ANTIRETROVIRAL THERAPY

Updated January 2014

What's New — January 2014 Update
Section VI. A: *Virologic and Immunologic Monitoring*
January 2013 Update
Section III: *When to Initiate ART in Patients with Chronic Infection*

I. INTRODUCTION

Antiretroviral therapy (ART) refers to the use of pharmacologic agents that have specific inhibitory effects on HIV replication. The use of less than three active agents is not recommended for initiating treatment. 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 CCR5 co-receptor antagonists, and the integrase strand transfer inhibitors (INSTIs). 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.

II. GOALS, BENEFITS, AND RISKS OF ART

Updated March 2006; reviewed 2013

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*). 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. When to Initiate ART in Patients with Chronic Infection

January 2013

Preface

Public health guidance currently recommends that all patients living with HIV be treated with antiretroviral therapy (ART) to reduce transmission of HIV in a strategy commonly known as "treatment as prevention." This Committee strongly supports the idea of treatment as prevention.

This clinical practice guideline governs how physicians interact with and treat patients to ensure that health is maximized for each individual patient. In keeping with recent evidence supporting earlier initiation of ART, New York State now recommends that all patients with established HIV infection, regardless of CD4 count, be evaluated for initiation of ART. This recommendation is based on increasing evidence that patients with established HIV infection benefit from ART at all stages of disease and on recent data that demonstrate a dramatic reduction of HIV transmission risk from ART-treated patients.

Table 3
Recommendations for Initiating ART

1. All patients with chronic HIV infection should be evaluated for initiation of ART, regardless of CD4 count. (AII)

2. Certain conditions increase the urgency for initiation of ART. Clinicians should strongly recommend initiation of ART in patients who meet any one of the following criteria[a]:

- AIDS-defining condition (AI)
- **pregnancy[b]** (AI)
- **two successive measurements of CD4 counts ≤500 cells/mm^3** (AII)
- symptomatic **from HIV** (AI)**, regardless of CD4 count, including any of the following:**
  - **HIV-associated neurocognitive disorder (HAND)[c]** (AII)
  - **Severe thrombocytopenia** (AII)
  - **HIV-associated nephropathy** (AII)
  - **HIV-related malignancies** (AII)
- **chronic hepatitis B or C infection[d,e]** (AII)
- **age 50 or older** (AII)
- **rapidly declining CD4 counts (>100 cells/mm^3 per year)** (AIII)

3. Patients with seronegative partners should be counseled about the reduction of HIV transmission risk when effective ART is initiated; ART is strongly recommended in these patients. (AI)

[a] *See Appendix C for evidence and ratings.*
[b] For recommendations on initiating ART in HIV-infected pregnant women, refer to *Use of Antiretroviral Therapy in HIV-Infected Pregnant Women.*
[c] 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) (see *Cognitive Disorders and HIV/AIDS*).
[d] Initial ART regimens for patients with chronic hepatitis B must include NRTIs that are active against hepatitis B (see *Hepatitis B Virus* guidelines).
[e] In co-infected patients with HCV genotype 1 and CD4 counts >500 cells/mm^3, some clinicians would defer ART until HCV treatment is concluded due to significant interactions between some antiretroviral agents and NS3/4A protease inhibitors used as part of hepatitis C therapy (see *Hepatitis C Virus* guidelines).

RECOMMENDATIONS:

Evaluation and preparation for ART initiation includes each of the following essential components:

- **Full discussion with the patient about risks and benefits of ART** (see Section A: *Counseling and Education Before Initiating ART*)
- **Assessment of patient readiness**
- **Identification and amelioration of factors that might interfere with successful adherence to treatment, including inadequate access to medication, inadequate supportive services, psychosocial factors, active substance use, or mental health disorders**

Clinicians should refer patients for supportive services as necessary to address modifiable barriers to adherence. An ongoing plan for coordination of care should be established.

Clinicians should involve patients in the decision-making process regarding initiation of ART. The patient should make the final decision of whether and when to initiate ART.

When the decision to initiate treatment is made, ART should be prescribed and monitored by, or in consultation with, clinicians who have experience in managing ART.

Increasingly strong cohort data suggest that untreated HIV infection may lead to increased morbidity and mortality from non-HIV-related conditions, even at high CD4 counts. Together with the dramatic reduction of transmission risk with effective treatment, these data support the initiation of ART regardless of CD4 count in adequately prepared patients. Randomized studies are still lacking to help define the treatment benefit in asymptomatic patients with CD4 counts >500 cells/mm^3, although one protocol is in progress (the START trial is currently enrolling and will evaluate initiating treatment at CD4 counts >500 cells/mm^3 compared with initiating at CD4 counts $\leq$350 cells/mm^3). Patients in care who are documented *long-term nonprogressors* or *elite controllers* are another group for whom data are lacking and warrant special consideration (see Section B: *Deferring ART*). Insufficient data exist to categorically recommend for or against starting all patients with acute HIV infection on immediate therapy (for more discussion see *Diagnosis and Management of Acute Infection*). Patients with chronic infection and higher CD4 counts are at low risk for short-term adverse outcomes, allowing time for proper assessment, education, and engagement of the patient in the decision to treat.

