapy in patients with HIV-related neurocognitive impairment: Prevalence and risk factors. *J Acquir Immune Defic Syndr* 2007;45:174-182. [PubMed] **The severity of neurocognitive impairment at the time of ART initiation seems to be the strongest predictor of persistent neuropsychologic deficits despite long-term ART. These data indicate that ART should be initiated as soon as neurocognitive impairment is diagnosed to avoid potentially irreversible neurologic damage.**

6. Arranz Caso JA, Sanchez Mingo C, Garcia Tena J. Effect of highly active antiretroviral therapy on thrombocytopenia in patients with HIV infection. *N Engl J Med* 1999;341:1239-1240. [PubMed] **Significant increase in platelets in patients with moderate to severe thrombocytopenia after 3 months of ART.**

7. Aboulafia DM, Bundow D, Waide S, et al. Initial observations on the efficacy of highly active antiretroviral therapy in the treatment of HIV-associated autoimmune thrombocytopenia. *Am J Med Sci* 2000;320:117-123. [PubMed] **Increase in platelet count in patients with severe thrombocytopenia after 6 months of ART.**

8. Carbonara S, Fiorentino G, Serio G, et al. Response of severe HIV-associated thrombocytopenia to highly active antiretroviral therapy including protease inhibitors. *J Infect* 2001;42:251-256. [PubMed] **ART induced a sustained PLT response in HIV-associated severe thrombocytopenia. Authors conclude that an undetectable viral load is necessary for thrombocytopenia recovery.**

9. Atta MG, Gallant JE, Rahman MH, et al. Antiretroviral therapy in the treatment of HIV-associated nephropathy. *Nephrol Dial Transplant* 2006;21:2809-2813. [PubMed] **Patients with biopsy-proven HIVAN treated with ART had better renal survival compared with patients who did not receive ART.**

10. Schwartz EJ, Szczech LA, Ross MJ, et al. Highly active antiretroviral therapy and the epidemic of HIV+ end-stage renal disease. *J Am Soc Nephrol* 2005;16:2412-2420. [PubMed] **Data from a mathematical model concluded that prevention of progression to ESRD should focus on early ART for HIV-infected patients who have evidence of HIV-associated nephropathy.**

11. Wilkin TJ, Gulick RM. When to start antiretroviral therapy? *Clin Infect Dis* 2008;47:1580-1586. [PubMed] **Recent review of data suggesting initiation of ART in patients with CD4 count >350 cells/mm^3 *and* comorbidities, including HIV-associated nephropathy, active HBV or HCV co-infection.**

12. Lucas GM, Eustace JA, Sozios S, et al. Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: A 12-year cohort study. *AIDS* 2004;18:541-546. [PubMed] **ART was associated with a substantial reduction in HIVAN incidence.**

13. Dezube BJ, Pantanowitz L, Aboulafia DM. Management of AIDS-related Kaposi sarcoma: Advances in target discovery and treatment. *AIDS Read* 2004;14:236-238, 243-244, 251-253. [PubMed] **Review of literature concluding that patients with Kaposi's sarcoma should be advised to initiate ART.**

14. Ratner L, Lee J, Tang S, et al. Chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma in combination with highly active antiretroviral therapy. *J Clin Oncol* 2001;19:2171-2178. [PubMed] **Patients with non-Hodgkin's lymphoma who were receiving ART experienced a decrease in viral load and increase in CD4 count, despite concurrent chemotherapy. Improved immune function as a result of ART may result in improved bone marrow function.**

15. Hoffman C, Chow KU, Wolf E, et al. Strong impact of highly active antiretroviral therapy on survival in patients with human immunodeficiency virus-associated Hodgkin's disease. *Br J Haematol* 2004;125:455-462. [PubMed] **Demonstrated significant improvement in survival for patients with HIV-associated Hodgkin's disease who were receiving effective ART.**

16. Hentrich M, Maretta L, Chow KU, et al. Highly active antiretroviral therapy (HAART) improves survival in HIV-associated Hodgkin's disease: Results of a multicenter study. *Ann Oncol* 2006;17:914-919. [PubMed] **Use of ART significantly improved the overall survival of patients with HIV-associated Hodgkin's disease.**

17. Weiss R, Mitrou P, Arasteh K, et al. Acquired immunodeficiency syndrome-related lymphoma: Simultaneous treatment with combined cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy and highly active antiretroviral therapy is safe and improves survival. Results of the German Multicenter Trial. *Cancer* 2006;106:1560-1568. [PubMed] **Study concluded that patients with AIDS-related lymphoma should receive ART and CHOP concurrently as firstline therapy.**

18. Guiget M, Boue F, Cadranel J, et al. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): A prospective cohort study. *Lancet Oncol* 2009;10:1152-1159. [PubMed] **Risk for malignancies is decreased when CD4 counts are maintained above 500 cells/mm^3.**

19. Monforte A, Abrams D, Pradier C, et al., Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS* 2008;22:2143-2153. [PubMed] **Initiating ART at CD4 counts <500 cells/mm^3, active hepatitis B, and older age were independently associated with higher risk of death due to AIDS-defining and non-AIDS-defining malignancies.**

20. Tedaldi E, Peters L, Neuhaus J, et al. For the SMART Study Group and INSIGHT. Opportunistic disease and mortality in patients coinfected with hepatitis B or C virus in the Strategic Management of Antiretroviral Therapy (SMART) study. *Clin Infect Dis* 2008;47:1468-1475. [PubMed] **Both HBV and HCV co-infected patients not receiving ART had increased rates of opportunistic diseases and death compared to patients treated with ART.**

21. When to Start Consortium. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: A collaborative analysis of 18 HIV cohort studies. *Lancet* 2009;373:1352-1363. [PubMed] **Deferring ART until a CD4 count of 251-350 cells/mm^3 was associated with higher rates of AIDS and death than starting treatment in the range of 351-450 cells/mm^3.**

22. Lewden C, Chene G, Morlat P, et al. HIV-infected adults with a CD4 cell count greater than 500 cells/mm^3 on long-term combination antiretroviral therapy reach same mortality rates as the general population. *J Acquir Immune Defic Syndr* 2007;46:72-77. [PubMed] **During the 5,402 person-years spent with a CD4 count ≥500 cells/mm^3, mortality rate reached the level of the general population after the sixth year after combination ART initiation.**

23. Egger M, May M, Chene G, et al. Prognosis of HIV-1–infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002;360:119-129. [PubMed] **Baseline HIV-1 viral load was associated with a higher probability of progression when 100,000 copies/microL or above.**

24. Wood E, Hogg RS, Yip B, et al. Higher baseline levels of plasma human immunodeficiency virus type 1 RNA are associated with increased mortality after initiation of triple-drug antiretroviral therapy. *J Infect Dis* 2003;188:1421-1425. [PubMed] **Baseline levels of HIV RNA of ≥100,000 copies/mL are independently associated with mortality.**

25. Marine-Barjoan E, Saint-Paul MC, Pradier C, et al. Impact of antiretroviral treatment on progression of hepatic fibrosis in HIV/hepatitis C virus co-infected patients. *AIDS* 2004;18:2163-2170. [PubMed] **Patients with severe fibrosis had greater intervals between presumed date of HCV infection and initiation of ART than those with none to moderate fibrosis (median duration of ART was the same). The mean rate of fibrosis progression was significantly slower among patients exposed to ART.**

26. Bani-Sadr F, Bedossa P, Rosenthal E, et al. Does early antiretroviral treatment prevent liver fibrosis in HIV/HCV-coinfected patients? *J Acquir Immune Defic Syndr* 2009;50:234-236. [PubMed] **Increased risk of fibrosis (OR 1.084 per year) with longer interval between HIV diagnosis and ART initiation.**

27. Shafran SD. Early initiation of antiretroviral therapy: The current best way to reduce liver-related deaths in HIV/HCV-coinfected patients. *J Acquir Immune Defic Syndr* 2007;44:551-556.[PubMed] **Review of eleven cohort studies that have shown that ART is associated with a reduced rate of progression of HCV liver disease, and 4 of these studies demonstrated a reduction in liver-related mortality.**

28. Gras L, Kesselring AM, Griffin JT, et al. CD4 cell counts of 800 cells/mm^3 or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm^3 or greater. *J Acquir Immune Defic Syndr* 2007;45:183-192. [PubMed] **CD4 counts ≥800 cells/mm^3 can be achieved within 7 years of initiation of ART in most HIV-infected patients starting therapy with ≥350 cells/mm^3 and achieving sufficient suppression of viral replication. The CD4 counts of patients who were ≥50 years of age at initiation of ART reached a plateau at a less than normal range after 5 years of therapy**.

29. Phillips A, Pezzotti P. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naïve individuals and those treated in the monotherapy era. *AIDS* 2004;18:51-58. [PubMed] **Age was significantly associated with AIDS rate, with older people experiencing a higher rate [rate ratio 1.23 per 10 years older].**

30. Streeck H, Jessen H, Alter G, et al. Immunological and virological impact of highly active antiretroviral therapy initiated during acute HIV-1 infection. *J Infect Dis* 2006;194:734-739. [PubMed] **Short-term ART for acute HIV infection resulted in suppression of viremia and an increase in CD4 count at termination of ART at 24 weeks; however, compared with untreated subjects, no differences in viremia or in CD4 count were found 6 months after ART was stopped.**

31. Pires A, Hardy G, Gazzard B, et al. Initiation of antiretroviral therapy during recent HIV-1 infection results in lower residual viral reservoirs. *J Acquir Immune Defic Syndr* 2004;36:783-790. [PubMed] **Initiation of ART during recent HIV infection reduced HIV-1 DNA to levels comparable to those seen in long-term non-progressors, which is not apparent if therapy is started during chronic infection, and suggests an association between timing of initiation of ART and decay of the HIV-1 reservoir.**

32. Koegl C, Wolf E, Hanhoff N, et al. Treatment during primary HIV infection does not lower viral set point but improves CD4 lymphocytes in an observational cohort. *Eur J Med Res* 2009;14:277-283. [PubMed] **Treatment during acute infection did not lower viral set point. However, patients treated during seroconversion had an increase in CD4 count, whereas untreated patients experienced a decrease in CD4 count. CD4 counts declined significantly quicker in untreated patients.**

33. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med* 2000;342:921-929. [PubMed] **Heterosexual transmission was rare among persons with HIV viral load levels <1500 copies/mL.**

34. Castilla J, del Romero J, Hernando V, et al. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. *J Acquir Immune Defic Syndr* 2005;40:96-101. [PubMed] **When compared with the pre-HAART era, a reduction of approximately 80% in heterosexual transmission of HIV was observed after ART became widely available.**

35. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* 2010;375:2092-2098. [PubMed] **Use of antiretroviral therapy was accompanied by a 92% reduction in HIV-1 transmission to the uninfected partner.**

36. HIV-Causal Collaboration. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. *AIDS* 2010;24:123-37. [PubMed] **Combination antiretroviral therapy halved the average mortality rate in HIV-infected individuals.**

37. Phillips AN, Gazzard B, Gilson R, et al. Rate of AIDS diseases or death in HIV-infected antiretroviral therapy-naïve individuals with high CD4 cell count. *AIDS* 2007;21:1717-1721. [PubMed] **The rate of AIDS or death in persons with most recent CD4 cell count 350-499, 500-649 and >650 cells/mm^3 was 2.49, 1.54, and 0.96 per 100 person-years, respectively. The trend of decreasing rate of AIDS and death with higher CD4 cell count continues throughout the CD4 cell count ≥350 cells/mm^3 range in ART-naive people.**

38. Ho JE, Deeks SG, Hecht FM, et al. Initiation of antiretroviral therapy at higher nadir CD4+ T-cell counts is associated with reduced arterial stiffness in HIV-infected individuals. *AIDS* 2010;24:1897-1905. [PubMed] D**ata suggest that cardiovascular risk among HIV-infected individuals could be reduced when ART is initiated at higher nadir CD4 counts.**

39. Uy J, Armon C, Buchacz K, et al. Initiation of HAART at higher CD4 cell counts is associated with a lower frequency of antiretroviral drug resistance mutations at virologic failure. *J Acquir Immune Defic Syndr* 2009;51:450-453 [PubMed] **Patients failing ART who initiated at <350 cells/mm^3 were more likely to develop resistance mutations than failing patients who initiated ART at CD4 counts >350 cells/mm^3.**

40. Zolopa A, Anderson J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: A multicenter randomized strategy trial. *PLoS ONE* 2009;4:e5575. [PubMed] **Initiation of early ART in patients with acute AIDS-related opportunistic infections resulted in less AIDS progression/death with no increase in adverse events or loss of virologic response compared to deferred ART.**

41. Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: Role of hepatitis C and B infections. *Hepatology* 2002;35;182-189. [PubMed] **The greatest risk of NNRTI-associated severe hepatotoxicity was observed in patients taking NVP, those with hepatitis B or C co-infection, and those co-administered PIs.**

42. Röling J, Schmid H, Fischereder M, et al. HIV-associated renal diseases and highly active antiretroviral therapy-induced nephropathy. *Clin Infect Dis* 2006;42:1488-1495. [PubMed] **Long-term survival contributes to an increase in HAART-induced metabolic alterations, diabetes, and hypertension and is likely to be associated with an increase in secondary renal damage.**

43. Zimmerman AE, Pizzoferrato T, Bedford J, et al. Tenofovir-associated acute and chronic kidney disease: A case of multiple drug interactions. *Clin Infect Dis* 2006;42:283-290. [PubMed] **TDF-associated acute renal failure (ARF) manifests as acute tubular necrosis that may not resolve with tenofovir withdrawal. Tenofovir is associated with multiple drug interactions, leading to an increased risk of ARF.**

44. Karras A, Lafaurie M, Furco A, et al. Tenofovir-related nephrotoxicity in HIV-infected patients: Three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. *Clin Infect Dis* 2003;36:1070-1073. [PubMed] **Renal biopsy of 2 cases revealed severe tubular necrosis with characteristic nuclear changes. Use of tenofovir by patients with mild renal dysfunction and/or use for longer durations might be associated with renal toxicity.**

45. Deeks SG, Hoh R, Neilands TB, et al. Interruption of treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. *J Infect Dis* 2005;192:1537-1544. [PubMed] **Nucleoside analogues often exert continued antiviral activity in the setting of drug-resistance mutations and both nucleoside analogues and PIs can select for drug-resistance mutations that reduce viral fitness.**

APPENDIX A

CHARACTERISTICS OF ANTIRETROVIRAL DRUGS

FDA Pregnancy Categories

A Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters).

B Animal reproduction studies fail to demonstrate a risk to the fetus and adequate and well-controlled studies of pregnant women have not been conducted.

C Safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.

D Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

X Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

ABACAVIR (ABC) *(Updated January 2008)*	
Trade Name	Ziagen
Classification	Nucleoside Reverse Transcriptase Inhibitor
Form	300-mg tablets; 20-mg/mL oral solution Each Trizivir tablet contains ZDV 300 mg, 3TC 150 mg, and ABC 300 mg Each Epzicom tablet contains ABC 600 mg and 3TC 300 mg
Dosing Recommendations	300 mg twice daily ***or*** with ZDV and 3TC as Trizivir,[a] 1 twice daily ***or*** with 3TC as Epzicom, 1 once daily
Hepatic Impairment Dosing	Child-Pugh Score 5-6: 200 mg (10 mL of oral solution) bid. Limited clinical data. Child-Pugh Score 7-12: not recommended by manufacturer
Food Effect	No known food interactions Alcohol ↑ ABC levels 41%; no effect on alcohol
Oral Bioavailability	83%
Serum Half-life	1.5 h□urs
Intracellular Half-life	21 hours
Elimination	Metabolized by alcohol dehydrogenase and glucuronyl transferase Renal excretion of metabolites 82%
Adverse Events	Hypersensitivity reaction (can be fatal)[b]: fever, skin rash, nausea, vomiting, diarrhea, abdominal pain, malaise, fatigue, loss of appetite, and respiratory symptoms (sore throat, cough, shortness of breath) Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs
FDA Pregnancy Category	C
Long-Term Animal Carcinogenicity Studies	Not completed
Animal Teratogen Studies	Positive [rodent anasarca and skeletal malformations at 1000 mg/kg (35x human

Black Box Warnings	Fatal hypersensitivity reactions reported: • Signs or symptoms include fever, skin rash, fatigue, gastrointestinal symptoms (nausea, vomiting, diarrhea, or abdominal pain), and respiratory symptoms (pharyngitis, dyspnea, or cough) • Abacavir should be discontinued as soon as hypersensitivity reaction is suspected • Abacavir SHOULD NOT be restarted. If restarted, more severe symptoms will recur within hours and may include life-threatening hypotension and death Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.
Drugs to Avoid	**As part of the ARV regimen:**

[a] Trizivir should not be used in patients with renal insufficiency. Separate components and dose based on glomerular filtration rate (GFR).
[b] HLA-B*5701 is a pharmacogenetic test (HLA-B*5701) used to identify patients who are predisposed to abacavir hypersensitivity. Clinicians should perform HLA-B*5701 testing before initiating abacavir-based therapy.