Data from NA-ACCORD, a large observational cohort study, showed that both morbidity and mortality were improved by initiation of ART in patients with CD4 counts in the high or even normal range.[1] A significantly decreased risk of death was observed in patients who initiated therapy at CD4 counts >500 cells/mm^3 compared to those who deferred to <500 cells/mm^3, as well as in the cohort who initiated ART in the 350-500 cells/mm^3 range compared to those deferring to <350 cells/mm^3.[1] Although other cohort studies demonstrated only a minimal survival advantage[2] or no survival advantage among those starting ART at the highest CD4 counts, they did confirm the benefits of initiating ART at levels $\leq$500 cells/mm^3.[3-5] Another showed an approximately 33% reduction in the risk of death from end-stage liver disease, non-AIDS infections, and non-AIDS-defining cancers with each 100 cells/mm^3 increase in

CD4 count.[6] The only randomized study of early versus deferred therapy in patients with CD4 counts in the 350-550 cells/mm^3 range showed no mortality benefit but a higher incidence of drug-related adverse effects[7]; however, this study has significant limitations, most notably a relatively brief follow-up period.

Accumulating evidence suggests that patients who initiate ART earlier or spend less cumulative time with detectable plasma viremia are less likely to suffer certain complications, such as cardiovascular disease,[6,8-11] neurocognitive dysfunction,[12-15] and some non-HIV-related malignancies.[16-19] Cohort data also demonstrate that although older patients are likely to achieve virologic suppression, they are less likely to achieve an immunologic response, as measured by an increase of CD4 count by 100 cells/mm^3, and that patients >55 years old may be at higher clinical risk even after starting therapy.[20] The poor immunologic recovery seen in older patients is associated with higher morbidity and mortality, particularly cardiovascular events.[21] In one study, men $\geq$50 years of age who initiated ART with CD4 counts in the 351-500 cells/mm^3 range were able to achieve similar immunologic responses as younger men who initiated at lower CD4 counts.[22]

In addition, a recent study showed a 96% reduction in transmission between serodiscordant heterosexual couples when the positive partner was receiving ART,[7] adding to the body of evidence that lower viral load reduces transmission risk. ART is now part of the established strategy aimed at reducing HIV transmission and is an essential component of prevention interventions along with risk-reduction counseling, safer-sex practices, and avoidance of needle-sharing (see *Prevention with Positives: Integrating HIV Prevention into HIV Primary Care*).

While newer data focus on those with higher CD4 counts, it should be recognized that this group is only a minority of those with known HIV infection. Most newly diagnosed and previously diagnosed patients with HIV infection have CD4 counts <500 cells/mm^3, other signs of symptomatic HIV infection or AIDS, or other indications for initiation of ART (e.g., concurrent hepatitis B or hepatitis C, age over 50), and would therefore already have been strongly encouraged to initiate ART promptly according to the 2010 New York State recommendations. In New York City, 70% of newly diagnosed patients have CD4 counts <500 cells/mm^3. NA-ACCORD data[23] showed that the median CD4 count at presentation in 2007 was 317 cells/mm^3, and a 2010 report from the US Centers for Disease Control and Prevention (CDC)[24] documented that only 7% of newly diagnosed patients have a CD4 count over 500 cells/mm^3. The CDC also reported that in 2008, 36% of people newly diagnosed with HIV progress to AIDS within 1 year.[25] Ongoing efforts to offer universal HIV testing to all 13- to 64-year-old patients may begin to identify patients earlier in their disease.

Key Point:
To be successful over time, initiation of ART is a process that involves both the selection of the most appropriate regimen for the individual *and* its acceptance by the patient with education and adherence counseling. All are critical in achieving the goal of durable and complete viral suppression.

The CEI Line provides primary care providers in New York State the opportunity to consult with clinicians who have experience managing ART. The CEI Line can be reached at 1-866-637-2342 or 1-585-273-2793.

The AIDS Institute maintains a voluntary HIV Provider Directory to assist with identification of experienced providers in New York State. Experienced providers can also be identified through the American Academy of HIV Medicine (AAHIVM) and the HIV Medicine Association (HIVMA).

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.

A. Counseling and Education Before Initiating ART

RECOMMENDATIONS:
Counseling and education should include the following:

- **Basic education about HIV, CD4 cells, viral load, and resistance**
- **Available treatment options and potential risks and benefits of therapy** (see Table 4)
- **The need for strict adherence to avoid the development of viral drug resistance** (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**

Clinicians should involve the patient in the decision-making process regarding initiation of ART.

Discussion of ART should occur at the start of care for all HIV-infected patients, regardless of CD4 count. The clinician and patient should discuss the risks and benefits of early ART (see Table 4) and individual factors that may affect the decision to initiate, such as patient readiness or reluctance and adherence barriers. Clinicians should involve the patient in the decision-making process regarding initiation of ART.[26] When clinicians and patients engage in shared decision-making, patients are more likely to choose to initiate ART and to achieve an undetectable viral load.[27] Misconceptions about treatment initiation should be addressed, including the implication that starting ART represents advanced HIV illness. Initiating ART before symptoms occur allows patients to stay healthier and live longer.

- Patients who do not have health insurance may qualify for Medicaid or the NYSDOH HIV Uninsured Care Program which provides access to free health care (HIV Drugs, Primary Care, Home Care, and the ADAP Plus Insurance Continuation Program, or APIC) for residents who are HIV-infected but uninsured or underinsured. The program is open Monday - Friday, 8:00AM - 5:00PM and can be reached at: In State - (800) 542-2437; Out of State - (518) 459-1641; TDD - (518) 459-0121.

- If eligible, patients may also consider treatment options through enrollment in clinical trials. A resource that may help with this process is the AIDS Clinical Trials Information Service (phone: 1-800-TRIALS-A; website: http://www.actis.org).

Table 4 outlines the risks and benefits of early ART to discuss with patients when making the decision of whether and when to initiate ART.

TABLE 4
BENEFITS AND RISKS OF EARLY ART IN ASYMPTOMATIC HIV-INFECTED PATIENTS
(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[1,6,9,17,28-31]
- Delay or prevention of immune system compromise[32]
- Possible lower risk of antiretroviral resistance[33]
- Decreased risk of sexual transmission of HIV*[7,34-36]

Disadvantages of early therapy

- Potential drug-related reduction in quality of life in otherwise asymptomatic individuals[37-39]
- Possibility of greater cumulative side effects from ART[40]
- Possibility for earlier development of drug resistance and limitation in future[41] antiretroviral options if adherence and viral suppression are suboptimal
- Possibility for earlier onset of treatment fatigue
- Higher prescription drug costs for the individual

* 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).[42]

B. Deferring ART

RECOMMENDATIONS:

Except in cases when initiation of treatment is urgent (see Section C: *Initiating ART Following Acute Opportunistic Infections*)**, clinicians should educate and prepare patients before initiating ART in those with potential barriers to adherence, including low health literacy; active alcohol or drug use; lack of insurance, transportation, or housing; depression; mistrust of medical providers; or a poor social support system.**

In patients with advanced HIV (or AIDS), ART should be initiated even if barriers to adherence are present. In these cases, referrals to specialized adherence programs should be made for intensified adherence support (see Appendix D: *New York State Adherence Services Contact List*)**.**

Decisions to initiate ART in long-term nonprogressors and elite controllers should be individualized. (AIII)

Potential Barriers to Adherence

Although the current first-line regimens used for ART are much easier to tolerate with fewer side effects than earlier combinations, they are not free of side effects. Their use requires a lifelong commitment from the patient. Patients who prefer not to take medication, or who do not understand the significance of skipping doses are at high risk for poor adherence and subsequent viral resistance. 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 and to address potential barriers or impediments to therapy. These may include but are not limited to low health literacy; active alcohol or drug use; lack of insurance, transportation, or housing; depression; mistrust of medical providers; or a poor social support system. These barriers should not necessarily preclude initiation of ART; some may not be completely modifiable before starting therapy and will require ongoing attention and use of supportive services throughout the course of therapy.

Patients who are at high risk for poor adherence may benefit if initiation of 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.[41] These patients should remain under particularly close observation for clinical and laboratory signs of disease progression.[43] ART should be initiated as soon as the patient seems prepared to adhere to a treatment regimen. In patients with advanced AIDS, it is appropriate to initiate ART even if some barriers to adherence are present. In these cases, referrals to specialized adherence programs should be made for intensified adherence support (see Appendix D: *New York State Adherence Services Contact List*).

Long-Term Nonprogressors and Elite Controllers

RECOMMENDATION:
Clinicians should consult with a provider experienced in the management of ART when considering whether to initiate ART in long-term nonprogressors and elite controllers.

Long-term nonprogressors demonstrate a lack of disease progression, marked by no symptoms and low viral loads in the absence of therapy during long-term follow-up. Most published studies of long-term nonprogressors include 7-10 years of follow-up. ***Elite controllers*** suppress HIV to low but detectable levels (<50-75 copies/mL) for many years.
See Ref. 44 for further definition of these groups and their characteristics.

The role of early ART initiation in *long-term nonprogressors* or *elite controllers* is unclear. At this time, there are not enough data to recommend for or against initiation of ART in long-term nonprogressors and elite controllers. Close monitoring of CD4 count and viral load level may be an acceptable approach. Declines in CD4 count should prompt consideration of initiation of ART. Elite controllers have demonstrated CD4 cell increases after initiation of ART.[45] The clinician and patient should discuss the risks and benefits of early ART as well as 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. If treatment is delayed, clinicians should counsel patients about the risk of HIV transmission to partners.

C. Initiating ART Following Acute Opportunistic Infections

RECOMMENDATIONS:
Clinicians should recommend that patients beginning treatment for acute opportunistic infections (OIs) initiate ART within 2 weeks (*see next recommendation for exceptions*)**.** (AI)

Clinicians should not immediately initiate ART in patients with tuberculous meningitis or cryptococcal meningitis. Consultation with a clinician with experience in management of ART in the setting of acute OIs is recommended.

For all other manifestations of tuberculosis (TB), clinicians should initiate ART in HIV-infected patients as follows:

- ***For patients with CD4 counts ≥50 cells/mm^3:*** **as soon as they are tolerating anti-TB therapy and no later than 8-12 weeks after initiating anti-TB therapy** (AI)
- ***For patients with CD4 counts <50 cells/mm^3:*** **within 2 weeks of initiating anti-TB therapy** (AI)

In a randomized study, patients who initiated ART at a median of 12 days from start of OI therapy had better outcomes, as measured by disease progression and death, without an increase in adverse events, compared to those who initiated ART at a median of 45 days from presentation.[46] Although this study excluded patients with active TB, three randomized controlled trials in patients newly diagnosed with HIV and pulmonary TB have demonstrated a significant mortality benefit when ART was initiated during the first 2 months of starting anti-TB therapy and a further benefit when those who were severely immunocompromised initiated

therapy in the first 2 weeks.[47-49] Although antiretroviral agents and anti-TB medications can have overlapping toxicities, ART should be initiated within the first 8 to 12 weeks of starting anti-TB therapy. Patients with CD4 counts <50 cells/mm^3 should receive ART within the first 2 weeks of initiating anti-TB therapy.