DIDANOSINE (DDI)* *(Updated January 2010)*	
Trade Name	Videx and Videx EC
Classification	Nucleoside Reverse Transcriptase Inhibitor
Form	100-, 167-, 250-mg buffered powder for oral solution 125-, 200-, 250-, 400-mg enteric coated (EC) capsules
Dosing Recommendations	≥60 kg: 250 mg twice daily (buffered powder) or 400 mg once daily (EC capsules) <60 kg: 167 mg twice daily (buffered powder) or 250 mg once daily (EC capsules)
Hepatic Impairment Dosing	No adjustment. Use with close monitoring
Renal Impairment Dosing	**CrCl (mL/min) / Weight / Dose** 30-59 / <60 kg / 125 mg once daily 30-59 / ≥60 kg / 200 mg once daily 10-29 / <60 kg / 100 mg once daily 10-29 / ≥60 kg / 125 mg once daily <10 / <60 kg / 75 mg once daily <10 / ≥60 kg / 125 mg once daily CAPD or hemodialysis / Same dose as CrCl <10 mL/min
Food Effect	Take 1 hour before or 2 hours after meals. TDF + ddI EC may be taken on an empty stomach or with a light meal. Food ↓ AUC 55% Alcohol may exacerbate toxicity. Avoid acidic beverages when taking ddI
Oral Bioavailability	30-40%
Serum Half-life	1.6 hours
Intracellular Half-life	25-40 hours
Elimination	Renal excretion 50%
Adverse Events	GI intolerance (EC generally better tolerated), nausea, diarrhea Pancreatitis, peripheral neuropathy, lipoatrophy Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity Non-cirrhotic portal hypertension has been reported. Monitor for signs of portal hypertension and esophageal varices and discontinue use in patients with evidence of portal hypertension
FDA Pregnancy Category	B (may be at increased risk of lactic acidosis)
Long-Term Animal Carcinogenicity Studies	Negative (no tumors, lifetime rodent study)
Animal Teratogen Studies	Negative

Black Box Warnings	Fatal and nonfatal pancreatitis have occurred with didanosine alone or in combination with other antiretroviral agents. Didanosine should be withheld if pancreatitis is suspected and discontinued if pancreatitis is confirmed. Fatal lactic acidosis has been reported among pregnant women who received a combination of didanosine and stavudine with other antiretroviral combinations. Didanosine and stavudine combination should only be used during pregnancy if the potential benefit clearly outweighs the potential risks. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.
Drugs to Avoid	**As part of the ARV regimen:** Stavudine Tenofovir + lamivudine Tenofovir + delavirdine Tenofovir + efavirenz Tenofovir + nevirapine Aluminum- or magnesium-containing antacids (may ↑ ddI levels; clinical significance unknown) **Contraindicated:** Allopurinol (ddI ↑ 113%) Ribavirin
Cautious Use or Dose Adjustment	
Antiretrovirals	**Atazanavir**: ATV AUC ↓ 87% – Take ATV (with food) 2 hours before or 1 hour after buffered ddI **Darunavir:** Administer ddI 1 hour before or 2 hours after DRV **Delavirdine**: DLV AUC ↓ – Take DLV 1 hour before buffered ddI **Indinavir**: IDV AUC ↓ – Take IDV 1 hour before or after buffered ddI on an empty stomach **Nelfinavir:** Administer NFV 1 hour after ddI **Stavudine**: Peripheral neuropathy, lactic acidosis, and pancreatitis have been reported with this combination – Use only if benefits clearly outweigh risks **Tenofovir**: ddI AUC ↑44%; Cmax ↑ 28% – Monitor for ddI-associated toxicities; for patients ≥60 kg, ↓ ddI EC dose to 250 mg once daily; for patients <60 kg ↓ ddI EC to 200 mg once daily. Avoid combination in patients with renal failure
Antifungals	**Itraconazole, ketoconazole**: Take 2 hours before buffered ddI or use ddI EC
Antimicrobials	**Fluoroquinolones:** Take ddI 2 hours after or 6 hours before fluoroquinolones
Antivirals	**Ganciclovir**: ddI AUC ↑ 111% with ddI buffered formulation, GCV AUC ↓ 21% – Use ddI EC with ganciclovir only if other antivirals not suitable; Monitor for ddI-associated toxicities

Synthetic Narcotics	**Methadone**: Buffered ddI AUC ↓ 30% – Do not co-administer with buffered ddI. Use standard ddI EC with close monitoring of viral load.
* Buffered ddI tablets were discontinued in fall of 2006; buffered ddI powder for oral solution and enteric coated capsules (EC) are still available.	

EMTRICITABINE (FTC) *(Updated January 2007)*	
Trade Name	Emtriva
Classification	Nucleoside Reverse Transcriptase Inhibitor
Form	200-mg capsules Each Truvada tablet contains TDF 300 mg and FTC 200 mg Each Atripla tablet contains EFV 600 mg, FTC 200 mg, and TDF 300 mg
Dosing Recommendations	200 mg once daily ***or*** with TDF as Truvada, 1 once daily ***or*** with EFV and TDF as Atripla, 1 once daily
Renal Impairment Dosing	**CrCl (mL/min)** — **Dose** 30-49 — 200 mg q48h 15-29 — 200 mg q72h <15 — 200 mg q96h Hemodialysis — 200 mg q96h; dose after dialysis on day of dialysis
Food Effect	No food effect
Oral Bioavailability	93%
Serum Half-life	10 hours
Intracellular Half-life	39 hours
Elimination	Renal excretion 86%
Adverse Events	Minimal toxicity for adults Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity
FDA Pregnancy Category	B
Long-Term Animal Carcinogenicity Studies	Not completed
Animal Teratogen Studies	Negative (mice and rabbits)
Black Box Warnings	Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals.
Drugs to Avoid	**As part of the ARV regimen**: Lamivudine

LAMIVUDINE (3TC) *(Updated January 2007)*	
Trade Name	Epivir
Classification	Nucleoside Reverse Transcriptase Inhibitor
Form	150-, 300-mg tablets; 10-mg/mL oral solution Each Combivir tablet contains ZDV 300 mg and 3TC 150 mg Each Trizivir tablet contains ZDV 300 mg, 3TC 150 mg, and ABC 300 mg Each Epzicom tablet contains ABC 600 mg and 3TC 300 mg
Dosing Recommendations	150 mg twice daily or 300 mg once daily <50 kg: 2 mg/kg twice daily ***or*** with ZDV as Combivir,[a] 1 twice daily ***or*** with ZDV and ABC as Trizivir,[a,b] 1 twice daily ***or*** with ABC as Epzicom,[b] 1 once daily
Renal Impairment Dosing	**CrCl (mL/min)** — **Dose** 30-49 — 150 mg once daily 15-29 — 150 mg first dose, then 100 mg once daily 5-14 — 150 mg first dose, then 50 mg once daily <5 — 50 mg first dose, then 25 mg once daily Hemodialysis — No data
Food Effect	No food effect
Oral Bioavailability	86%
Serum Half-life	5-7 hours
Intracellular Half-life	18 hours
Elimination	Renal excretion
Adverse Events	Minimal toxicity for adults Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity
FDA Pregnancy Category	C
Long-Term Animal Carcinogenicity Studies	Negative (no tumors, lifetime rodent study)
Animal Teratogen Studies	Negative
Black Box Warnings	Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination. Epivir tablets and oral solution (used to treat HIV infection) contain a higher dose of lamivudine than Epivir-HBV tablets and oral solution (used to treat chronic hepatitis B). Patients with HIV infection should receive only doses and formulations appropriate for treatment of HIV infection.

Drugs to Avoid	As part of the ARV regimen: Abacavir + tenofovir Emtricitabine Tenofovir + didanosine

[a] Combivir and Trizivir should not be used in patients with renal insufficiency. Separate components and dose based on glomerular filtration rate (GFR).

[b] HLA-B*5701 is a pharmacogenetic test (HLA-B*5701) used to identify patients who are predisposed to abacavir hypersensitivity. Clinicians should perform HLA-B*5701 testing before initiating abacavir-based therapy.

STAVUDINE (D4T) *(Updated February 2009)*			
Trade Name	Zerit		
Classification	Nucleoside Reverse Transcriptase Inhibitor		
Form	15-, 20-, 30-, 40-mg capsules; 1 mg/mL for oral solution		
Dosing Recommendations	≥60 kg: 40 mg twice daily <60 kg: 30 mg twice daily		
Hepatic Im□airment Dosing	No adjustment. Use with close monitoring		
Renal Impairment Dosing	**CrCl (mL/min)**	**Weight**	**Dose**
	26-50	<60 kg ≥60 kg	15 mg q12h 20 mg q12h
	10-25	<60 kg ≥60 kg	15 mg q24h 20 mg q24h
	Hemodialysis	Same dose as CrCl 10-25 mL/min; dose after dialysis on day of dialysis	
Food Effect	No food effect		
Oral Bioavailability	86%		
Serum Half-life	1.0 hour		
Intracellular Half-life	3.5 hours		
Elimination	Renal excretion 50%		
Adverse Events	Peripheral neuropathy (most common), pancreatitis, lipodystrophy, rapidly progressive ascending neuromuscular weakness (rare) Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity		
FDA Pregnancy Category	C (may be at increased risk of lactic acidosis)		
Long-Term Animal Carcinogenicity Studies	Not completed		
Animal Teratogen Studies	Negative (but sternal bone calcium decreases in rodents)		
Black Box Warnings	Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination. Fatal lactic acidosis has been reported in pregnant women who received a combination of stavudine and didanosine with other ARV combinations. Stavudine and didanosine combination should only be used during pregnancy if the potential benefit clearly outweighs the potential risks. Fatal and non-fatal pancreatitis have occurred when stavudine was part of a combination regimen with didanosine with or without hydroxyurea.		

Drugs to Avoid	**As part of the ARV regimen:** Zidovudine
Cautious Use or Dose Adjustment	
Antiretrovirals	**Didanosine:** Peripheral neuropathy, lactic acidosis, and pancreatitis have been reported with this combination – Use only if benefits clearly outweigh risks

TENOFOVIR (TDF) *(Updated January 2007)*	
Trade Name	Viread
Classification	Nucleotide Reverse Transcriptase Inhibitor
Form	300-mg tablets Each Truvada tablet contains TDF 300 mg and FTC 200 mg Each Atripla tablet contains EFV 600 mg, FTC 200 mg, and TDF 300 mg
Dosing Recommendations	300 mg once daily ***or*** with FTC as Truvada, 1 once daily ***or*** with EFV and FTC as Atripla, 1 once daily
Renal Impairment Dosing	**CrCl (mL/min)** — **Dose** 30-49 — 300 mg q48h 10-29 — 300 mg bi wk ESRD — 300 mg q wk
Food Effect	Fatty meal ↑ TDF AUC 40% Co-administration of TDF + ddI buffered tablets should be on an empty stomach TDF + ddI EC may be taken on an empty stomach or with a light meal
Oral Bioavailability	25% in fasting state; 39% with high-fat meal
Serum Half-life	17 hours
Intracellular Half-life	10-50 hours
Elimination	Renal excretion
Adverse Events	Asthenia, headache, diarrhea, nausea, vomiting, flatulence Although there have been no cases of lactic acidosis reported with TDF use, lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs Rare reports of renal insufficiency
FDA Pregnancy Category	B (one study showed normal growth; however, there was a decrease in fetal bone porosity and insulin-like growth factor was observed)
Long-Term Animal Carcinogenicity Studies	Negative (rats); in female mice, liver adenomas were increased at exposures 16 times that in humans
Animal Teratogen Studies	Negative (osteomalacia when given to juvenile animals at high doses)
Black Box Warnings	Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals.

	Viread has *in vitro* activity against HBV but is not indicated for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of Viread have not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV and have discontinued Viread. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Viread and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.
Drugs to Avoid	**As part of the ARV regimen:** Atazanavir without ritonavir Didanosine + delavirdine Didanosine + efavirenz Didanosine + nevirapine Lamivudine + abacavir Lamivudine + didanosine
Cautious Use or Dose Adjustment	
Antiretrovirals	**Atazanavir + ritonavir:** ATV AUC ↓ 25%, Cmin ↓ 23% – Use ATV 300 mg + RTV 100 mg once daily **Didanosine:** ddI AUC ↑ 44%, Cmax ↑ 28% – Monitor for ddI-associated toxicities; for patients ≥60 kg, ↓ ddI EC dose to 250 mg once daily; for patients <60 kg ↓ ddI EC to 200 mg once daily. Avoid combination in patients with renal failure
Antivirals	**Cidofovir, ganciclovir, valganciclovir:** May ↑ serum concentration of these drugs and/or TDF – Monitor for dose-related toxicities
Uricosuric Agents	**Trimethoprim, probenecid:** May ↑ serum concentration of these drugs and/or TDF – Monitor for dose-related toxicities

ZIDOVUDINE (ZDV) *(Updated February 2009)*	
Trade Name	Retrovir
Classification	Nucleoside Reverse Transcriptase Inhibitor
Form	100-mg capsules, 300-mg tablets, 10-mg/mL IV solution, 10-mg/mL oral solution Each Combivir tablet contains ZDV 300 mg and 3TC 150 mg Each Trizivir tablet contains ZDV 300 mg, 3TC 150 mg, and ABC 300 mg
Dosing Recommendations	200 mg tid or 300 mg twice daily ***or*** with 3TC as Combivir,[a] 1 twice daily ***or*** with ABC and 3TC as Trizivir,[a,b] 1 twice daily
Hepatic Impairment Dosing	Use with close monitoring
Renal Impairment Dosing	**CrCl (mL/min)** — **Dose** <15 — 100 mg q6-8h (or 300 mg once daily) Hemodialysis — 100 mg q6-8h (or 300 mg once daily)
Food Effect	Absorption similar with or without food. Fatty food may decrease bioavailability (clinical significance unknown)
Oral Bioavailability	60%
Serum Half-life	1.1 hour
Intracellular Half-life	3 hours
Elimination	Metabolized to AZT glucuronide (GAZT); renal excretion of GAZT
Adverse Events	GI intolerance, headache, insomnia, asthenia, lipoatrophy Bone marrow suppression: anemia, neutropenia, and, less commonly, thrombocytopenia Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity
FDA Pregnancy Category	C (no maternal toxicity or fetal defects noted with long-term follow-up)
Long-Term Animal Carcinogenicity Studies	Positive (rodent, non-invasive vaginal epithelial tumors)
Animal Teratogen Studies	Negative (mice and rabbits)
Black Box Warnings	Zidovudine may be associated with hematologic toxicities, including granulocytopenia and severe anemia, particularly in advanced HIV-infected patients. Prolonged zidovudine use has been associated with symptomatic myopathy. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.

Drugs to Avoid	**As part of the ARV regimen:** Stavudine Doxorubicin (additive bone marrow suppression)
Cautious Use or Dose Adjustment	
Antivirals	**Ganciclovir**: Additive bone marrow suppression **Ribavirin**: Additive anemia – May require use of EPO
Erythropoiesis-Stimulating Agents (ESAs)	**Hold dose when Hgb >13 g/dL, and reinitiate with a 25% reduction or when Hgb <12 g/dL. Monitor Hct q1-2 wk until maintenance dose established**

[a] Combivir and Trizivir should not be used in patients with renal insufficiency. Separate components and dose based on glomerular filtration rate (GFR).

[b] HLA-B*5701 is a pharmacogenetic test (HLA-B*5701) used to identify patients who are predisposed to abacavir hypersensitivity. Clinicians should perform HLA-B*5701 testing before initiating abacavir-based therapy.

DELAVIRDINE (DLV) *(Updated February 2009)*	
Trade Name	Rescriptor
Classification	Non-nucleoside Reverse Transcriptase Inhibitor
Form	100-, 200-mg tablets
Dosing Recommendations	400 mg tid, ***or*** four 100-mg tablets in ≥3 oz water to produce slurry
Hepatic Impairment Dosing	Use with caution in patients with hepatic impairment
Food Effect	No food effect
Oral Bioavailability	85%
Serum Half-life	5.8 hours
Elimination	Metabolized by cytochrome P450 (3A4 inhibitor) 51% excreted in urine (<5% unchanged), 44% in feces
Adverse Events	Rash,[a] headaches Increased transaminase levels
FDA Pregnancy Category	C
Long-Term Animal Carcinogenicity Studies	Not completed
Animal Teratogen Studies	Positive (rodent-ventricular septal defect)
Black Box Warnings	None
Drugs to Avoid	**As part of the ARV regimen:** Fosamprenavir Nelfinavir Alprazolam, astemizole, carbamazepine, cisapride, ergot derivatives, garlic supplements, H2 blockers, ketoconazole, lovastatin, midazolam,[b] phenobarbital, phenytoin, pimozide, proton pump inhibitors, rifampin, rifapentine, rifabutin, simvastatin, St. John's wort, terfenadine, triazolam
Cautious Use or Dose Adjustment	
Antiretrovirals	**Didanosine (buffered)**: May ↓ DLV – Separate dosing of buffered ddI and DLV by >1 hour **Indinavir**: ↑ IDV – ↓ IDV dose to 600 mg q8h **Maraviroc**: ↑ MVC – ↓ MVC dose to 150 mg twice daily **Ritonavir:** RTV AUC ↑**,** Cmax ↑**,** Cmin ↑**.** Combination dosing not established

Antacids	↓ DLV – Separate by at least 1 hour
Anticoagulants	**Warfarin**: ↑ warfarin – Monitor INR
Antifungals	**Voriconazole**: Potential for bi-directional inhibition – Monitor frequently for toxicities
Antimycobacterials	**Clarithromycin**: CL ↑ 100%; DLV ↑ 44% – ↓ CL dose in renal impairment
Calcium Channel Blockers	**Bepridil**: ↑ bepridil – Use with caution
Corticosteroids	**Fluticasone:** Avoid long-term co-administration
Erectile Dysfunction Agents	**Sildenafil**: May ↑ sildenafil AUC – Use cautiously, start with reduced dose of 25 mg q48h and monitor for adverse effects **Tadalafil**: Substantial ↑ in tadalafil AUC and half-life – Start with a 5-mg dose; do not exceed a single 10-mg dose of tadalafil in 72 hours **Vardenafil**: May ↑ vardenafil AUC – Start with 2.5-mg dose; do not exceed a single 2.5-mg dose of vardenafil in 72 hours
Lipid-Lowering Agents	**Atorvastatin**: ATO may ↑ substantially – Use lowest possible starting dose of ATO

[a] In clinical trials, DLV was discontinued because of rash in 4.3% of patients. Rare cases of Stevens-Johnson syndrome have been reported.
[b] Can be used with caution as a single dose in a monitored situation for procedural sedation.

EFAVIRENZ (EFV) *(Updated April 2010)*	
Trade Name	Sustiva
Classification	Non-nucleoside Reverse Transcriptase Inhibitor
Form	50-, 200-mg capsules; 600-mg tablets Each Atripla tablet contains EFV 600 mg, FTC 200 mg, and TDF 300 mg
Dosing Recommendations	600 mg once daily, preferably at bedtime on an empty stomach ***or*** with FTC and TDF as Atripla, 1 once daily
Hepatic Impairment Dosing	Monitor serum liver enzymes before and during treatment in patients with underlying hepatic disease, including hepatitis B or C co-infection, marked transaminase elevations, or who are taking medications associated with liver toxicity
Food Effect	Take on an empty stomach. Avoid meals with >40-60 g fat. Fatty meal ↑ EFV AUC 28%. Most experts recommended taking on an empty stomach during the first 2 weeks to minimize CNS side effects, but co-administration with food after 2 weeks is acceptable.
Oral Bioavailability	Data not available
Serum Half-life	40-55 hours
Elimination	Metabolized by cytochrome P450 2B6>3A4 (3A4 mixed inducer/inhibitor *in vitro*, but 3A4 inducer *in vivo*); 14%-34% excreted in urine (glucuronidated metabolites, <1% unchanged), 16%-61% in feces
Adverse Events	Rash,[a] central nervous system symptoms (dizziness, somnolence, insomnia, abnormal dreams, confusion, impaired concentration, amnesia),[b] psychiatric symptoms (agitation, depression, depersonalization, hallucinations, euphoria, suicidal ideation) Increased transaminase levels False-positive cannabinoid test
FDA Pregnancy Category	D (reported cases of neural tube defect in human fetuses). Birth defects occurred in 14 of 501 live births (first trimester exposure) and 2 of 55 live births (second/third-trimester exposure)
Long-Term Animal Carcinogenicity Studies	Not completed
Animal Teratogen Studies	Positive (cynomolgus monkey-anencephaly, anophthalmia, microphthalmia)
Black Box Warnings	None
Drugs to Avoid	**As part of the ARV regimen**: Unboosted atazanavir (for therapy-experienced patients) Fosamprenavir without ritonavir Any other NNRTIs (e.g., DLV, ETR, NVP) Astemizole, bepridil, cisapride, ergot derivatives, garlic supplements, midazolam,[c] pimozide, rifapentine, St. John's wort, terfenadine, triazolam

Cautious Use or Dose Adjustment	
Antiretrovirals	**Atazanavir:** For therapy-naïve patients – Use ATV 400 mg + RTV 100 mg once daily with food **Darunavir:** DRV Cmin ↓ 31%; EFV AUC and Cmin↑ 21% and 17%, respectively – Studied dose lower than FDA approved dose. Consider using DRV/r 600/100 mg twice daily with EFV 600 mg qhs ***or*** DRV/r 900/100 mg once daily with EFV 600 mg qhs (based on PK data) **Fosamprenavir:** FPV Cmin ↓ 36% when dosed at FPV 1400 mg + RTV 200 mg once daily – Use FPV 700 mg + RTV 100 mg twice daily, or FPV 1400 mg + RTV 300 mg once daily **Indinavir:** IDV ↓ 31% – ↑ IDV dose to 1000 mg q8h, or consider IDV 800 mg + RTV 200 mg q12h **Lopinavir/ritonavir:** LPV AUC ↓ 40% – ↑ LPV/r dose to 500/125 mg twice daily with food **Maraviroc**: ↓ MVC AUC – ↑ MVC dose to 600 mg twice daily (if not co-administered with a PI) **Saquinavir:** SQV ↓ 62%; EFV ↓ 12% – Use SQV 1000 mg + RTV 100 mg q12h **Tipranavir/ritonavir:** Use TPV 500 mg + RTV 200 mg twice daily
Anticoagulants	**Warfarin:** Potential ↑ or ↓ warfarin levels – Monitor warfarin levels
Anticonvulsants	**Carbamazepine, phenobarbital, phenytoin:** Unknown – Avoid co-administration. If no alternatives available, use with close monitoring of anticonvulsant levels
Antifungals	**Itraconazole, ketoconazole:** ↓ itra/keto – Consider alternative antifungal **Voriconazole:** ↑ voriconazole to 400 mg q12h plus EFV 300 mg qhs. EFV should not be co-administered with voriconazole at the standard doses. In severe cases of invasive aspergillosis, consider voriconazole therapeutic drug monitoring **Posaconazole** – avoid concomitant use unless benefit outweighs risk. Monitor posaconazole serum concentrations with co-administration
Antimycobacterials	**Clarithromycin:** CL ↓ 39% – Monitor for efficacy; or, if possible, use alternative agent, such as azithromycin **Rifabutin:** RFB ↓ 35% – ↑ RFB dose to 450-600 mg once daily or 600 mg 3x/wk **Rifampin:** EFV ↓ 22% – Consider ↑ EFV dose to 800 mg once daily in persons >60 kg
Calcium Channel Blocker	**Diltiazem:** ↓ diltiazem – Diltiazem dose adjustment should be guided by clinical response
Oral Contraceptives	**Ethinyl estradiol:** EE ↑ 37% – Use alternative barrier form or additional method of contraception. Monitor for contraceptive adverse drug reactions

Selective Serotonin Reuptake Inhibitors (SSRIs)	**Sertraline:** ↓ sertraline – Sertraline dose adjustment should be guided by clinical response
Synthetic Narcotics	**Methadone:** ↓ methadone levels significantly – Monitor and titrate dose to effect

[a] In clinical trials, EFV was discontinued because of rash in 1.7% of patients. Rare cases of Stevens-Johnson syndrome have been reported.
[b] Symptoms usually subside spontaneously after 2-4 weeks.
[c] Patients experiencing serious psychiatric symptoms should be evaluated to assess whether symptoms may be related to EFV. If so, the clinician should discontinue use of EFV if the risks outweigh the benefits.

ETRAVIRINE (ETR) *(Updated March 2010)*	
Trade Name	Intelence
Classification	Non-nucleoside Reverse Transcriptase Inhibitor
Form	100-mg tablets
Dosing Recommendations	For ARV-experienced patients: 200 mg twice daily with food
Hepatic Impairment Dosing	Use with caution in patients with severe hepatic impairment (Child-Pugh class C); pharmacokinetics of etravirine have not been studied in these patients
Food Effect	Take after a meal (50% decrease in bioavailability when taken on an empty stomach)
Oral Bioavailability	Absolute bioavailability unknown
Serum Half-life	40 (± 20) hours
Elimination	Inducer of CYP3A4 and inhibitor of CYP2C9 and CYP2C19; 81.2%-86.4% excreted in feces. Mild inducer of 2B6 and glucuronidation *in vitro*
Storage	Store at room temperature
Adverse Events	In patients who were also treated with DRV/r, rash occurred in 16.9% in etravirine treated group compared to 9.3% in placebo-treated patients. In general, the rash was mild to moderate (but Grade 3 and 4 rashes were reported in 1.3% of patients), occurred in the second week, and resolved within 1-2 weeks on continued therapy. However, 2% of patients required etravirine discontinuation due to rash. Severe and potentially life-threatening skin reactions have occurred in patients taking etravirine, including Stevens-Johnson syndrome, hypersensitivity reaction, and erythema multiforme. Etravirine should be discontinued for severe rash or if rash is accompanied by fever, hepatitis, and other systemic symptoms. Moderate to severe (grade 2-4) nausea, abdominal pain, diarrhea, and vomiting were reported in approximately 15% of patients. This was comparable to placebo-treated patients. LFTs and bilirubin elevations (more common in patients co-infected with HBV and HCV). Immune reconstitution syndrome.
FDA Pregnancy Category	B
Long-Term Animal Carcinogenicity Studies	Not completed
Animal Teratogen Studies	Not teratogenic in animal studies
Black Box Warnings	None
Drugs to Avoid	**As part of the ARV regimen**: Atazanavir/ritonavir (unclear clinical significance) Fosamprenavir/ritonavir (unclear clinical significance) Tipranavir/ritonavir Other NNRTIs Any unboosted protease inhibitors (administered without ritonavir) Carbamazepine, phenobarbital, phenytoin, rifampin, rifapentine, St. John's wort

Cautious Use or Dose Adjustment	
Antiarrhythmics	**Antiarrhythmics:** May be ↓ – Use with caution and monitor antiarrhythmic levels
Anticoagulants	**Warfarin:** May ↑ warfarin levels – Monitor INR levels
Antifungals	**Posaconazole, fluconazole, itraconazole, ketoconazole:** May ↑ ETR **Itraconazole, ketoconazole:** May ↓ itra/keto . **Voriconazole:** Concomitant use may ↑ plasma concentration of both drugs **Posaconazole, fluconazole:** Concomitant use of ETR is unlikely to affect posaconazole or fluconazole plasma concentrations Consider monitoring serum concentrations of itraconazole, voriconazole, and posaconazole with ETR co-administration. Dose adjustments may be necessary
Anti-infectives	**Clarithromycin:** CL exposure ↓ – Use alternative agent, such as azithromycin, for MAC. Clinical significance unclear for infections involving *S. pneumoniae* and *H. influenzae* since 14-OH-clarithromycin metabolite is active
Antimycobacterials	**Rifabutin:** If ETR is NOT used with boosted PI, use RFB 300 mg once daily. If ETR is co-administered with darunavir/ritonavir or saquinavir/ritonavir, do not use RFB with ETR
Antiplatelets	**Clopidogrel:** ETR ↓ clopidogrel (active) metabolite conversion and may decrease clopidogrel's efficacy. Consider alternative to clopidogrel
Benzodiazepines	**Diazepam:** May ↑ diazepam – Diazepam dose ↓ may be needed **Midazolam**: ↓ midazolam serum concentrations (limited data)
Corticosteroids	**Dexamethasone:** May ↓ ETR – Use with caution or consider alternatives
Erectile Dysfunction Agents	**Sildenafil: S**ildenafil AUC ↓ 57%; titrate dose to effect
HMG-CoA Reductase Inhibitors	**Atorvastatin:** May need to be dose adjusted to patient response **Lovastatin, simvastatin:** May ↓ concentration levels of these agents, dose adjustments may be necessary **Fluvastatin:** May ↑ levels of these agents, dose adjustments may be necessary **Rosuvastatin:** No data, but may slightly ↑ rosuvastatin serum concentrations
Immunosuppressants	**Cyclosporine, sirolimus, tacrolimus:** May ↓ immunosuppressant concentrations. Use with close monitoring of immunosuppressant's serum concentrations
Integrase Inhibitors	**Raltegravir:** No significant drug interactions
Synthetic Narcotics	**Methadone:** No significant interactions. Monitor for withdrawal symptoms and titrate dose to effect

NEVIRAPINE (NVP) *(Updated February 2009)*	
Trade Name	Viramune
Classification	Non-nucleoside Reverse Transcriptase Inhibitor
Form	200-mg tablets; 50 mg/5 mL oral suspension
Dosing Recommendations	200 mg once daily x 14 days, then 200 mg twice daily with or without food
Hepatic Impairment Dosing	Should not be administered in patients with moderate to severe hepatic impairment; patients with hepatic fibrosis or cirrhosis may be at risk for drug accumulation
Food Effect	No food effect
Oral Bioavailability	>90%
Serum Half-life	25-30 hours
Elimination	Metabolized by cytochrome P450 (3A4 inducer); 80% excreted in urine (glucuronidated metabolites, <5% unchanged), 10% in feces
Adverse Events	Rash,* fever, nausea, headache Increased transaminase levels, symptomatic hepatitis, including hepatic necrosis
FDA Pregnancy Category	C (no fetal defect was found in HIVNET 006 trial)
Long-Term Animal Carcinogenicity Studies	Not completed
Animal Teratogen Studies	Negative
Black Box Warnings	Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, has been reported in patients treated with nevirapine. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Women and patients with higher CD4 counts are at increased risk of these hepatic events. Women with CD4 counts >250 cells/mm^3, including pregnant women receiving chronic treatment for HIV infection, are at considerably higher risk for these events. Patients with signs or symptoms of hepatitis must discontinue nevirapine and seek medical evaluation immediately. Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue nevirapine and seek medical evaluation immediately. It is essential that patients be monitored intensively during the first 18 weeks of therapy with nevirapine to detect potentially life-threatening hepatotoxicity or skin reactions. The greatest risk of severe rash or hepatic events (often associated with rash) occurs in the first 6 weeks of therapy. However, the risk of any hepatic event, with or without rash, continues past this period, and

	monitoring should continue at frequent intervals. In some cases, hepatic injury has progressed despite discontinuation of treatment. Nevirapine should not be restarted following severe hepatic, skin or hypersensitivity reactions. In addition, the 14-day lead-in period with nevirapine 200 mg daily dosing must be strictly followed.
Drugs to Avoid	**As part of ARV regimen:** Atazanavir Other NNRTIs (e.g., ETR, EFV, and DLV) Garlic supplements, ketoconazole, rifampin, rifapentine, St. John's wort
Cautious Use or Dose Adjustment	
Antiretrovirals	**Indinavir:** IDV ↓ 28% – ↑ IDV dose to 1000 mg q8h, or consider IDV 800 mg + RTV 100 mg twice daily **Lopinavir/ritonavir:** LPV Cmin ↓ 55% – ↑ LPV/r dose to 600/150 mg (3 tabs or 7.5 mL) twice daily with food **Saquinavir:** SQV ↓ 25% – Use SQV 1000 mg + RTV 100 mg twice daily
Anticonvulsants	**Carbamazepine, phenobarbital, phenytoin:** Unknown – Avoid co-administration. If no alternatives available, use with close monitoring of anticonvulsant levels
Antifungals	**Fluconazole:** Significant ↑ in NVP not observed – Monitor for NVP-associated adverse effects **Voriconazole:** Potential for bi-directional inhibition; may significantly ↓ voriconazole – Monitor voriconazole serum concentrations and nevirapine toxicities
Antimycobacterials	**Clarithromycin:** NVP ↑ 26%; CL ↓ 31% – Monitor for efficacy or use alternative agent (azithromycin)
Oral Contraceptives	**Ethinyl estradiol:** EE ↓~20% – Use alternative or additional method of contraception **Norethindrone:** ↓ norethindrone – Use alternative or additional method of contraception
Synthetic Narcotics	**Methadone:** ↓ methadone levels significantly – Monitor and titrate dose to effect
* In clinical trials, NVP was discontinued because of rash in 7% of patients. Rare cases of Stevens-Johnson syndrome have been reported.	