Tuberculous meningitis and *cryptococcal meningitis* are exceptions; there are data showing that early initiation of ART increases mortality in this setting.[50,51] Close attention should be paid to possible drug-drug interactions between OI therapy and ART. In some cases, determining the optimal timing for initiating ART in patients with OIs can be complex and may require consultation with a clinician with experience in management of ART in this context.

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*).

IV. The Importance of Patient Adherence

July 2004, currently under revision

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. 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. Improved pharmacokinetics has produced ART regimens that simplify dosing; however, it is still important that clinicians devote sufficient time at each patient visit to assess the degree of adherence to prescribed therapies. Concern about potential side effects prompts some patients to diminish adherence, often without confiding in the healthcare team.

In November 2011, New York State adopted customized patient medication packaging, sometimes referred to as "comingling" of medications, which is a process whereby several different drugs are packaged together to be taken at the same time.[52] Customized patient medication packaging has been shown to increase adherence to complex therapeutic regimens such as those required for patients with HIV/AIDS.[52] In addition, customized patient medication packaging simplifies dosing and may reduce reliance on daily "pill-minders" that patients often package themselves, which has a potential for error that would be avoided with use of customized patient packaging.

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).

V. Selecting an Initial Antiretroviral Regimen

September 2011

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 INSTI. (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 5A-C. Clinicians should consult with a provider who has experience with ART when a patient's resistance profile indicates the need for a regimen not listed in Tables 5-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 5-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*	INSTI
• **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. When combination pills are used, patients should be educated about which drugs are combined in that pill.
‡ 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 twice-daily dosing; however, the benefit of increased tolerability may outweigh the limitation of twice-daily dosing. For more information regarding raltegravir, see *New Antiretroviral Drugs*.

Alternative antiretroviral regimens are effective and tolerable but have potential disadvantages compared with the preferred regimens in Table 5-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 5-B may be effective but are unlikely to be necessary as components of initial regimens.

TABLE 5-B
ALTERNATIVE ANTIRETROVIRAL AGENTS FOR INITIAL TREATMENT OF HIV-1 INFECTION IN NON-PREGNANT TREATMENT-NAÏVE ADULTS AND ADOLESCENTS*

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

* Options are listed alphabetically.
† Fixed-dose combinations should not be used in patients who need dose adjustment due to renal failure. When combination pills are used, patients should be educated about which drugs are combined in that pill.
‡ 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] When rilpivirine is used with tenofovir plus emtricitabine, Complera, a fixed-dose, three-drug combination pill, can be prescribed when clinically indicated. *Note:* When prescribing Complera, clinicians should be aware that a vitamin preparation has a similar trade name (i.e., Complera); confirmation that the correct prescription is dispensed to patients should be ensured. For more information regarding rilpivirine, see *New Antiretroviral Drugs*.
[d] 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.
[e] For more information regarding maraviroc, see *New Antiretroviral Drugs*.

TABLE 5-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*)
• 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. A table of advantages and disadvantages of ARV components is available in the Department of Health and Human Services guidelines, see *Table 6*.

VI. Monitoring of Patients Receiving ART

Periodic laboratory tests are necessary to evaluate the response to ART and its potential related side effects. In the setting of ART failure, viral resistance assays should be used.

A. Virologic and Immunologic Monitoring

January 2014

January 2014

- **Routine quarterly monitoring of CD4 count is no longer recommended for non-pregnant patients receiving antiretroviral therapy (ART) who have consistently undetectable HIV RNA levels and CD4 counts >200 cells/mm^3** (see Table 6 for recommended intervals)**.** (AIII)

- **Regular monitoring of HIV RNA levels remains the most meaningful measure of effective ART.** (AI)

RECOMMENDATIONS:

Clinicians should monitor HIV RNA levels and CD4 counts according to the recommended intervals in Table 6.

In addition to recommended intervals for assessment of HIV RNA levels (see Table 6)**, clinicians should continue to schedule visits in accordance with clinical necessity to address any issues that may have an impact on adherence to ART or retention in care, such as substance use, mental health, unstable housing, lack of transportation, or social support, as well as non-HIV-related medical conditions. This may necessitate more frequent follow-up between monitoring visits.** (AIII)

Regular monitoring of CD4 counts in patients with consistently undetectable HIV viral loads and CD4 counts >200 cells/mm^3 offers little utility in clinical practice today. Clinicians rarely use this information to guide decision-making for clinically stable, virologically suppressed patients. Measurement of HIV RNA levels to confirm appropriate response to treatment and durable viral suppression is a more meaningful measure of the effectiveness of ART.

A retrospective study of 1820 patients with 25,463 paired measurements of HIV RNA level and CD4 count followed over 13 years showed a 97.1% probability that patients with HIV RNA levels <200 copies/mL and CD4 counts >300 cells/mm^3 would maintain CD4 levels >200 cells/mm^{3}over a 4-year period. This probability increased to 99.2% over 5 years when non-HIV causes for decline, such as interferon therapy or chemotherapy, were excluded.[53]

Very few studies address the appropriate frequency of viral load monitoring. Although standard practice has been to monitor viral load on a quarterly schedule, a recent retrospective study showed that when suppressed at entry, failure rates at 12 months were similar in patients scheduled for 3-, 4-, or 6-month follow-up appointments. It should be noted that far fewer were scheduled for the longer follow-up interval, with only 8% at 6 months versus 66% and 26% in the 3- and 4-month groups, respectively.[54] This study also noted that the single strongest predictor of virologic failure at 12 months was a missed or cancelled appointment, highlighting the importance of retention in care. This and other similar studies[55,56] have important limitations, including their retrospective nature and short follow-up periods.