ATAZANAVIR (ATV) *(Updated April 2010)*	
Trade Name	Reyataz
Classification	Protease Inhibitor
Form	100-, 150-, 200-, 300-mg capsules
Dosing Recommendations	**For ARV-naïve patients**: **(able to tolerate RTV)**: ATV 300 mg + RTV 100 mg once daily with food ***or*** **For ARV-naïve patients (unable to tolerate RTV)**: 400 mg once daily with food **For ARV-experienced patients**: ATV 300 mg + RTV 100 mg once daily with food
Hepatic Impairment Dosing	Child-Pugh Score 7-9: consider 300 mg once daily Child-Pugh Score >9: do not use *Note:* Do not use ATV with RTV in patients with hepatic impairment
Renal Impairment Dosing	**For ARV-naïve patients with ESRD**: ATV 300 mg + RTV 100 mg once daily **For ARV-experienced patients with ESRD**: Avoid unboosted ATV. Higher ATV/r may be needed
Food Effect	Light meal increases AUC 70% and Cmax 57% Take with food
Oral Bioavailability	Not determined (varies with food)
Serum Half-life	7 hours
Route of Metabolism	Hepatic cytochrome P450 3A4 inhibitor and substrate
Storage	Room temperature
Adverse Events	GI intolerance, rash Hyperglycemia,[a] indirect hyperbilirubinemia, nephrolithiasis PR interval prolongation (some patients experience asymptomatic 1st degree AV block) Possible increased bleeding episodes in patients with hemophilia
FDA Pregnancy Category	B
Long-Term Animal Carcinogenicity Studies	Not completed
Animal Teratogen Studies	Negative (rats and rabbits)
Black Box Warnings	None
Drugs to Avoid	**As part of the ARV regimen:** Efavirenz (for therapy-experienced patients) Etravirine (clinical significance unclear) Indinavir Nevirapine Tenofovir (when ATV is not combined with RTV) Tipranavir/ritonavir

	Alfuzosin, alprazolam, astemizole, bepridil, cisapride, ergot derivatives, garlic supplements, irinotecan, lovastatin, midazolam,[b] pimozide, proton pump inhibitors, ranolazine, rifampin, rifapentine, high-dose sildenafil, simvastatin, St. John's wort, terfenadine, triazolam
Cautious Use or Dose Adjustment	
Antiretrovirals	**Darunavir:** Dose DRV/r 600/100 mg twice daily + ATV 300 mg once daily **Didanosine:** ATV AUC ↓ 87% – Take ATV (with food) 2 hours before or 1 hour after buffered ddI **Efavirenz:** For therapy-naïve patients – Use ATV 400 mg + RTV 100 mg once daily with food and EFV 600 mg once daily on empty stomach at bedtime for initial 2 weeks, then may take EFV with or without food **Lopinavir/ritonavir:** Use ATV 300 mg once daily + LPV/r 400/100 mg twice daily **Maraviroc:** ↑ MVC AUC – ↓ MVC dose to 150 mg twice daily **Ritonavir:** ATV AUC ↑ 238% – Use ATV 300 mg + RTV 100 mg once daily **Tenofovir:** ATV Cmin ↓ 40% – Use ATV 300 mg + RTV 100 mg + TDF 300 mg once daily
Antacids	**Antacids and buffered medications:** May ↓ ATV concentrations – ATV should be taken 2 hours before or 1 hour after these medications
Antiarrhythmics	**Amiodarone, lidocaine (systemic), quinidine:** ↑ antiarrhythmics – Monitor concentrations
Anticoagulants	**Warfarin:** ↑ warfarin – Monitor INR
Anticonvulsants	**Carbamazepine, phenobarbital, phenytoin:** May ↓ ATV significantly. Avoid co-administration. If no alternatives, use with close monitoring of anticonvulsant levels and consider ATV therapeutic drug monitoring
Antidepressants	**Amitriptyline, imipramine:** ↑ tricyclics – Monitor tricyclic antidepressant concentrations
Antifungals	**Voriconazole:** Potential for bi-directional inhibition; when boosted with RTV, may significantly ↓ voriconazole – Monitor for toxicities and voriconazole therapeutic drug monitoring
Antigout	**Colchicine:** For treatment of gout flares – 0.6 mg (1 tablet) x 1 dose, then 0.3 mg (½ tablet) 1 h later. Do not repeat dose before 3 days. For prophylaxis of gout flares – adjust dose to ¼ original regimen For treatment of familial Mediterranean fever (FMF) – Max: 0.6 mg daily Do not co-administer in patients with hepatic or renal impairment
Antimycobacterials	**Clarithromycin:** ATV AUC ↑ 28%; CL AUC ↑ 94% and may cause QTc prolongation – Use 50% of CL dose (further reduction needed with ESRD). Consider alternative therapy (azithromycin) **Rifabutin:** RFB AUC ↑ 250% – ↓ RFB dose to 150 mg qod or 3x/wk[c]
Bronchodilators	**Salmeterol:** Co-administration not recommended. Consider formoterol

Calcium Channel Blockers	**Diltiazem:** AUC ↑ 125% – Start with 50% diltiazem dose (may prolong PR interval) **Other:** Use with caution; dose titration should be considered; ECG monitoring is recommended
Erectile Dysfunction Agents	**Sildenafil:** May ↑ sildenafil AUC – Use cautiously, start with reduced dose of 25 mg q48h and monitor for adverse effects **Tadalafil:** Substantial ↑ in tadalafil AUC and half-life – Start with a 5-mg dose; do not exceed a single 10-mg dose of tadalafil in 72 hours. If tadalafil is used for pulmonary hypertension, see "Pulmonary Hypertension Agents" **Vardenafil:** May ↑ vardenafil AUC – Start with 2.5-mg dose; do not exceed a single 2.5-mg dose of vardenafil in 72 hours
H_2 Receptor Antagonists	**Avoid co-administration if possible. If co-administration is needed:** **For therapy-naïve patients:** ATV 300 mg/RTV 100 mg once daily ≥10 hours after H2 blocker; 40 mg famotidine twice daily (Max) **For therapy-experienced patients**: ATV 300 mg/RTV 100 mg once daily administered >10 hours after H2 blocker; 20 mg famotidine twice daily (Max). ATV 400 mg/RTV 100 mg if patient also taking TDF and H2 blocker ↓ ATV concentrations – Give ATV 2 hours before or 10 hours after H2 blocker
Immunosuppressants	**Cyclosporine, sirolimus, tacrolimus:** significant ↑ immunosuppressants – Monitor immunosuppressant concentrations
Lipid-Lowering Agents	**Atorvastatin:** May ↑ ATO substantially – Use lowest possible starting dose (10mg) of ATO with careful monitoring
Oral Contraceptives	**Ethinyl estradiol (EE), norethindrone:** Co-administered with ATV/RTV, OC should contain at least 35 mcg EE. Co-administered with ATV without RTV, OC should contain no more than 30 mcg EE. If other OC are used, use alterative method of nonhormonal contraceptive. May ↑ progesterone exposure substantially
Proton-pump Inhibitors	**For ARV-naïve patients**: Do not exceed 20 mg omeprazole – Take 12 hours prior to ATV 300 mg/RTV 100 mg dose, but not recommended by most experts **For ARV-experienced patients**: Do not use proton-pump inhibitors
Pulmonary Hypertension Agents	**Bosentan:** In patients already taking boosted ATV for ≥10 days, co-administer bosentan at a reduced dose of 62.5 mg once daily or qod based on tolerability. If patient is already taking bosentan, discontinue bosentan for ≥36 hrs prior to initiating boosted ATV. After boosted ATV has been given for >10 days, once daily or qod bosentan can be reintroduced. Co-administration of bosentan and ATV without RTV is not recommended. **Tadalafil:** In patients already taking boosted ATV for ≥1 wk, co-administer tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability. In patients already taking tadalafil, avoid use of tadalafil during initiation of boosted ATV. Stop tadalafil ≥24 h prior to starting boosted ATV. At least ≥1 wk after initiating boosted ATV, resume tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability.

With CYP2C8 substrates (e.g., paclitaxel, repaglinide)	**Unboosted ATV may ↑ CYP2C8 substrates.** Monitor closely with co-administration

[a] Cases of worsening glycemic control in patients with preexisting diabetes, and cases of new-onset diabetes including diabetic ketoacidosis have been reported with the use of all protease inhibitors.
[b] Can be used with caution as a single dose in a monitored situation for procedural sedation.
[c] Rifabutin 3x/wk is recommended if CD4 count <100 cells/mm^3.

DARUNAVIR (DRV) *(Updated April 2010)*	
Trade Name	Prezista
Classification	Protease Inhibitor
Form	75, 150, 300-, 400-, 600-mg tablets
Dosing Recommendations	Must be co-administered with ritonavir (RTV) – **For ARV-naïve patients:** DRV 800 mg + RTV 100 mg once daily with food **For ARV-experienced patients:** DRV 600 mg + RTV 100 mg twice daily with food
Hepatic Impairment Dosing	No dose adjustment necessary for patients with either mild or moderate hepatic impairment. No data available for patients with severe hepatic impairment – not recommended for use in patients with severe hepatic impairment
Food Effect	Food increases AUC and Cmax 30%
Oral Bioavailability	37-82%
Serum Half-life	15 hours
Route of Metabolism	P450 cytochrome 3A4 inhibitor and substrate (DVR/r co-administration has a net CYP3A4 inhibitory effect)
Storage	Room temperature
Adverse Events	Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with DVR/RTV. Patients with preexisting liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatitis. If there is evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients receiving DRV/RTV, interruption or discontinuation of treatment must be considered. Severe skin rash, including erythema multiforme and Stevens-Johnson Syndrome, has been reported – Discontinue if severe rash develops. Rare events of hypersensitivity including facial edema and rhabdomyolysis associated with co-administration with HMG-CoA reductase inhibitors. Angioedema and urticaria have been reported with DRV/r. Osteonecrosis has been associated with DRV/r-based regimen. PI class adverse effects that include – GI intolerance, headache, nasopharyngitis, lipodystrophy syndrome, hyperglycemia, increased triglycerides and/or cholesterol, transaminase elevation. Contains a sulfonamide moiety – Use with caution in patients with severe sulfa allergy.
FDA Pregnancy Category	C Not embryotoxic or teratogenic in mice, rats, and rabbits. Based on animal studies, serum concentrations may be significantly decreased in pregnancy

Long-Term Animal Carcinogenicity Studies	Not determined
Animal Teratogen Studies	None
Black Box Warnings	None
Drugs to Avoid	**As part of the ARV regimen:** Lopinavir/ritonavir Saquinavir Tipranavir/ritonavir Alfuzosin, alprazolam, astemizole, cisapride, ergot derivatives, lovastatin, midazolam, phenobarbital, phenytoin, pimozide, ranolazine, rifampin, high-dose sildenafil, simvastatin, St. John's wort, terfenadine, triazolam
Cautious Use or Dose Adjustment	
Antiretrovirals	**Atazanavir:** Dose ATV 300 mg once daily + DRV/r 600/100 mg twice daily **Didanosine:** Administer ddI 1 hr before or 2 hr after DRV/r **Efavirenz:** EFV AUC and Cmin ↑ 21% and 17%, respectively; DRV Cmin ↓ 31% – Studied dose lower than FDA approved dose. Consider DRV/r 600/100 mg twice daily with EFV 600 mg qhs or DRV/r 900/100 mg once daily (PI-naïve only) with EFV 600 mg qhs. **Etravirine:** DRV AUC ↑ 15%. ETR AUC and Cmin ↓ 37% and 49%, respectively. Good clinical data with co-administration. Use standard dose **Indinavir:** IDV AUC and Cmin ↑ 23% and 125%, respectively; DRV AUC and Cmin ↑ 24% and 44%, respectively. Dose not established – Co-administration may ↑ risk of nephrolithiasis **Maraviroc:** ↑ MVC AUC – ↓ MVC dose to 150 mg twice daily **Nevirapine:** DRV and NVP AUC ↑ 24% and 27%, respectively. Limited clinical data; consider standard dose **Raltegravir:** Usual dose **Ritonavir:** DRV AUC ↑, Cmax ↑, Cmin ↑
Antiarrhythmics	May ↑ antiarrhythmics (amiodarone, dofetilide, propafenone, flecainide, quinidine) – Avoid or use with caution. Monitor concentrations of antiarrhythmics
Anticoagulants	**Warfarin:** ↓ S-warfarin AUC 21% – Monitor INR closely with co-administration
Anticonvulsants	**Carbamazepine:** No significant ↓ in DRV/r AUC. Carbamazepine serum concentrations may be ↑. Monitor carbamazepine serum concentrations with co-administration
Antidepressants	**Trazodone:** ↑ Trazodone – Use with caution and consider a lower dose of trazodone **Paroxetine:** Paroxetine AUC ↓ 39% **Sertraline:** Sertraline AUC ↓ by 49%

Antifungals	**Itraconazole:** Itraconazole AUC may be ↑. Monitor itraconazole serum concentrations with co-administration **Ketoconazole:** Ketoconazole AUC ↑ 212%; DRV AUC ↑ 42% – Ketoconazole dose should not exceed 200 mg once daily **Voriconazole:** Voriconazole AUC may be ↓. Monitor voriconazole serum concentrations with co-administration
Antigout	**Colchicine:** For treatment of gout flares – 0.6 mg (1 tablet) x 1 dose, then 0.3 mg (½ tablet) 1 h later. Do not repeat dose before 3 days. For prophylaxis of gout flares – adjust dose to ¼ original regimen For treatment of familial Mediterranean fever (FMF) – Max: 0.6 mg daily Do not co-administer in patients with hepatic or renal impairment
Antimycobacterials	**Clarithromycin:** CL AUC ↑ 57%. For patients with: CrCl 30-60 mL/min: dose CL at 250 mg q12h CrCl <30 mL/min: dose CL at 250 mg once daily Avoid with QTc prolongation **Rifabutin:** Administer RFB dose at 150 mg every other day; monitor for adverse events (i.e., uveitis)
Bronchodilators	**Salmeterol:** Co-administration not recommended. Consider formoterol
Calcium Channel Blockers	May ↑ calcium channel blockers – Use with caution and monitor patients
Corticosteroids	**Fluticasone propionate:** Use with caution and consider alternatives (beclomethasone) for long-term use
Erectile Dysfunction Agents	**Sildenafil:** do not exceed a single dose of 25 mg in 48 hr. High-dose sildenafil used for pulmonary hypertension is not recommended **Tadalafil:** do not exceed a single dose of 10 mg in 72 hr **Vardenafil:** do not exceed a single dose of 2.5 mg in 72 hr
Immunosuppressants	↑ AUC immunosuppressants (cyclosporine, tacrolimus, sirolimus) – Monitor concentration of immunosuppressive agent
Lipid-Lowering Agents	**Atorvastatin:** ATO ↑ by 4-fold – Start with atorvastatin 10 mg once daily titrate slowly, and monitor carefully **Pravastatin:** Pravastatin AUC ↑ 81% – Start with 10 mg and titrate slowly
Oral Contraceptives	**Ethinyl estradiol/norethindrone:** EE and norethindrone AUC ↓ by 44% and 14% respectively – Use alternative or additional method of contraception
Pulmonary Hypertension Agents	**Bosentan:** In patients already taking boosted DRV for ≥10 days, co-administer bosentan at a reduced dose of 62.5 mg once daily or qod based on tolerability. If patient is already taking bosentan, discontinue bosentan for ≥36 hrs prior to initiating boosted DRV. After boosted DRV has been given for >10 days, once daily or qod bosentan can be reintroduced.

	Tadalafil: In patients already taking boosted DRV for ≥1 wk, co-administer tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability. In patients already taking tadalafil, avoid use of tadalafil during initiation of boosted DRV. Stop tadalafil ≥24 h prior to starting boosted DRV. At least ≥1 wk after initiating boosted DRV, resume tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability.
Selective Serotonin Reuptake Inhibitors (SSRIs)	**Paroxetine, sertraline:** ↓ SSRIs (sertraline and paroxetine) – titrate dose to therapeutic effect – Monitor patients starting DRV who are already receiving stable dose of SSRI
Synthetic Narcotics	**Methadone:** May ↓ R-methadone AUC 26% – Monitor and titrate dose to effect

FOSAMPRENAVIR (FPV)* *(Updated April 2010)*	
Trade Name	Lexiva
Classification	Protease Inhibitor
Form	700-mg tablets; 50-mg/mL oral solution
Dosing Recommendations	**For ARV-naïve patients:** FPV 1400 mg + RTV 100 once daily ***or*** FPV 700 mg + RTV 100 mg twice daily ***or*** FPV 1400 mg twice daily (use only in PI-naïve patients who can not tolerate RTV) **For PI-experienced patients:** FPV 700 mg + RTV 100 mg twice daily
Hepatic Impairment Dosing	Child-Pugh Score 5-6: 700 mg twice daily without RTV (therapy-naïve) ***or*** FPV 700 twice daily + RTV 100 mg once daily (therapy-experienced or therapy naive) Child-Pugh Score 7-9: 700 mg twice daily without RTV (therapy-naïve) ***or*** FPV 450 mg twice daily + RTV 100 mg once daily (therapy-experienced or therapy-naive) Child-Pugh Score 10-15: Use with caution due to limited clinical data. Consider FPV 350 mg twice daily (therapy-naïve) ***or*** FPV 300 mg twice daily + RTV 100 mg once-daily (therapy-naïve or PI-experienced) No data with FPV/r in patients with severe hepatic impairment
Food Effect	**Tablets** – take with or without food **Oral solution** – take without food
Oral Bioavailability	Not established
Serum Half-life	7.7 hours
Route of Metabolism	Hepatic cytochrome P450 3A4 inhibitor, inducer, and substrate
Storage	Room temperature
Adverse Events	Myocardial infarction and hypercholesterolemia Increases in cholesterol[a] GI intolerance, nausea, vomiting, diarrhea, rash, headache Transaminase elevation, hyperglycemia,[b] fat redistribution and lipid abnormalities[c] Possible increased bleeding episodes in patients with hemophilia Nephrolithiasis – rare
FDA Pregnancy Category	C. FPV AUC decreased 36% in the third trimester, but trough adequate in PI-naïve patients.
Long-Term Animal Carcinogenicity Studies	Not completed Studies for amprenavir showed an increase in the incidence of hepatocellular adenomas plus carcinoma in male rats and mice

Animal Teratogen Studies	No major effects on embryo-fetal development in rats and rabbits; increased incidence of abortion in rabbits
Black Box Warnings	None
Drugs to Avoid	**As part of the ARV regimen:** Delavirdine Etravirine (clinical significance unknown) Lopinavir/ritonavir Tipranavir/ritonavir Alfuzosin, alprazolam, astemizole, bepridil, cisapride, ergot derivatives, ethinyl estradiol, garlic supplements, lovastatin, midazolam,[d] norethindrone, pimozide, ranolazine, rifampin, rifapentine, high-dose sildenafil, simvastatin, St. John's wort, terfenadine, triazolam
Cautious Use or Dose Adjustment	
Antiretrovirals	**Efavirenz:** FPV Cmin ↓ 36% when FPV 1400 mg + RTV 200 mg once daily is used – Use FPV 1400 mg + RTV 300 mg once daily or FPV 700 mg + RTV 100 mg twice daily **Maraviroc:** ↑ MVC AUC – ↓ MVC dose to 150 mg twice daily **Ritonavir:** FPV AUC ↑ 100%, Cmin ↑ 400% when combined with 200 mg RTV – ARV-experienced patients should receive RTV-boosted regimen (FPV 700 mg + RTV 100 mg twice daily)
Antiarrhythmics	**Amiodarone, lidocaine (systemic), quinidine:** ↑ antiarrhythmics – Monitor concentrations
Anticoagulants	**Warfarin:** ↑ or ↓ warfarin – Monitor INR
Anticonvulsants	**Carbamazepine, phenobarbital, phenytoin:** May ↓ FPV levels substantially – Monitor anticonvulsant levels and virologic response. Consider obtaining FPV levels
Antidepressants	**Amitriptyline, imipramine:** ↑ tricyclics – Monitor tricyclic antidepressant concentrations **Paroxetine:** Significant ↓ paroxetine – titrate to effect
Antifungals	**Itraconazole, ketoconazole:** FPV and itra/keto ↑ – Consider ↓ itra/keto dose if dose is > 400 mg/day. If FPV is boosted with RTV, use with caution; do not exceed 200 mg/day itra/keto **Voriconazole:** Potential for bi-directional inhibition; when boosted with RTV, may significantly ↓ voriconazole – Monitor voriconazole serum concentrations and for toxicities
Antigout	**Colchicine:** For treatment of gout flares – If FPV is given without RTV, 1.2 mg (2 tablets) x 1 dose. Do not repeat dose before 3 days. For prophylaxis of gout flares – adjust dose to ½ original regimen For treatment of familial Mediterranean fever (FMF) – Max: 1.2 mg daily Do not co-administer in patients with hepatic or renal impairment
Antimycobacterials	**Rifabutin:** FPV AUC ↓ 15%; RFB ↑ 193% – ↓ RFB dose to 150 mg once daily or 300 mg 3x/wk with unboosted FPV.[d] If FPV is boosted with RTV, ↓ RFB dose to 150 mg qod or 3x/wk[e]

Bronchodilators	**Salmeterol:** Co-administration not recommended. Consider formoterol
Calcium Channel Blockers	↑ calcium channel blockers – Use with caution
Corticosteroids	**Dexamethasone:** ↓ FPV – Use with caution
Erectile Dysfunction Agents	**Sildenafil:** Sildenafil AUC ↑ 2- to 11-fold – Use cautiously, start with reduced dose of 25 mg q48h and monitor for adverse effects **Tadalafil:** Substantial ↑ in tadalafil AUC and half-life – Start with a 5-mg dose; do not exceed a single 10-mg dose of tadalafil in 72 hours **Vardenafil:** May ↑ vardenafil AUC – Start with 2.5-mg dose; do not exceed a single 2.5-mg dose of vardenafil in 72 hours
Histamine H2 Blockers	**FPV** ↓ 30% – Use with caution; when using boosted FPV, interaction is unlikely to be significant
Immunosuppressants	**Cyclosporine, tacrolimus, rapamycin:** ↑ immunosuppressants – Monitor immunosuppressant concentrations
Lipid-Lowering Agents	**Atorvastatin:** ATO AUC ↑ 150% – Max ATO dose 20 mg/day; use with careful monitoring or consider using alternative agent
Oral Contraceptives	**Ethinyl estradiol/norethindrone**: Use alternative form of birth control
Proton Pump Inhibitors	No significant interaction
Pulmonary Hypertension Agents	**Bosentan:** In patients already taking boosted FPV for ≥10 days, co-administer bosentan at a reduced dose of 62.5 mg once daily or qod based on tolerability. If patient is already taking bosentan, discontinue bosentan for ≥36 hrs prior to initiating boosted FPV. After boosted FPV has been given for >10 days, once daily or qod bosentan can be reintroduced. **Tadalafil:** In patients already taking boosted FPV for ≥1 wk, co-administer tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability. In patients already taking tadalafil, avoid use of tadalafil during initiation of boosted FPV. Stop tadalafil ≥24 h prior to starting boosted FPV. At least ≥1 wk after initiating boosted FPV, resume tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability.
Synthetic Narcotics	**Methadone:** Methadone ↓ 13%; FPV Cmin ↓ 25% – Monitor and titrate methadone if needed. No withdrawal symptoms observed

* Because of the availability of fosamprenavir, amprenavir capsules are no longer available, used, or recommended. Fosamprenavir oral solution is for patients unable to tolerate pills or for short-term use in patients with an NG or J tube.

[a] Triglyceride and cholesterol testing should be performed prior to initiating FPV; monitor lipid profile.

[b] Cases of worsening glycemic control in patients with preexisting diabetes, and cases of new-onset diabetes including diabetic ketoacidosis have been reported with the use of all protease inhibitors.

[c] Discontinuation of PIs may be required to reverse fat redistribution. Patients with hypertriglyceridemia or hypercholesterolemia should be evaluated for risks for cardiovascular events and pancreatitis.

[d] Can be used with caution as a single dose in a monitored situation for procedural sedation.

[e] Rifabutin 3x/wk is recommended if CD4 count <100 cells/mm^3.

INDINAVIR (IDV) *(Updated April 2010)*	
Trade Name	Crixivan
Classification	Protease Inhibitor
Form	100-, 200-, 333-, 400-mg capsules
Dosing Recommendations	IDV 800/RTV 100 mg twice daily ***or*** IDV 400/RTV 400 mg twice daily (no longer recommended due to high GI intolerance) ***or*** IDV 800 mg q8h (lower barrier to PI-resistance)
Hepatic Impairment Dosing	Mild to moderate hepatic impairment due to cirrhosis: 600 mg q8h
Food Effect	**Unboosted:** Take on empty stomach 1 hour before or 2 hours after meals; food ↓ AUC 77%. May take with skim milk or low-fat meal. Drink plenty of fluids (8-10 cups/day) Grapefruit juice ↓ IDV AUC 26% [a]; 1 g/day of Vitamin C ↓ IDV AUC 14%, ↓ Cmin 32% **Boosted:** No food effect
Oral Bioavailability	65% (on empty stomach)
Serum Half-life	1.5-2 hours
Route of Metabolism	P450 cytochrome 3A4 inhibitor and substrate
Storage	Room temperature
Adverse Events	GI intolerance, nausea, headache, asthenia, blurred vision, dizziness, rash, metallic taste, alopecia, paronychia Nephrolithiasis, hyperglycemia,[b] fat redistribution and lipid abnormalities,[c] thrombocytopenia, hemolytic anemia, possible increased bleeding episodes in patients with hemophilia, increased indirect bilirubinemia (inconsequential)
FDA Pregnancy Category	C (potential ↑ bilirubin and nephrolithiasis in neonates)
Long-Term Animal Carcinogenicity Studies	Not completed
Animal Teratogen Studies	Negative (but extra ribs in rodents)
Black Box Warnings	None
Drugs to Avoid	**As part of the ARV regimen:** Atazanavir (potential for additive increased indirect bilirubin) Etravirine Tipranavir/ritonavir Alfuzosin, alprazolam, astemizole, cisapride, ergot derivatives, garlic supplements, lovastatin, midazolam,[d] pimozide, ranolazine, rifampin, rifapentine, high-dose sildenafil, simvastatin, St. John's wort, terfenadine, triazolam

Cautious Use or Dose Adjustment	
Antiretrovirals	**Darunavir:** DRV AUC and Cmin ↑ 24% and 44%, respectively; IDV AUC and Cmin ↑ 23% and 125% respectively. Dose not established. Co-administration may increase risk of nephrolithiasis **Delavirdine:** ↑ IDV – ↓ IDV dose to 600 mg q8h **Didanosine:** IDV AUC ↓ 84% – Take IDV 1 hour before or after buffered ddI on an empty stomach (no interaction with ddI EC) **Efavirenz:** IDV ↓ 31% – ↑ IDV dose to 1000 mg q8h, or consider IDV 800 mg + RTV 200 mg q12h **Lopinavir/ritonavir:** ↑ IDV – ↓ IDV dose to 600 mg twice daily or 666 mg twice daily **Maraviroc:** ↑ MVC AUC – ↓ MVC dose to 150 mg twice daily **Nelfinavir:** IDV ↑ 50%; NFV ↑ 80% – Consider IDV 1200 mg + NFV 1250 mg twice daily (limited data) **Nevirapine:** IDV ↓ 28% – ↑ IDV dose to 1000 mg q8h, or consider IDV + RTV **Ritonavir:** IDV ↑ 2- to 5-fold – Use IDV 800 mg + RTV 100 mg twice daily; renal events may be increased with higher IDV Cmax
Anticonvulsants	**Carbamazepine:** Markedly ↓ IDV – Consider phenytoin, phenobarbital, valproic acid, levetiracetam, or topiramate
Antidepressants	**Trazodone:** May lead to substantial ↑ in trazodone – Consider ↓ dose of trazodone
Antifungals	**Itraconazole:** ↓ unboosted IDV dose to 600 mg tid – Do not exceed 200 mg itraconazole twice daily **Ketoconazole:** IDV ↑ 68% – ↓ IDV dose to 600 mg tid **Voriconazole:** No interaction with IDV but when IDV is boosted with RTV, potential for bi-directional inhibition – Monitor for toxicities
Antigout	**Colchicine:** For treatment of gout flares – 0.6 mg (1 tablet) x 1 dose, then 0.3 mg (½ tablet) 1 h later. Do not repeat dose before 3 days. For prophylaxis of gout flares – adjust dose to ¼ original regimen For treatment of familial Mediterranean fever (FMF) – Max: 0.6 mg daily Do not co-administer in patients with hepatic or renal impairment
Antimycobacterials	**Rifabutin:** IDV ↓ 32%; RFB ↑ 204% – ↓ RFB dose to 150 mg once daily or 300 mg 3x/wk.[e] ↑ IDV dose to 1000 mg q8h. If IDV is boosted with RTV, use RFB 150 mg qod + IDV 400 mg + RTV 400 mg twice daily
Bronchodilators	**Salmeterol:** Co-administration not recommended. Consider formoterol
Erectile Dysfunction Agents	**Sildenafil:** Sildenafil AUC ↑ 3-fold – Use cautiously, start with reduced dose of 25 mg q48h and monitor for adverse effects

	Tadalafil: Substantial ↑ in tadalafil AUC and half-life – Start with a 5-mg dose, and do not exceed a single dose of 10 mg in 72 hours **Vardenafil:** Vardenafil ↑ 16-fold; IDV (unboosted) ↓ 30% – For unboosted IDV, consider using sildenafil instead; for IDV + RTV, do not exceed 2.5 mg vardenafil in 72 hours
Lipid-Lowering Agents	**Atorvastatin:** Potential for ATO AUC ↑ – Use lowest possible starting dose of ATO with careful monitoring (consider pravastatin or rosuvastatin)
Pulmonary Hypertension Agents	**Avoid unboosted IDV with bosentan and tadalafil co-administration.** **Bosentan:** In patients already taking boosted IDV for ≥10 days, co-administer bosentan at a reduced dose of 62.5 mg once daily or qod based on tolerability. If patient is already taking bosentan, discontinue bosentan for ≥36 hrs prior to initiating boosted IDV. After boosted IDV has been given for >10 days, once daily or qod bosentan can be reintroduced. **Tadalafil:** In patients already taking boosted IDV for ≥1 wk, co-administer tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability. In patients already taking tadalafil, avoid use of tadalafil during initiation of boosted IDV. Stop tadalafil ≥24 h prior to starting boosted IDV. At least ≥1 wk after initiating boosted IDV, resume tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability.

[a] Contrary to package insert, one study found no effect on IDV pharmacokinetics when given with orange juice or grapefruit juice (Penzak SR, et al. *J Clin Pharmacol* 2002;42:1165).
[b] Cases of worsening glycemic control in patients with preexisting diabetes, and cases of new-onset diabetes including diabetic ketoacidosis have been reported with the use of all protease inhibitors.
[c] Discontinuation of PIs may be required to reverse fat redistribution. Patients with hypertriglyceridemia or hypercholesterolemia should be evaluated for risks for cardiovascular events and pancreatitis.
[d] Can be used with caution as a single dose in a monitored situation for procedural sedation.
[e] Rifabutin 3x/wk is recommended if CD4 count <100 cells/mm^3.

LOPINAVIR/RITONAVIR (LPV/R) *(Updated April 2010)*	
Trade Name	Kaletra
Classification	Protease Inhibitor
Form[a]	LPV 200 mg/RTV 50 mg film-coated tablets LPV 100 mg/RTV 25 mg film-coated tablets LPV 80 mg/RTV 20 mg per mL oral solution (contains 42% alcohol)
Dosing Recommendations	LPV 400 mg/RTV 100 mg (2 tablets) twice daily with or without food ***or*** LPV 800 mg/RTV 200 mg (4 tablets) once daily* with or without food[b] ***or*** LPV 400 mg/RTV 100 mg (5 mL) twice daily with food ***or*** LPV 800 mg/RTV 200 mg (10 mL) once daily* with food[b] * FDA recommended only in patients with <3 LPV resistance-associated substitutions, but some experts would recommend LPV/r 400/100 mg twice-daily in these patients
Hepatic Impairment Dosing	Use with caution in patients with hepatic impairment
Food Effect	**Tablets:** May take with or without food; swallow whole **Oral solution:** Must take with food. To increase absorption by 50%-80%, take with meal containing >15 g of fat
Oral Bioavailability	Not determined in humans
Serum Half-life	5-6 hours
Route of Metabolism	P450 cytochrome 3A4 inhibitor and substrate (may be an inducer at steady-state)
Storage	**Tablets:** store at room temperature. Do not expose to high humidity outside original container for longer than 2 weeks **Refrigerated oral solution:** stable until expiration date on label. If stored at room temperature, stable for 2 months
Adverse Events	GI intolerance, nausea, vomiting, diarrhea, asthenia Rare: Pancreatitis, including marked triglyceride elevations; in some cases, fatalities have been observed PR interval prolongation may occur. Second- and third-degree AV block have been reported. Use with caution in patients with underlying structural heart disease, preexisting conduction system abnormalities, ischemic heart disease or cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities. The impact on the PR interval of co-administration of LPV/r with other drugs that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digoxin and atazanavir) has not been evaluated; co-administration of LPV/r with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A. QT interval prolongation and torsade de pointes have been reported. Avoid use in patients with congenital long QT syndrome, those with hypokalemia, and with other drugs that prolong the QT interval.