Until more definitive data are available, patients who are given longer monitoring intervals for HIV RNA level should be carefully selected based on length of suppression, CD4 count, and general adherence to medical care, including visit attendance. Quarterly monitoring may remain appropriate for some patients, especially those with a history of non-adherence, mental health disorders, substance use, homelessness, poor social support system, or other major medical conditions.

Key Point:

Table 6 provides a guide for monitoring HIV RNA levels and CD4 counts. Patients with a history of non-adherence, mental health disorders, substance use, homelessness, poor social support system, or other major medical conditions may need to be monitored more closely or may require more frequent visits.

Table 6 Virologic and Immunologic Monitoring		
	HIV RNA Levels (copies/mL)	**CD4 Lymphocyte Count (cells/mm^3)**
Baseline	Yes (AI)	Yes (AI)
Following initiation of ART or change of ART regimen	• Within 4 weeks of initiation of ART or change in regimen (BIII) • At least every 8 weeks until complete suppression[a] is documented (BIII)	• At 12 weeks, then every 4 months until CD4 is ≥200 cells/mm^3 (AI) on two measurements obtained at least 4 months apart
Treatment Monitoring		
• Patients on ART who achieve complete suppression	• At least every 3 months for one year after complete suppression (BIII) • May extend intervals to at least every 6 months in selected stable patients with CD4 count >200 cells/mm^3 after 1 year of complete suppression[54] (BIII)	• At least every 6 months for patients with CD4 ≤300 cells/mm^3 (BIII) • At least every 12 months for patients with CD4 >300 cells/mm^3 (BIII)
• Patients on previously suppressive ART with new HIV RNA[b] above the upper limit of a sensitive assay	Repeat viral load test within 4 weeks to differentiate low level transient viremia ("blip") from virologic failure.[c] If viral load remains detectable on repeat test: • Assess adherence (AIII) • Assess for drug-drug interactions (AIII) • Obtain resistance testing (AI) • Obtain CD4 count if not done within previous 6 months (BIII)	
Patients not on ART (According to NYSDOH recommendations, all HIV-infected patients should be evaluated for initiation of ART.[d])	• At least every 4 months in patients with CD4 counts ≤500 cells/mm^3 (BIII) • At least every 6 months in patients with CD4 counts >500 cells/mm^3 (BIII) • Continue to discuss ART initiation (AIII)	• At least every 4 months for patients with CD4 ≤500 cells/mm^3 (BIII) • At least every 6 months for patients with CD4 counts >500 cells/mm^3 (BIII) • Continue to discuss ART initiation (AIII)

[a] Complete suppression is generally considered below the level of quantitation of a highly sensitive assay (< 20 to < 50 copies/mL).
[b] Patients with repeated intermittent low level viremia < 200 copies/mL over a period of years without demonstrated failure may continue routine testing intervals.
[c] ART should not be changed based on a single viral load elevation. The risk of virologic rebound (breakthrough) increases when values are > 500 copies/mL.[57]
[d] See Section III: *When to Initiate ART in Patients with Chronic Infection*.

Plasma HIV-1 RNA Level (Viral Load)

Measurement of HIV RNA levels provides the most precise means of establishing whether a response to ART has occurred. Because absolute CD4 cell counts are calculated values that fluctuate widely, they are a less precise indicator of antiretroviral response than HIV RNA level.

For patients beginning ART, or those changing therapy as a result of virologic failure, HIV RNA measured at 4 weeks after initiation of therapy should decrease by at least 1 log (10-fold) in the presence of effective therapy[58] (see Table 7). For patients who do not have background antiretroviral resistance, an undetectable viral load (<50 copies/mL) is usually achieved within 3 months. Patients with resistance or a baseline HIV viral load > 100,000 copies/mL typically achieve an undetectable viral load within 6 months of effective treatment. An absent or incomplete response of viral load to ART should raise concerns about poor adherence to therapy and/or viral resistance[59] (see Section IV: *The Importance of Patient Adherence* and Section VIII: *Failure to Achieve Goals of Initial ART*).

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 ART (see Appendix E and Appendix F).

Lymphocyte Subsets (CD4 Cell Count)

CD4 lymphocyte count is used to evaluate immunologic staging, predict the risk of clinical progression, and make decisions regarding prophylaxis of opportunistic infections (see *Opportunistic Infection Prophylaxis*). Historically, CD4 cell count has been used to establish a threshold for initiating ART. However, current guidelines in New York State recommend that all HIV-infected patients be evaluated for ART, regardless of CD4 cell count. For patients who may not be ready to initiate ART, CD4 cell count can be used to guide discussions between patient and provider regarding the urgency of initiating ART.

Clinicians are unlikely to use CD4 counts to guide clinical decision-making in practice for virologically suppressed patients once their CD4 count remains above 200 cells/mm^3. However, for persons infected with HIV-2 or HIV-1 variants that cannot be accurately quantitated using viral load assays, CD4 count remains the most effective monitoring tool for progression of disease. See *Human Immunodeficiency Virus Type-2*.