	Elevated serum transaminase, hyperglycemia,[c] fat redistribution and lipid abnormalities,[d] possible increased bleeding episodes in patients with hemophilia Increased potential for sildenafil-associated adverse events such as visual abnormalities, hypotension, prolonged erections, and syncope when co-administered when sildenafil is used for the treatment of pulmonary arterial hypertension. Avoid high-dose sildenafil and use with caution.
FDA Pregnancy Category	C
Long-Term Animal Carcinogenicity Studies	Not completed
Animal Teratogen Studies	Negative (but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses)
Black Box Warnings	None
Drugs to Avoid	**As part of the ARV regimen:** Darunavir/ritonavir Tipranavir/ritonavir Alfuzosin, alprazolam, astemizole, cisapride, ergot derivatives, flecainide, fluticasone, garlic supplements, lovastatin, midazolam,[e] pimozide, propafenone, ranolazine, rifampin,[f] rifapentine, high-dose sildenafil, salmeterol, simvastatin, St. John's wort, terfenadine, triazolam
Cautious Use or Dose Adjustment	
Antiretrovirals	**Atazanavir:** ATV 300 mg once daily plus LPV/r 400/100 mg twice daily. Monitor for PR interval prolongation **Efavirenz:** LPV AUC ↓ 40% – ↑ LPV/r dose to 500/125 mg twice daily with food. LPV/r once daily should not be co-administered with EFV **Etravirine:** Use standard dose **Fosamprenavir:** Not recommended by some. Consider FPV 1400 mg twice daily plus LPV/r 500/125 mg twice daily. Consider therapeutic drug monitoring. LPV/r once daily should not be co-administered with FPV **Indinavir:** ↑ IDV – ↓ IDV dose to 600 mg twice daily or 666 mg twice daily **Maraviroc:** ↑ MVC AUC – ↓ MVC dose to 150 mg twice daily **Nelfinavir: ↓ NFV AUC –** Not recommended by some. ↑ LPV/r dose to 500/125 mg twice daily with food. LPV/r once daily should not be co-administered with NFV **Nevirapine:** LPV Cmin ↓ 55% – ↑ LPV/r dose to 500/125 mg twice daily with food. LPV/r once daily should not be co-administered with NVP **Raltegravir:** Use standard dose **Saquinavir:** SQV AUC and Cmin ↑ – Use SQV 1000 mg twice daily

Antiarrhythmics	**Amiodarone, bepridil, lidocaine (systemic), quinidine:** ↑ antiarrhythmics – Use with caution. Monitor concentrations of antiarrhythmics
Anticonvulsants	**Carbamazepine, phenobarbital, phenytoin:** Levels ↑ when co-administered with RTV – Use with caution; monitor anticonvulsant levels. Do not use with once-daily dosing of LPV/r. **Valproic acid:** May ↓ valproic acid. LPV AUC ↑ 75% **Lamotrigine:** LPV not affected, but lamotrigine AUC ↓ 50%. Titrate to effect
Antidepressants	**Trazodone:** Trazodone AUC ↑ 240%, Cmax ↑ 34% – Use lowest dose; monitor for CNS and CV adverse effects **Bupropion:** Bupropion AUC ↓ 46%. Titrate to effect
Antifungals	**Itraconazole:** Itraconazole ↑ – Use with caution, do not exceed 200 mg itraconazole daily **Ketoconazole:** LPV AUC ↓ 13%; keto ↑ 3-fold – Use with caution, do not exceed 200 mg keto daily **Voriconazole:** Potential for bi-directional inhibition; when boosted with RTV, may significantly ↓ voriconazole – Monitor for toxicities and voriconazole serum concentrations (target trough >2 mcg/mL)
Antigout	**Colchicine:** For treatment of gout flares – 0.6 mg (1 tablet) x 1 dose, then 0.3 mg (½ tablet) 1 h later. Do not repeat dose before 3 days. For prophylaxis of gout flares – adjust dose to ¼ original regimen For treatment of familial Mediterranean fever (FMF) – Max: 0.6 mg daily Do not co-administer in patients with hepatic or renal impairment
Antihypertensive	**Beta-blocker:** May ↑ PR interval; use with close monitoring **Calcium channel blocker:** May ↑ PR interval; use with close monitoring
Antimycobacterials	**Clarithromycin:** CL AUC ↑ 77% – Adjust CL dose for moderate and severe renal impairment. For creatinine clearance 30-60 mL/min, administer clarithromycin 500 mg orally once daily. For creatine clearance <30 mL/min administer clarithromycin 250 mg orally once daily. Monitor for QTc prolongation with co-administration **Rifabutin:** RFB AUC ↑ 3-fold; 25-O-desacetyl metabolite ↑ 47.5-fold – ↓ RFB dose to 150 mg qod. Monitor rifabutin serum concentrations
Bronchodilators	**Salmeterol:** Co-administration not recommended. Consider formoterol
Cardiac Glycosides	**Digoxin:** Digoxin AUC ↑ 81% with LPV/r co-administration. Monitor digoxin serum concentrations and PR interval with co-administration
Erectile Dysfunction Agents	**Sildenafil:** Sildenafil AUC ↑ 11-fold when co-administered with RTV – Use cautiously, start with reduced dose of 25 mg q48h, and monitor for adverse effects **Tadalafil:** Substantial ↑ in tadalafil AUC and half-life – Start with a 5-mg dose, and do not exceed a single 10-mg dose in 72 hours **Vardenafil:** May substantially ↑ vardenafil AUC – Start with a 2.5-mg dose, and do not exceed a single 2.5-mg dose in 72 hours

Lipid-Lowering Agents	**Atorvastatin:** ATO AUC ↑ 5.88-fold – Use lowest possible starting dose of ATO with careful monitoring. Consider pravastatin **Rosuvastatin:** ROS AUC ↑ 108%. Use lowest possible starting dose 5-10 mg/day **Pravastatin:** Pravastatin AUC ↑ 33%. Use standard dose
Oral Contraceptives	**Ethinyl estradiol:** EE ↓ 42% – Use alternative or additional method of contraception
Pulmonary Hypertension Agents	**Bosentan:** LPV/r ↑ bosentan AUC 48-fold on day 4 and 5-fold on day 10 (steady-state). Co-administer bosentan at a reduced dose of 62.5 mg only after RTV dosing has reached steady-state (after 10 days of RTV). If patient is taking bosentan, discontinue bosentan for ≥36 hrs prior to initiating RTV and restart bosentan 62.5 mg 10 days after initiating RTV **Tadalafil:** In patients already taking LPV/r for ≥1 wk, co-administer tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability. In patients already taking tadalafil, avoid use of tadalafil during initiation of LPV/r. Stop tadalafil ≥24 h prior to starting LPV/r. At least ≥1 wk after initiating LPV/r, resume tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability.

[a] Capsules discontinued in early 2006.
[b] Lopinavir/ritonavir should not be administered as a once-daily regimen in combination with efavirenz, nevirapine, fosamprenavir, or nelfinavir.
[c] Cases of worsening glycemic control in patients with preexisting diabetes, and cases of new-onset diabetes including diabetic ketoacidosis have been reported with the use of all protease inhibitors.
[d] Discontinuation of PIs may be required to reverse fat redistribution. Patients with hypertriglyceridemia or hypercholesterolemia should be evaluated for risks for cardiovascular events and pancreatitis.
[e] Can be used with caution as a single dose in a monitored situation for procedural sedation.
[f] In one small study, an increased dose of LPV/r 800/200 mg was used to offset rifampin-inducing activity of LPV; the standard dose of rifampin was used. 28% of patients discontinued this regimen due to increases in LFTs. The safety of this combination has not been established, and if used, close monitoring, including measuring LPV concentrations, is recommended.

NELFINAVIR (NFV) *(Updated April 2010)*	
Trade Name	Viracept
Classification	Protease Inhibitor
Form	250-, 625-mg tablets, 50 mg/g oral powder
Dosing Recommendations	750 mg tid or 1250 mg twice daily
Hepatic Impairment Dosing	Should not be used or used with caution in patients with moderate to severe hepatic impairment
Food Effect	Levels increase 2- to 3-fold; take with meal or snack To increase absorption, take with meal containing 500-1000 kcal (20-50% fat)
Oral Bioavailability	20-80%
Serum Half-life	3.5-5 hours
Route of Metabolism	P450 cytochrome 3A4 inhibitor (less than ritonavir)
Storage	Room temperature
Adverse Events	Diarrhea (most common), hyperglycemia,[a] serum transaminase elevation, fat redistribution and lipid abnormalities [b] Possible increased bleeding episodes in patients with hemophilia
FDA Pregnancy Category	B (of 757 births reported to the Registry, the rate of birth defects was comparable to the general population)
Long-Term Animal Carcinogenicity Studies	Not completed
Animal Teratogen Studies	Negative
Black Box Warnings	None
Drugs to Avoid	**As part of the ARV regimen:** Etravirine Tipranavir/ritonavir Alfuzosin, alprazolam, amiodarone, astemizole, cisapride, ergot derivatives, garlic supplements, lovastatin, midazolam,[c] pimozide, proton pump inhibitors, quinidine, ranolazine, rifampin, rifapentine, high-dose sildenafil, simvastatin, St. John's wort, terfenadine, triazolam
Cautious Use or Dose Adjustment	
Antiretrovirals	**Indinavir:** Not recommended because of high pill burden **Maraviroc:** ↑ MVC AUC – ↓ MVC dose to 150 mg twice daily **Ritonavir:** NFV ↑ 1.5-fold – Consider NFV 500-750 mg + RTV 400 mg twice daily (limited data; only a modest benefit with RTV boosting) **Saquinavir:** Not recommended because of high pill burden

Anticonvulsants	**Carbamazepine, phenobarbital, phenytoin:** May ↓ NFV levels substantially – Monitor anticonvulsant levels and virologic response. Consider obtaining NFV levels (target Cmin >0.8)
Antifungals	**Voriconazole:** Potential for bi-directional inhibition – Monitor for toxicities
Antigout	**Colchicine:** For treatment of gout flares – 0.6 mg (1 tablet) x 1 dose, then 0.3 mg (½ tablet) 1 h later. Do not repeat dose before 3 days. For prophylaxis of gout flares – adjust dose to ¼ original regimen For treatment of familial Mediterranean fever (FMF) – Max: 0.6 mg daily Do not co-administer in patients with hepatic or renal impairment
Antimycobacterials	**Azithromycin:** ↑ azithromycin – Monitor for adverse effects **Rifabutin:** NFV AUC ↓ 32%; RFB ↑ 207% – ↓ RFB dose to 150 mg once daily or 300 mg 3x/wk.[d] ↑ NFV dose to 1000 mg q8h. If NFV is boosted with RTV, use RFB 150 mg qod + NFV 500-750 mg twice daily + RTV 400 mg twice daily (limited data)
Bronchodilators	**Salmeterol:** Co-administration not recommended. Consider formoterol
Erectile Dysfunction Agents	**Sildenafil:** Sildenafil AUC ↑ 2- to 11-fold – Use cautiously, start with reduced dose of 25 mg q48h and monitor for adverse effects **Tadalafil:** Substantial ↑ in tadalafil AUC and half-life – Start with a 5-mg dose; do not exceed a single 10-mg dose of tadalafil in 72 hours **Vardenafil:** May ↑ vardenafil AUC – Start with 2.5-mg dose; do not exceed a single 2.5-mg dose of vardenafil in 72 hours
Lipid-Lowering Agents	**Atorvastatin:** ATO AUC ↑ 74% – Use lowest possible starting dose of ATO with careful monitoring
Oral Contraceptives	**Ethinyl estradiol:** EE ↓ 47% – Use alternative or additional method of contraception **Norethindrone:** ↓ 18% – Use alternative or additional method of contraception
Pulmonary Hypertension Agents	**Bosentan:** For patients who have been treated with NFV for >10 days, co-administer bosentan at 62.5 mg once daily or qod based on tolerability **Tadalafil:** For patients who have been treated with NFV for >10 days, co-administer tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability
Synthetic Narcotics	**Methadone:** May ↓ methadone levels – Monitor and titrate dose if needed. No significant change in the R-methadone (active). No withdrawal symptoms observed

[a] Cases of worsening glycemic control in patients with preexisting diabetes, and cases of new-onset diabetes including diabetic ketoacidosis have been reported with the use of all protease inhibitors.
[b] Patients with hypertriglyceridemia or hypercholesterolemia should be evaluated for risks for cardiovascular events and pancreatitis.
[c] Can be used with caution as a single dose in a monitored situation for procedural sedation.
[d] Rifabutin 3x/wk is recommended if CD4 cell count <100 cells/mm^3.

RITONAVIR (RTV) *(Updated April 2010)*	
Trade Name	Norvir
Classification	Protease Inhibitor
Form	100-mg capsules; 100-mg tablets; 600 mg/7.5 mL oral solution
Dosing Recommendations	100 – 200 mg once or twice a day in combination with another PI. RTV is used as a pharmacokinetic booster Separate dosing with didanosine (buffered) by 2.5 hours
Hepatic Impairment Dosing	No dose adjustment for mild hepatic impairment; use with caution for moderate to severe hepatic impairment
Food Effect	**Tablets:** Tablets must be taken with food and should be swallowed whole, and not chewed, broken, or crushed **Capsules:** Take with food that contains both protein and fat. Absorption ↑ 15% with food; take with a meal containing >15 g fat
Oral Bioavailability	When tablets are taken with a high-fat or moderate-fat meal, an approximate 22% ↓ in mean AUC and Cmax were observed relative to fasting conditions
Serum Half-life	3-5 hours
Route of Metabolism	P450 cytochrome 3A4 substrate (3A4 >2D6; potent 3A4 inhibitor)
Storage	**Tablets:** Room temperature **Capsules:** Refrigerate (capsules can be left at room temperature ≤30 days) **Oral solution:** Should NOT be refrigerated
Adverse Events	GI intolerance, nausea, vomiting, diarrhea, taste alteration Paresthesias (circumoral and extremities) associated with high-dose RTV >400 mg twice daily. Transaminase elevation and hepatitis, pancreatitis (secondary to elevated triglyceride), asthenia, elevated CPK and uric acid, possible increased bleeding episodes in patients with hemophilia Triglycerides increase >200%, hyperglycemia,[a] fat redistribution and lipid abnormalities[b] QTc and PR interval prolongation with RTV 400 mg twice daily. First-, second-, and third-degree AV block; right bundle branch block have been reported. Use with caution in patients with structural heart disease, with preexisting or at-risk for conduction system abnormalities
FDA Pregnancy Category	B
Long-Term Animal Carcinogenicity Studies	Positive (rodent, liver adenomas and carcinomas in male mice)
Animal Teratogen Studies	Negative (but cryptorchidism in rodents)

Black Box Warnings	Co-administration of ritonavir with certain non-sedating antihistamines (e.g., terfenadine and astemizole), sedative hypnotics (e.g., midazolam and triazolam), antiarrhythmics, or ergot alkaloids may result in potentially serious and/or life-threatening adverse events due to possible effects of ritonavir on hepatic metabolism of certain drugs
Drugs to Avoid	Alfuzosin, alprazolam, amiodarone, astemizole, bepridil, cisapride, desipramine, ergot derivatives, flecainide, fluticasone, garlic supplements, lovastatin, midazolam,[c] pimozide, propafenone, quinidine, ranolazine, rifampin, rifapentine, salmeterol, high-dose sildenafil, simvastatin, St. John's wort, terfenadine, triazolam, voriconazole[d]
Cautious Use or Dose Adjustment	
Antiretrovirals	**Atazanavir:** ATV AUC ↑ 238% – Use ATV 300 mg + RTV 100 mg once daily **Darunavir:** DRV AUC ↑, Cmax ↑, Cmin ↑. ARV-experienced patients: DRV 600 mg twice daily + RTV 100 mg twice daily ARV-naïve patients: DRV 800 mg once daily + RTV 100 mg once daily **Delavirdine:** RTV AUC ↑, Cmax ↑, Cmin ↑. Combination dosing not established **Didanosine (buffered):** Dosing should be separated by 2.5 hours to avoid formulation incompatibility **Etravirine:** Standard doses **Fosamprenavir:** FPV AUC ↑ 100%, Cmin ↑ 400% when combined with 200 mg RTV ARV-experienced patients should receive RTV-boosted regimen: FPV 700 mg twice daily + RTV 100 mg twice daily PI-naïve patients only: FPV 1400 mg once daily + RTV 100-200 mg once daily **Indinavir:** IDV ↑ 2- to 5-fold – Use IDV 800 mg + RTV 100 mg twice daily; renal events may be increased with higher IDV Cmax **Maraviroc:** ↑ MVC AUC – ↓ MVC dose to 150 mg twice daily **Nelfinavir:** NFV ↑ 1.5-fold – Limited clinical data; only a modest benefit with RTV boosting with significant GI intolerance **Raltegravir:** Standard doses **Saquinavir:** SQV ↑ 20-fold – Use SQV 1000 mg + RTV 100 mg twice daily or SQV 400 mg + RTV 400 mg twice daily (higher GI intolerance) **Tipranavir:** TPV AUC ↑, Cmax ↑, Cmin ↑. Use TPV/r 500/200 mg twice daily. Monitor closely for signs of hepatotoxicity
Antialcoholics	**Disulfiram/metronidazole:** RTV liquid formulations contain alcohol, which can produce disulfiram-like reactions when combined with antialcoholics
Antiarrhythmics	**Disopyramide, lidocaine, mexiletine:** Therapeutic concentration monitoring of antiarrhythmics recommended. Monitor closely for conduction abnormalities
Anticoagulants	**Warfarin:** Initial frequent monitoring of the INR during ritonavir and warfarin co-administration is indicated. Increased INR initially, but may require higher warfarin dose after 2 weeks. Monitor closely

Anticonvulsants	**Carbamazepine, phenobarbital, phenytoin:** May ↑ or ↓ anticonvulsant serum levels; may ↓ RTV – Use with caution; monitor anticonvulsant levels (consider valproic acid or levetiracetam)
Antidepressants	**Trazodone:** Trazodone AUC ↑ 240%, Cmax ↑ 34% – Use lowest dose; monitor for CNS and CV adverse effects
Antifungals	**Itraconazole, ketoconazole:** Itra/keto ↑ 3-fold – Use with caution; do not exceed 200 mg itra/keto daily **Voriconazole:** RTV (100 mg twice daily used to boost other PIs) decreases voriconazole by 39%. Consider higher voriconazole dose for invasive fungal disease. Monitor voriconazole serum concentrations
Antigout	**Colchicine:** For treatment of gout flares – 0.6 mg (1 tablet) x 1 dose, then 0.3 mg (½ tablet) 1 h later. Do not repeat dose before 3 days. For prophylaxis of gout flares – adjust dose to ¼ original regimen For treatment of familial Mediterranean fever (FMF) – Max: 0.6 mg daily Do not co-administer in patients with hepatic or renal impairment
Antimycobacterials	**Clarithromycin:** CL ↑ 77% – ↓ CL dose for moderate and severe renal impairment (CrCL <30 ml/min: Use 50% Clarithromycin dose) **Rifabutin:** RFB ↑ 430% – ↓ RFB dose to 150 mg qod or 3x/wk[e]. Consider monitoring RFB serum concentrations
Beta Blockers	**Metoprolol, timolol, carvedilol, propranolol, labetalol:** Beta blockers ↑ – Clinical monitoring of patients recommended
Bronchodilators	**Theophylline:** Theophylline ↓ – May require ↑ in theophylline dosage; consider therapeutic monitoring **Salmeterol:** Co-administration not recommended. Consider formoterol
Calcium Channel Blockers	**Diltiazem, amlodipine, felodipine, nifedipine, verapamil:** Channel blockers ↑ – Consider ↓ dose. Clinical monitoring recommended
Cardiac Glycosides	**Digoxin:** Digoxin AUC ↑ 49% with RTV/SQV co-administration. Use with close monitoring of digoxin serum concentrations
Corticosteroids	**Fluticasone:** Fluticasone ↑ – Co-administration not recommended. Consider beclomethasone **Prednisone:** Prednisolone AUC ↑ 30-40% with RTV (200 mg twice-daily) co-administration. May require lower prednisone dose with long-term co-administration
Erectile Dysfunction Agents	**Sildenafil:** Sildenafil ↑ 11-fold – Use cautiously, start with reduced dose of 25 mg q48h and monitor for adverse effects **Tadalafil:** Tadalafil ↑ 124% – Start with a 5-mg dose, and do not exceed a single dose of 10 mg in 72 hours **Vardenafil:** Vardenafil ↑ 49-fold; RTV ↓ 20% – Start with a 2.5-mg dose, and do not exceed a single 2.5-mg dose in 72 hours
Immunosuppressants	**Cyclosporine, tacrolimus, sirolimus:** Significant ↑ immunosuppressants – Monitor immunosuppressant concentrations closely with appropriate dose reduction

Lipid-Lowering Agents	**Atorvastatin:** ATO ↑ 450% when combined with SQV/RTV – Use lowest possible starting dose (10 mg) of ATO with careful monitoring **Rosuvastatin:** May ↑ rosuvastatin concentrations. With co-administration, start with rosuvastatin 5 mg/d. Use with close monitoring
Narcotic Analgesics	**Meperidine:** ↓ meperidine; ↑ normeperidine (metabolite) – Dosage ↑ and long-term use of meperidine with RTV are not recommended
Neuroleptics	**Perphenazine, risperidone, thioridazine:** ↑ Neuroleptics – Dose ↓ may be necessary
Oral Contraceptives	**Ethinyl estradiol:** EE ↓ 40% – Use alternative or additional method of contraception
Pulmonary Hypertension Agents	**High-dose sildenafil:** Avoid co-administration **Bosentan:** With all RTV-boosted PI co-administration, significant ↑ in bosentan concentrations likely. Co-administer bosentan only after RTV has reached steady-state. In patients taking RTV >10 days: Start bosentan at 62.5 mg once daily or every other day. In patients already taking bosentan: Discontinue bosentan for >36 hrs prior to initiation of RTV-boosted PIs and restart bosentan at 62.5 mg once daily or every other day after RTV has reached steady-state (after 10 days) **Tadalafil:** In patients already taking RTV for ≥1 wk, co-administer tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability. In patients already taking tadalafil, avoid use of tadalafil during initiation of RTV. Stop tadalafil ≥24 h prior to starting RTV. At least ≥1 wk after initiating RTV, resume tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability.
Synthetic Narcotics	**Methadone:** Methadone ↓ 37% – Monitor and titrate dose if needed; S-methadone (inactive) more affected. No withdrawal symptoms observed. Use with caution – may cause prolongation of QTc

[a] Cases of worsening glycemic control in patients with preexisting diabetes, and cases of new-onset diabetes including diabetic ketoacidosis have been reported with the use of all protease inhibitors.
[b] Discontinuation of PIs may be required to reverse fat redistribution. Patients with hypertriglyceridemia or hypercholesterolemia should be evaluated for risks for cardiovascular events and pancreatitis.
[c] Can be used with caution as a single dose in a monitored situation for procedural sedation.
[d] RTV (400 mg q12h) decreased voriconazole AUC by 82%. RTV level was not affected by voriconazole. RTV (400 mg q12h) should not be co-administered with voriconazole. RTV (100 mg twice daily used to boost other PIs) decreases voriconazole by 39%. Use with caution. Monitor voriconazole serum concentrations with co-administration.
[e] Rifabutin 3x/wk is recommended if CD4 count <100 cells/mm^3.

SAQUINAVIR (SQV) *(Updated April 2010)*	
Trade Name	Invirase[a]
Classification	Protease inhibitor
Form	200-mg hard-gel capsules and 500-mg tablets
Dosing Recommendations	Must be co-administered with ritonavir (RTV) – SQV 1000 mg + RTV 100 mg twice daily ***or*** SQV 400 mg + RTV 400 mg twice daily
Hepatic Impairment Dosing	Use with caution in patients with hepatic impairment
Food Effect	Grapefruit juice may increase retention
Oral Bioavailability	4% erratic
Serum Half-life	1-2 hours
Route of Metabolism	P450 cytochrome 3A4 inhibitor and substrate (weak inhibitor)
Storage	Room temperature
Adverse Events	GI intolerance, nausea, diarrhea, headache Elevated transaminase enzymes, possible increased bleeding episodes in patients with hemophilia Hyperglycemia,[b] fat redistribution and lipid abnormalities[c] Use of SQV/RTV in patients with a history of QT interval prolongation, preexisting conduction system disease, ischemic heart disease, cardiomyopathy, or underlying structural heart disease is not recommended. Use of SQV/RTV in patients currently taking Class IA (quinidine) or Class III (amiodarone) antiarrhythmic drugs or other drugs that may prolong the QT or PR interval is not recommended.
FDA Pregnancy Category	B
Long-Term Animal Carcinogenicity Studies	Not completed
Animal Teratogen Studies	Negative
Black Box Warnings	May be used only if it is combined with ritonavir
Drugs to Avoid	**As part of the ARV regimen:** Darunavir/ritonavir Etravirine (when SQV co-administered without RTV) Tipranavir/ritonavir Alfuzosin, alprazolam, amiodarone, astemizole, bepridil, cisapride, ergot derivatives, flecainide, garlic supplements (can be used with boosted SQV), lovastatin, midazolam,[d] pimozide, propafenone, quinidine, ranolazine, rifabutin,[e] rifampin, rifapentine, high-dose sildenafil, simvastatin, St. John's wort, terfenadine, triazolam

Cautious Use or Dose Adjustment	
Antiretrovirals	**Delavirdine:** SQV ↑ 5-fold – ↓ SQV dose to 800 mg tid and monitor transaminase levels **Efavirenz:** SQV ↓ 62%; EFV ↓ 12% – Use SQV 400 mg + RTV 400 mg twice daily **Lopinavir/ritonavir:** SQV AUC and Cmin ↑ – Use SQV 800-1000 mg twice daily **Maraviroc:** ↑ MVC AUC – ↓ MVC dose to 150 mg twice daily **Nelfinavir:** SQV ↑ 3- to 5-fold; NFV ↑ 20% – ↓ SQV dose to 800 mg tid or 1200 mg twice daily **Nevirapine:** SQV ↓ 25% – SQV 400 mg + RTV 400 mg or SQV 1000 mg + RTV 100 mg twice daily **Ritonavir:** SQV ↑ 20-fold – Use SQV 1000 mg + RTV 100 mg twice daily or SQV 400 mg + RTV 400 mg twice daily
Anticoagulants	**Warfarin:** ↑ or ↓ warfarin – Monitor INR
Anticonvulsants	**Carbamazepine, phenobarbital, phenytoin:** May ↓ SQV levels – Monitor anticonvulsant levels. Consider alternative anticonvulsant
Antidepressants	**Amitriptyline, imipramine:** May ↑ tricyclics – Monitor tricyclic antidepressant concentrations
Antifungals	**Ketoconazole:** SQV ↑ 3-fold – If keto dose is >200 mg/day, monitor for excessive diarrhea, nausea, and abdominal discomfort, and adjust doses accordingly **Voriconazole:** Potential for bi-directional inhibition; when boosted with RTV, may significantly ↓ voriconazole – Monitor for toxicities
Antigout	**Colchicine:** For treatment of gout flares – 0.6 mg (1 tablet) x 1 dose, then 0.3 mg (½ tablet) 1 h later. Do not repeat dose before 3 days. For prophylaxis of gout flares – adjust dose to ¼ original regimen For treatment of familial Mediterranean fever (FMF) – Max: 0.6 mg daily Do not co-administer in patients with hepatic or renal impairment
Bronchodilators	**Salmeterol:** Co-administration not recommended. Consider formoterol
Cardiac Glycosides	**Digoxin:** Digoxin AUC ↑ 49% with RTV/SQV co-administration. Use with close monitoring
Corticosteroids	**Dexamethasone:** ↓ SQV – Use with caution
Erectile Dysfunction Agents	**Sildenafil:** Sildenafil AUC ↑ 2-fold – Use cautiously, start with reduced dose of 25 mg q48h and monitor for adverse effects **Tadalafil:** Substantial ↑ in tadalafil AUC and half-life – Start with a 5-mg dose; do not exceed a single 10-mg dose of tadalafil in 72 hours **Vardenafil:** Vardenafil may ↑ substantially – Start with a 2.5-mg dose, and do not exceed a single 2.5-mg dose in 72 hours

Immunosuppressants	**Cyclosporine, tacrolimus, rapamycin:** ↑ immunosuppressants – Monitor immunosuppressant concentrations
Lipid-Lowering Agents	**Atorvastatin:** ATO ↑ 450% when combined with SQV/RTV – Use lowest possible starting dose of ATO with careful monitoring
Oral Contraceptives	**Ethinyl estradiol:** ↓ EE – Use alternative or additional method of contraception
Proton Pump Inhibitors	**Omeprazole:** SQV ↑ 54-82% – Clinical significance unclear – Monitor for SQV toxicities
Pulmonary Hypertension Agents	**Bosentan:** In patients already taking boosted SQV for ≥10 days, co-administer bosentan at a reduced dose of 62.5 mg once daily or qod based on tolerability. If patient is already taking bosentan, discontinue bosentan for ≥36 hrs prior to initiating boosted SQV. After boosted SQV has been given for >10 days, once daily or qod bosentan can be reintroduced. **Tadalafil:** In patients already taking boosted SQV for ≥1 wk, co-administer tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability. In patients already taking tadalafil, avoid use of tadalafil during initiation of boosted SQV. Stop tadalafil ≥24 h prior to starting boosted SQV. At least ≥1 wk after initiating boosted SQV, resume tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability.
Synthetic Narcotics	**Methadone:** R-methadone (active) AUC ↓ 20% when combined with SQV 400 mg + RTV 400 mg twice daily – Monitor and titrate according to methadone response

[a] Fortovase (soft-gel capsule) was discontinued during the first quarter of 2006.
[b] Cases of worsening glycemic control in patients with preexisting diabetes, and cases of new-onset diabetes including diabetic ketoacidosis have been reported with the use of all protease inhibitors.
[c] Discontinuation of PIs may be required to reverse fat redistribution. Patients with hypertriglyceridemia or hypercholesterolemia should be evaluated for risks for cardiovascular events and pancreatitis.
[d] Can be used with caution as a single dose in a monitored situation for procedural sedation.
[e] Rifabutin may be used with saquinavir only if it is boosted with ritonavir.

TIPRANAVIR (TPV) *(Updated April 2010)*	
Trade Name	Aptivus
Classification	Protease Inhibitor
Form	250-mg capsules; 100 mg/ml solution
Dosing Recommendations	Must be co-administered with ritonavir (RTV) – TPV 500 mg + RTV 200 mg twice daily (+/- EFV or NVP)
Hepatic Impairment Dosing	Should not be administered in patients with moderate to severe hepatic impairment (Child-Pugh Class B and C). Discontinue TPV/RTV in patients who: develop asymptomatic elevations in AST/ALT >10 x ULN ***or*** show elevations in AST/ALT between 5-10 x ULN + increases in total bilirubin >2.5 x ULN
Food Effect	Take with food. Bioavailability is increased with a high-fat meal
Oral Bioavailability	Absolute bioavailability is not known but is increased with fatty meals
Serum Half-life	4.8-6.0 hours
Route of Metabolism	Hepatic enzyme CYP 3A4; CYP 3A inhibitor
Storage	Capsules should be stored in a refrigerator 2°-8°C (36°-46°F) prior to opening the bottle. After opening the bottle, the capsules may be stored at room temperature and must be used within 60 days
Adverse Events	Fatal and nonfatal intracranial bleeding. PI class adverse effect that includes GI intolerance (N/V/D; abdominal pain), lipodystrophy syndrome, hyperglycemia, increased triglycerides and/or cholesterol, and transaminase elevation. Rash was observed in 8-14% of pts in phase 2/3 trials. TPV contains a sulfonamide moiety; therefore, should be used with caution in patients with severe sulfa allergy. TPV resulted in higher incidence of grade 2-4 LFTs elevation (17.5% vs. 9.9% in LPV/r, APV/r, SQV/r, and IDV/r comparator)
FDA Pregnancy Category	C
Long-Term Animal Carcinogenicity Studies	Currently underway
Animal Teratogen Studies	Conflicting animal studies. Not teratogenic in rats and rabbits studies or a decreased sternebrae ossification and body weight when given 0.1-fold to 1.1-fold human exposure
Black Box Warnings	Aptivus co-administered with 200 mg ritonavir has been associated with reports of both fatal and non-fatal intracranial hemorrhage and clinical hepatitis and hepatic decompensation including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity.
Drugs to Avoid	**As part of the ARV regimen:** Etravirine Fosamprenavir Lopinavir Saquinavir Or any other PIs

	Alfuzosin, amiodarone, astemizole, bepridil, cisapride, ergot derivatives, flecainide, lovastatin, midazolam, pimozide, propafenone, quinidine, ranolazine, rifampin, high-dose sildenafil, simvastatin, St. John's wort, terfenadine, triazolam
Cautious Use or Dose Adjustment	
Antiretrovirals	**Abacavir:** ABC AUC ↓ 40% – Clinical significance unknown; no dose adjustment recommended at this time **Didanosine (EC):** ddI AUC ↓ by 33% – Clinical significance unknown, but take ddI-EC at least 2 hours before or after TPV/r **Ritonavir:** TPV AUC ↑**,** Cmax ↑**,** Cmin ↑**.** Use TPV/r 500/200 mg twice daily **Zidovudine:** ZDV AUC ↓ 35% – Clinical significance unknown; no dose adjustment recommended at this time
Antacids	TPV AUC ↓ by approximately 30% – Avoid co-administration or separate administration time by 2 hours
Antialcoholics	**Disulfiram/metronidazole:** TPV capsules contain alcohol, which can produce disulfiram-like reactions
Anticoagulants	**Warfarin:** Monitor INR. Use with caution in patients who may be at risk for increased bleeding or who are receiving medications known to increase the risk of bleeding
Anticonvulsants	**Carbamazepine, phenobarbital, phenytoin:** May ↑ or ↓ anticonvulsants – Monitor levels; TPV may ↓ – use with caution. Consider alternate
Antidepressants	**Desipramine:** Desipramine ↑ or ↓ – ↓ desipramine dose and monitor concentration
Antifungals	**Fluconazole:** TPV AUC ↑ 50% – Do not use fluconazole doses >200 mg/day **Itraconazole:** Use with caution; do not use itraconazole doses >200 mg/day **Ketoconazole:** Use with caution; do not use ketoconazole doses >200 mg/day **Voriconazole:** Voriconazole levels may be↓– Use with caution
Antigout	**Colchicine:** For treatment of gout flares – 0.6 mg (1 tablet) x 1 dose, then 0.3 mg (½ tablet) 1 h later. Do not repeat dose before 3 days. For prophylaxis of gout flares – adjust dose to ¼ original regimen For treatment of familial Mediterranean fever (FMF) – Max: 0.6 mg daily Do not co-administer in patients with hepatic or renal impairment
Antimycobacterials	**Clarithromycin:** TPV AUC ↑ 66%; CL AUC ↑ 19%; 14-hydroxy-CL metabolite ↓ – No dose adjustment necessary for patients with normal renal function; Clarithromycin dose with CrCl 30-60 mL/min=50% of dose. CrCl <30mL/min=25% of dose **Rifabutin:** RFB ↑; desacetyl-RFB ↑ – RFB 150 mg qod; monitor patients for adverse events
Bronchodilators	**Salmeterol:** Co-administration not recommended. Consider formoterol