Although a significant CD4 count increase often occurs among patients treated with effective ART, the absence of such an increase should not be interpreted as treatment failure if the viral load declines appropriately. ART regimens are generally not changed in patients with undetectable viral loads who experience immunologic failure, although patients should remain on appropriate prophylaxis for opportunistic infections based on CD4 count. See *Opportunistic Infection Prophylaxis*. Lack of correlation between viral load and CD4 cell response is particularly common among patients ≥ 50 years old[60,61] and patients with low initial CD4 cell counts (<100 cells/mm^3).[62-64]

TABLE 7 INTERPRETATION OF VIRAL LOAD			
HIV-1 RNA Copy Number			
Copies/mm^3			**Log$_{10}$**
1,000,000			6.0
100,000			5.0
10,000			4.0
1,000			3.0
100			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

B. HIV Resistance Assays

October 2006

RECOMMENDATIONS:

Clinicians should perform resistance testing under the following circumstances:

- **At baseline, regardless of whether ART is 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: https://www.iasusa.org/

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/index)

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*.

C. 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*. A table of common and/or severe adverse affects associated with ART is available in the Department of Health and Human Services guidelines, see *Table 13*.

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.

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.

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.

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.[65] 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*.

Renal Toxicity

September 2012

RECOMMENDATIONS:

For all HIV-infected patients receiving ART:
Clinicians should routinely assess kidney function in all HIV-infected patients. A renal assessment should include:

- **Glomerular filtration rate estimated from serum creatinine (baseline and at least every 6 months)** (AII)
- **Blood urea nitrogen (baseline and at least every 6 months)** (AIII)
- **Urinalysis (baseline and at least annually)** (AIII)
- **For patients with diabetes and no known proteinuria: calculation of urine albumin-to-creatinine ratio to detect microalbuminuria (baseline and at least annually)** (AI)

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

Clinicians should adjust tenofovir dosing when glomerular filtration rate approaches 50 mL/min or discontinue tenofovir according to clinical status. (AII)

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.[66,67] 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 one of the following equations:

1. *Chronic Kidney Disease Epidemiology Consortium (CKD-EPI):* Estimates GFR based on age, race, and serum creatinine. A CKD-EPI calculator can be found at http://mdrd.com
2. Modification of diet in renal disease (MDRD): Estimates GFR 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

3. 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

Tenofovir is excreted by glomerular filtration and tubular secretion. Renal impairment has been reported in patients receiving tenofovir.[67,68] The extent of this toxicity is unclear. 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.

For additional information regarding renal assessment and management of kidney disease in HIV-infected patients, see *Kidney Disease in HIV-Infected Patients*.

D. 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) *Mild reaction*: mild skin rash	*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:* ▪ Manage with antihistamines and close monitoring *Continues....*

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
Raltegravir	Rashes, including severe skin rashes and cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported	▪ Discontinue if rash is accompanied by constitutional symptoms (i.e., fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema)

* 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 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.[69]

IX. SECOND-LINE REGIMENS AND SALVAGE ART

March 2006 – Currently under revision

RECOMMENDATIONS:

Clinicians should consult with a provider with 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 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 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://ziptrials.us/study/aids-community-research-initiative-of-america-hiv-study/

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://ziptrials.us/study/aids-community-research-initiative-of-america-hiv-study/). 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.

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. Wright ST, Carr A, Woolley I, et al. CD4 cell responses to combination antiretroviral therapy in patients starting therapy at high CD4 cell counts. *J Acquir Immune Defic Syndr* 2011;58:72-79. [PubMed] **Minimal reduction in risk of AIDS incidence and/or death shown in patients who initiate ART with CD4 count >500 cells/mm^3 vs those who initiate with CD4 counts 351-500 cells/mm^3.**

3. Writing Committee for the CASCADE Collaboration. Timing of HAART initiation and clinical outcomes in human immunodeficiency virus type 1 seroconverters. *Arch Intern Med* 2011;171:1560-1569. [PubMed]

4. Cain LE, Logan R, Robins JM, et al, and the HIV-CAUSAL Collaboration. When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: An observational study. *Ann Intern Med* 2011;154:509-515. [PubMed] **Initiation of ART at a CD4 threshold of 500 cells/mm^3 increased AIDS-free survival compared with initiation at ≤350 cells/mm^3.**

5. The Opportunistic Infections Project Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. CD4 cell count and the risk of AIDS or death in HIV-infected adults on combination antiretroviral therapy with a suppressed viral load: A longitudinal cohort study from COHERE. *PLoS Med* 2012;9:e1001194. [PubMed] **Although new AIDS-defining events and death are uncommon among patients whose viral load is suppressed by ART, the risk of a new AIDS-defining event or death follows a CD4 cell count gradient with the patients with the highest CD4 cell counts having the lowest risk of a new AIDS-defining event or death.**

6. Marin B, Thiébaut R, Bucher HC, et al. Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy. *AIDS* 2009;23:1743-1753. [PubMed]

7. Cohen MS, Chen YQ, McCauley M, et al., HPTN 052 Study Team Prevention of HIV-infection with early antiretroviral therapy. *N Engl J Med* 2011;365:493-505. [PubMed] **Early initiation of ART reduced rates of sexual HIV transmission and clinical events, indicating both personal and public health benefits from early initiation.**

8. Strategies for Management of Antiretroviral Therapy (SMART) Study Group, El-Sadr WM, Lundgren JD, Neaton JH, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006;355:2283-2296. [PubMed] **In addition to showing that continuous use of ART is better than episodic use, this study also found a higher rate of cardiovascular disease in the group who did not receive continuous ART.**

9. 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.**

10. Ho JE, Scherzer R, Hecht FM, et al. The association of CD4+ T-cell count on cardiovascular risk in treated HIV disease. *AIDS* 2012;26:1115-1120. Epub ahead of print. [PubMed] **Data suggest that delayed therapy results in sustained harm to endothelial function.**