Calcium Channel Blockers	Clinical monitoring of patients is recommended
Erectile Dysfunction Agents	**Sildenafil:** May ↑ sildenafil – Use cautiously, start with reduced dose of 25 mg q48h and monitor for adverse effects **Tadalafil:** May ↑ tadalafil – Start with a 5-mg dose; do not exceed a single 10-mg dose of tadalafil in 72 hours **Vardenafil:** May ↑ vardenafil – Start with a 2.5-mg dose, and do not exceed a single 2.5-mg dose in 72 hours
H2 Blocker and Proton Pump Inhibitor	No data. TPV absorption may be ↓ – Use with caution
Immunosuppressants	**Cyclosporine, sirolimus, tacrolimus:** May ↑ or ↓ immunosuppressants – Monitor immunosuppressant concentrations closely
Lipid-Lowering Agents	**Atorvastatin:** ATO AUC ↑ by 8-fold – Use lowest possible starting dose of ATO with careful monitoring (consider pravastatin or rosuvastatin with close monitoring)
Narcotic Analgesics	**Meperidine:** Meperidine ↓; normeperidine (metabolite) ↑ – Dosage increase and long-term use of meperidine with TPV are not recommended
Oral Contraceptives	**Ethinyl estradiol:** EE ↓ 50% – Use alternative or additional method of contraception
Pulmonary Hypertension Agents	**Bosentan:** In patients already taking TPV/r for ≥10 days, co-administer bosentan at a reduced dose of 62.5 mg once daily or qod based on tolerability. If patient is already taking bosentan, discontinue bosentan for ≥36 hrs prior to initiating TPV/r. After TPV/r has been given for >10 days, once daily or qod bosentan can be reintroduced. **Tadalafil:** In patients already taking TPV for ≥1 wk, co-administer tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability. In patients already taking tadalafil, avoid use of tadalafil during initiation of TPV. Stop tadalafil ≥24 h prior to starting TPV. At least ≥1 wk after initiating TPV, resume tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability.
Synthetic Narcotics	**Methadone:** Methadone ↓ 50% – Clinical significance unknown. May need to ↑ methadone dose

ENFUVIRTIDE (T-20) *(Updated January 2007)*	
Trade Name	Fuzeon
Classification	Fusion Inhibitor
Form	Injectable lyophylized powder; each single use vial contains 108 mg of T-20 to be reconstituted with 1.1 mL of sterile water for injection of approximately 90 mg/1 mL
Dosing Recommendations	90 mg (1 mL) sc twice daily into the upper arm, anterior thigh, or abdomen at a site different from the preceding injection site, and only where no current injection site reaction exists. Do not inject where large nerves course close to skin, over a blood vessel, into moles, scar tissue, tattoos, burn sites, or around the navel
Food Effect	No known food interactions
Bioavailability	84.3% (sc compared to IV)
Serum Half-life	3.8 hours
Route of Metabolism	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool
Storage	Room temperature; reconstituted solution should be refrigerated at 2º-8ºC (36º-46ºF) and used within 24 hours
Adverse Events	With use of Biojector needle-free device: nerve pain (neuralgia and/or paresthesia) lasting up to 6 months at anatomical sites where large nerves course close to the skin; bruising; hematomas. Patients receiving anticoagulants or persons with hemophilia, or other coagulation disorders, may have a higher risk of post-injection bleeding Local injection site reactions (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) Increased rate of bacterial pneumonia Hypersensitivity reaction (<1%) – symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases; may recur upon rechallenge
FDA Pregnancy Category	B
Long-Term Animal Carcinogenicity Studies	Not completed
Animal Teratogen Studies	Negative
Black Box Warnings	None

MARAVIROC (MVC)* *(Updated May 2010)*	
Trade Name	Selzentry
Classification	CCR5 Co-receptor Antagonist
Form	150-, 300-mg film-coated tablets
Dosing Recommendations	300 mg twice daily Indicated in combination with other antiretroviral agents in adult patients infected with CCR5-tropic HIV-1 With other drugs that are not strong CYP3A inhibitors or CYP3A inducers, including tipranavir/ritonavir, nevirapine, all NRTIs, and enfuvirtide – 300 mg twice daily
Hepatic Impairment Dosing	Dose adjustment necessary with severe hepatic impairment; no dose adjustment likely with mild to moderate hepatic impairment. Use with caution in patients receiving a concomitant/potent CYP3A4 inhibitor
Renal Impairment Dosing	Do not use in patients with severe renal impairment or ESRD (CrCl <30 mL/min) who are receiving potent CYP3A inhibitors or CYP3A inducers. For patients with severe renal impairment or ESRD not receiving potent CYP3A inhibitors or inducers who experience any symptoms of postural hypotension, reduce maraviroc dose to 150 mg twice daily. No studies have been performed in subjects with severe renal impairment or ESRD co-treated with potent CYP3A inhibitors or inducers. Therefore, no dose for maraviroc can be recommended in this setting. No dose adjustment likely with mild to moderate renal impairment (CrCl ≥30 mL/min).
Food Effect	Can be taken with or without food
Oral Bioavailability	23-33%
Serum Half-life	14-18 hours
Route of Metabolism	Hepatic metabolism via cytochrome P450 3A4 20% of metabolite and parent drug excreted in the urine P-gp substrate
Storage	Room temperature
Adverse Events	More cardiovascular events including myocardial ischemia and/or infarction were observed in treatment-experienced patients who received maraviroc compared to placebo (1.3% vs. 0%), but clinical significance unclear. Use with caution in patients at increased risk of cardiovascular events. More treatment-naïve patients experienced virologic failure and developed lamivudine resistance compared to efavirenz-based regimen; however, this was likely due to the less sensitive trophile essay used during the study period. Postural hypotension at higher doses.

	Use with caution in patients with mild or moderate renal impairment. If postural hypotension occurs in patients with severe renal impairment or ESRD, decrease MVC dose to 150 mg twice daily. Risk of immune reconstitution syndrome, potential theoretical risk of malignancy. Cough, pyrexia, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness.
FDA Pregnancy Category	B
Long-Term Animal Carcinogenicity Studies	Negative in mice Positive in rats – exposures were 11 times higher than in humans
Animal Teratogen Studies	Negative
Black Box Warnings	Hepatotoxicity has been reported which may be preceded by evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia, or elevated IgE). Consider discontinuing maraviroc in patients with signs or symptoms of hepatitis, or with increased liver transaminases combined with rash or other systemic symptoms. Use with caution in patients with preexisting liver dysfunction or co-infected with viral hepatitis B or C
Drugs to Avoid	St. John's wort
Cautious Use or Dose Adjustment	
With CYP3A inhibitors (with or without a CYP3A inducer)	Increased MVC serum concentrations with co-administration. ↓ MVC to 150 mg twice daily when used in combination with PIs (except tipranavir/ritonavir), delavirdine, ketoconazole, itraconazole, clarithromycin, and other strong CYP3A inhibitors (e.g., nefazodone, telithromycin) 150 mg twice daily in combination with lopinavir/ritonavir plus efavirenz ***or*** saquinavir/ritonavir plus efavirenz
With all NRTIs, enfuvirtide, tipranavir/ritonavir, nevirapine, raltegravir, and other drugs that are not potent CYP3A inhibitors or CYP3A inducers	300 mg twice daily 150 mg twice daily if patient with severe renal impairment or ESRD experiences postural hypotension
With CYP3A inducers (without a strong CYP3A inhibitor)	600 mg twice daily with efavirenz, rifampin, carbamazepine, phenobarbital, and phenytoin. Some experts recommend closely monitoring for postural hypotension during the first 10-14 days.
* A viral tropism assay (Trofile, Monogram Biosciences) is required before initiating therapy with maraviroc.	

RALTEGRAVIR (RAL) *(Updated July 2009)*	
Trade Name	Isentress
Classification	Integrase Inhibitor
Form	400-mg film-coated tablets
Dosing Recommendations	400 mg PO twice daily with or without food
Hepatic Impairment Dosing	No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of raltegravir has not been studied. Use with caution in patients with severe hepatic impairment
Food Effect	High fat meal increases RAL AUC by 19%; in clinical trials, RAL was administered without regard to meals
Oral Bioavailability	Absolute bioavailability not established; geometric mean $AUC_{0\text{-}12h}$ and Cmin were 14.3 μM ●hr and 142 nM, respectively
Serum Half-life	9 hours
Route of Metabolism	Eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway. RAL-glucuronide and RAL are excreted in feces and urine
Storage	Room temperature
Adverse Events	Nausea, headache, diarrhea, and pyrexia were reported but were comparable to placebo. Flatulence was more common in patients treated with RAL than EFV (6% vs 0%). Risk of immune reconstitution syndrome similar to other ARVs
FDA Pregnancy Category	C. No human data. Animal developmental studies found a higher incidence of supernumerary ribs compared to control.
Black Box Warnings	None
Drugs to Avoid	None
Cautious Use or Dose Adjustment	
Antiretrovirals	**Efavirenz**: RAL AUC ↓ 36%, Cmin not significantly affected; use standard dose **Etravirine:** RAL AUC ↓10%. Monitor for virologic efficacy with co-administration **Tipranavir/ritonavir**: RAL Cmin ↓ 55%, AUC not significantly affected; use with close monitoring
Anticonvulsants	**Phenobarbital and phenytoin**: May ↓ RAL levels substantially – Avoid co-administration or use with close monitoring
Antimycobacterials	**Rifampin:** ↓ AUC and Cmin of RAL by 40% and 61%, respectively; ↑ RAL to 800 mg twice daily. Use with close monitoring. Use with caution when RAL is co-administered with other strong UGT1A1 inducers
Proton Pump Inhibitors	**Omeprazole**: ↑ RAL AUC 3.12-fold. Unclear clinical significance; use standard RAL dose

APPENDIX B

When to Initiate ART: Comparison of NYSDOH, DHHS, IAS-USA Recommendations

NYSDOH AI Recommendations (2010)	DHHS Recommendations (2009)*	IAS-USA Recommendations (2010)†

1. Initiation of ART is recommended for each of the following patient groups after modifiable barriers to adherence are minimized[a]:
 	
Patients who
• are symptomatic from HIV, including any of the following conditions:
  o HIV-associated neurocognitive disorder (HAND)[b]
  o Severe thrombocytopenia
  o HIV-associated nephropathy
  o HIV-related malignancies
• have chronic hepatitis B virus
• have an AIDS-defining condition
• are pregnant
• have two successive measurements of CD4 counts ≤500 cells/mm^3
• have rapid decline in CD4 count, defined as >100 cells/mm^3 per year
• have two successive measurements of viral load >100,000 copies/mL
 	
2. The following coexisting conditions should prompt consideration and discussion with patients about initiation of ART at CD4 counts >500 cells/mm^3.[a] Clinicians should consult with a provider with extensive experience with management of ART:
• Chronic active hepatitis C virus infection
• Non-HIV-related malignancies
• Age >50 years
• Acute HIV infection
• Partner serodiscordance
 	
3. There should not be an upper CD4 limit for initiating ART in patients who wish to receive it
	Indication for Initiating Antiretroviral Therapy
	
	• CD4 count <500 cells/mm^3
	• HIV-associated nephropathy
	• Co-infection with hepatitis B virus when HBV treatment is indicated
	• History of AIDS-defining illness
	• Pregnancy
		ART is recommended regardless of CD4 count:
		
		• Symptomatic HIV disease
		• Pregnant women
		• HIV-1 RNA >100,000 copies/mL
		• Rapid decline in CD4 cell count, >100/mm^3 per year
		• Active hepatitis B or C virus co-infection
		• HIV-associated nephropathy
		• Symptomatic primary HIV infection
		• Risk for secondary HIV transmission is high, e.g., serodiscordant couples
		• Asymptomatic HIV disease with CD4 count ≤500 cells/mm^3
		
		ART should be considered for asymptomatic patients with CD4 count >500/mm^3 unless patient is an elite controller (HIV-1 RNA <50 copies/mL) or has a stable CD4 count and low-level viremia in the absence of ART

*Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009. Available at: www.aidsinfo.nih.gov

† Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society--USA Panel. *JAMA* 2010;304:321-333.

[a] See Table 3 for evidence and ratings.

[b] HAND is currently used to encompass a hierarchy of progressive patterns of central nervous system involvement ranging from asymptomatic neurocognitive impairment (ANI), to minor neurocognitive disorder (MND), to the more severe HIV-associated dementia (HAD).

APPENDIX C

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APPENDIX D

June 2010

HIV-RELATED DRUGS WITH OVERLAPPING TOXICITIES

TABLE 1 HIV-RELATED DRUGS WITH OVERLAPPING TOXICITIES	
Bone Marrow Suppression	amphotericin b, cidofovir, cotrimoxazole, cytotoxic chemotherapy, dapsone, flucytosine, ganciclovir, interferon- a, linezolid, peginterferon-a, primaquine, pyrimethamine, ribavirin, rifabutin, sulfadiazine, valganciclovir, zidovudine
Peripheral Neuropathy	didanosine, isoniazid, linezolid (with chronic administration), stavudine
Pancreatitis	cotrimoxazole, didanosine, lamivudine (children), pentamidine, ritonavir, stavudine
Nephrotoxicity	acyclovir (IV, high dose) adefovir, aminoglycosides, amphotericin B, cidofovir, foscarnet, indinavir, pentamidine, tenofovir
Hepatotoxicity	azithromycin, clarithromycin, delavirdine, efavirenz, etravirine, fluconazole, isoniazid, itraconazole, ketoconazole, nevirapine, NRTIs, all protease inhibitors, rifabutin, rifampin, voriconazole
Rash	abacavir, atovaquone, clarithromycin, cotrimoxazole, dapsone, darunavar, delavirdine, efavirenz, etravirine, fosamprenavir, nevirapine, sulfadiazine, tipranavir, voriconazole
Diarrhea	atovaquone, didanosine, clindamycin, all HIV protease inhibitors (especially nelfinavir, ritonavir, lopinavir/ritonavir)
Ocular Effects	didanosine, ethambutol, linezolid, rifabutin, voriconazole

Adapted from the DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents* (2009).

APPENDIX E

RISK OF PROGRESSION TO AIDS-DEFINING ILLNESS IN A COHORT OF HOMOSEXUAL MEN PREDICTED BY BASELINE CD4 T CELL COUNT AND VIRAL LOAD

TABLE 1
RISK OF PROGRESSION TO AIDS-DEFINING ILLNESS IN A COHORT OF HOMOSEXUAL MEN PREDICTED BY BASELINE CD4 T CELL COUNT AND VIRAL LOAD[A]

CD4 ≤200 Plasma Viral Load (copies/mL)[b]		% AIDS (AIDS-Defining Complication)[c]			
bDNA	**RT-PCR**	**n**	**3 years**	**6 years**	**9 years**
≤500	≤1,500	0[d]	-	-	-
501 – 3,000	1,501 – 7,000	3[d]	-	-	-
3,001 – 10,000	7,001 – 20,000	7	14.3	28.6	64.3
10,001 – 30,000	20,001 – 55,000	20	50.0	75	90.0
> 30,000	> 55,000	70	85.5	97.9	100.0
CD4 201 – 350[e] Plasma Viral Load (copies/mL)		**% AIDS (AIDS-Defining Complication)[c]**			
bDNA	**RT-PCR**	**n**	**3 years**	**6 years**	**9 years**
≤500	≤1,500	3[d]	-	-	-
501 – 3,000	1,501 – 7,000	27	0	20.0	32.2
3,001 – 10,000	7,001 – 20,000	44	6.9	44.4	66.2
10,001 – 30,000	20,001 – 55,000	53	36.4	72.2	84.5
> 30,000	> 55,000	104	64.4	89.3	92.9
CD4 >350 Plasma Viral Load (copies/mL)		**% AIDS (AIDS-Defining Complication)[c]**			
bDNA	**RT-PCR**	**n**	**3 years**	**6 years**	**9 years**
≤500	≤1,500	119	1.7	5.5	12.7
501 – 3,000	1,501 – 7,000	227	2.2	16.4	30.3
3,001 – 10,000	7,001 – 20,000	342	6.8	30.1	53.5
10,001 – 30,000	20,001 – 55,000	323	14.8	51.2	73.5
> 30,000	> 55,000	262	39.6	71.8	85.0

Adapted from the DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults*

and Adolescents (2006).

[a] Data from the Multi-Center AIDS Cohort Study (MACS).

[b] MACS numbers reflect plasma HIV RNA values obtained by version 2.0 bDNA testing. RT-PCR values are consistently 2- to 2.5-fold higher than bDNA values, as indicated. It should be noted that the current generation bDNA assay (3.0) gives similar HIV-1 RNA values as RT-PCR except at the lower end of the linear range (<1,500 copies/mL).

[c] In this study, AIDS was defined according to the 1987 CDC definition and does not include asymptomatic individuals with CD4 T cell counts <200 mm^3.

[d] Too few subjects were in the category to provide a reliable estimate of AIDS risk.

[e] A recent evaluation of data from the MACS cohort of 231 individuals with CD4 T cell counts >200 and <350 cells/mm^3 demonstrated that of 40 (17%) individuals with plasma HIV RNA <10,000 copies/mL, none progressed to AIDS by 3 years (Alvaro Munoz, personal communication). Of 28 individuals (29%) with plasma viremia of 10,000-20,000 copies/mL, 4% and 11% progressed to AIDS at 2 and 3 years, respectively. Plasma HIV RNA was calculated as RT-PCR values from measured bDNA values.

APPENDIX F

PROGNOSIS ACCORDING TO CD4 CELL COUNT AND VIRAL LOAD IN THE PRE-HAART AND HAART ERAS