11. Lichtenstein KA, Armon C, Buchacz K, et al. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV Outpatient Study. *Clin Infect Dis* 2010;51:435-447. [PubMed] **CD4 count <500 cells/mm^3 was an independent risk factor for incident cardiovascular disease in the HIV Outpatient Study cohort.**

12. 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.**

13. Garvey L, Surendrakumar V, Winston A. Low rates of neurocognitive impairment are observed in neuro-asymptomatic HIV-infected subjects on effective antiretroviral therapy. *HIV Clin Trials* 2011;12:333-338. [PubMed] **Rates of neurocognitive impairment were low in patients receiving ART.**

14. Winston A, Puls R, Kerr SJ, et al. Dynamics of cognitive change in HIV-infected individuals commencing three different initial antiretroviral regimens: A randomized, controlled study. *HIV Med* 2012;13:245-251. [PubMed] **Neurocognitive function improves over the first year of initiating ART in neuro-asymptomatic patients.**

15. Ellis RJ, Badiee J, Vaida F, et al. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. *AIDS* 2011;25:1747-1751. [PubMed] **Initiation of ART as early as possible may reduce the risk of developing HAND.**

16. Silverberg MJ, Chun C, Leyden W, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. *Cancer Epidemiol Biomarkers Prev* 2011;20:2551-2559. [PubMed] **Immunodeficiency was positively associated with the following non-HIV-related malignancies: lung cancer, colorectal cancer, and melanoma compared with HIV-uninfected individuals. Earlier ART initiation to maintain high CD4 levels might reduce the risk of cancer.**

17. Bruyand M, Thiébaut R, Lawson-Ayayi S, et al. Role of uncontrolled HIV RNA level and immunodeficiency in the occurrence of malignancy in HIV-infected patients during the combination antiretroviral therapy era: Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort. *Clin Infect Dis* 2009;49:1109-1116. [PubMed] **CD4 counts maintained at ≥500 cells/mm^3 helps to prevent the occurrence of malignancy.**

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. Sigel K, Wisnivesky J, Gordon K, et al. HIV as an independent risk factor for incident lung cancer. *AIDS* 2012;26:1017-1025. [PubMed] **HIV infection was an independent risk factor for lung cancer after controlling for other factors, such as smoking.**

20. Sabin CA, Smith CJ, d'Arminio Monforte A, et al., Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Study Group. Response to combination antiretroviral therapy: Variation by age. *AIDS* 2008;22:1463-1473.[PubMed] **Better virologic response but lower immunologic response in individuals 55 and older.**

21. van Lelyveld SFL, Gras L, Kesselring A, et al., on behalf of the ATHENA national observational cohort study. Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort. *AIDS* 2012;26:465-474. [PubMed] **Poor immunological recovery despite virological successful ART is associated with a higher risk for overall morbidity and mortality, underscoring the importance of starting ART at higher CD4 cell counts, particularly in older patients.**

22. Li X, Margolick JB, Jamieson BD, et al. CD4 T-cell counts and plasma HIV-1 RNA levels beyond 5 years of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2011;57:421-428. [PubMed] **Men >50 years of age who start ART with CD4 counts between 351-500 cells/mm^3 could achieve the same immunologic response as younger men who started with lower CD4 counts.**

23. Althoff KN, Gange SJ, Klein MB, et al. Late presentation for human immunodeficiency virus care in the United States and Canada. *Clin Infect Dis* 2010;50:1512-1520. [PubMed]

24. Centers for Disease Control and Prevention. Reported CD4+ T-lymphocyte results for adults and adolescents with HIV infection—37 atates, 2005–2007. *HIV Surveillance Supplemental Report* 2010;16(No. 1). Available at: http://www.cdc.gov/hiv/topics/surveillance/resources/reports/index.htm#supplemental Published March 2011.

25. Centers for Disease Control and Prevention. Diagnoses of HIV infection and AIDS in the United States and dependent areas, 2008. Vol. 20. Atlanta, Ga: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2010. Available at: http://www.cdc.gov/hiv/topics/surveillance/resources/reports/index.htm#supplemental. Published June 2010.

26. Salzburg Statement on Shared Decision Making. Salzburg Global Seminar, February 7, 2011. Available at: http://e-patients.net/u/2011/03/Salzburg-Statement.pdf

27. Beach MC, Duggan PS, Moore RD. Is patients' preferred involvment in health decisions related to outcomes for patients with HIV? *Gen Intern Med* 2007;22:1119-1124. [PubMed]

28. 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.**

29. 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.**

30. 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.**

31. Lewden C, Bouteloup V, De Wit S, et al, The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. All-cause mortality in treated HIV-infected adults with CD4 ≥500 cells mm^3 compared with the general population: Evidence from a large European observational cohort collaboration. *Int J Epidemiol* 2012;41:433-445. [PubMed] **Mortality patterns in HIV-infected individuals with high CD4 counts who were receiving ART were similar to those in the general population.**

32. 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.**

33. 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.**

34. 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.**

35. 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.**

36. 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.**

37. Erikkson LE, Bratt GA, Sandrström E, et al. The two-year impact of first generation protease inhibitor based antiretroviral therapy (PI-ART) on health-related quality of life. *Health Qual Life Outcomes* 2005;3:32. [PubMed]

38. Guaraldi G, Murri R, Orlando G, et al. Severity of lipodystrophy is associated with decreased health-related quality of life. *AIDS Patient Care STDs* 2008;22:577-578. [PubMed] **Health-related quality of life was strongly correlated with patient perception of the severity of lipodystrophy.**

39. Burgoyne RW, Tan DH. Prolongation and quality of life for HIV-infected adults treated with highly active antiretroviral therapy (HAART): A balancing act. *J Antimicrob Chemother* 2008;61:469-473. [PubMed]

40. Volberding PA, Deeks SG. Antiretroviral therapy and management of HIV infection. *Lancet* 2010;376:49-62. [PubMed]

41. Barth RE, Aitken SC, Tempelman H, et al. Accumulation of drug resistance and loss of therapeutic options precede commonly used criteria for treatment failure in HIV-1 subtype-C-infected patients. *Antivir Ther* 2012;17:377-386. [PubMed] **Rapid accumulation of drug resistance occurred when ART was continued despite virological failure. Treatment options were lost, even when failure criteria were not met.**

42. Politch JA, Mayer KH, Welles SL, et al. Highly active antiretroviral therapy does not completely suppress HIV in semen of sexually active HIV-infected men who have sex with men. *AIDS* 2012;26:1535-1543. Epub ahead of print. [PubMed]

43. Wallis CL, Papathanasopolous MA, Fox M, et al. Low rates of nucleoside reverse transcriptase inhibitor resistance in a well-monitored cohort in South Africa on antiretroviral therapy. *Antivir Ther* 2012;17:313-320. [PubMed] **Frequent viral load monitoring limits the level and complexity of resistance in HIV-1 subtype C, preserving susceptibility to second-line options.**

44. Casado C, Colombo S, Rauch A, et al. Host and viral genetic correlates of clinical definitions of HIV-1 disease progression. *PLoS One* 2010;5:e11079. [PubMed]

45. Okulicz JF, Grandits GA, Weintrob, et al. CD4 T cell count reconstitution in HIV controllers after highly active antiretroviral therapy. *Clin Infect Dis* 2010;50:1187-1191. [PubMed]

46. 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.**

47. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med* 2011;365:1471-1481. [PubMed]

48. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med* 2011;365:1482-1491. [PubMed]

49. Abdool Karim S, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med* 2011;365:1492-1501. [PubMed]

50. Lawn SD, Torok ME, Wood R. Optimum time to start antiretroviral therapy during HIV-associated opportunistic infections. *Curr Opin Infect Dis* 2011;24:34-42. [PubMed]

51. National Institute of Allergy and Infectious Diseases. Bulletin: HIV treatment study in patients with cryptococcal meningitis ends enrollment early: Higher mortality rate found with early antiretroviral therapy. May 30, 2012. [Bulletin]

52. New York State Education Department. Office of the Professions. Rules of the Board of Regents. Section 29.7. Customized patient packaging of medications for patients on complex medication regimens. Amended, effective November 9, 2011. Available at: http://www.regents.nysed.gov/meetings/2011Meetings/October2011/1011ppca1.pdf

53. Gale HB, Giettermann SR, Hoffman HJ, et al. Is frequent CD4+ T-lymphocyte count monitoring necessary for person swith counts >300 cells/mm3 and HIV-1 suppression? *Clin Infect Dis* 2013;56:1340-1343. [PubMed]

54. Buscher A, Mugavero M, Westfall AO, et al. The association of clinical follow-up intervals in HIV-infected persons with viral suppression on subsequent viral suppression. *AIDS Patient Care STDs* 2013;27:459-466. [PubMed]

55. Reekie J, Mocroft A, Sambatakou H, et al. Does less frequent routine monitoring of patients on a stable, fully suppressed cART regimen lead to an increased risk of treatment failure? *AIDS* 2008; 22:2381–2390. [PubMed]

56. Romih V, Zidovec Lepej S, Gedike K, et al. Frequency of HIV-1 viral load monitoring of patients initially successfully treated with combination antiretroviral therapy. *PLoS One* 2010; 5:e15051. [PubMed]

57. Grennan JT, Loutfy MR, Su D, et al. Magnitude of virologic blips is associated with a higher risk for virologic rebound in HIV-infected individuals: A recurrent events analysis. *J Infect Dis* 2012;205:1230-1238. [PubMed]

58. Haubrich RH, Riddler SA, Ribaudo H, et al. Initial viral decay to assess the relative antiretroviral potency of protease inhibitor-sparing, nonnucleoside reverse transcriptase inhibitor-sparing, and nucleoside reverse transcriptase inhibitor-sparing regimens for first-line therapy of HIV infection. *AIDS* 2011;25:2269-2278. [PubMed]

59. Townsend D, Troya J, Maida I, et al. First HAART in HIV-infected patients with high viral load: Value of HIV RNA levels at 12 weeks to predict virologic outcome. *J Int Assoc Physicians AIDS Care (Chic)* 2009;8:314-317. [PubMed]

60. 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]

61. Sabin CA, Smith CJ, d'Arminio Monforte A, et al., Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Study Group. Response to combination antiretroviral therapy: Variation by age. *AIDS* 2008;22:1463-1473. [PubMed]

62. Kelley CF, Kitchen CM, Hunt PW, et al. Incomplete peripheral CD4+ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment. *Clin Infect Dis* 2009;48:787-794. [PubMed]

63. Garcia F, de Lazzari E, Plana M, et al. Long-term CD4$^+$ T-cell response to highly active antiretroviral therapy according to baseline CD4$^+$ T-cell count. *J Acquir Immune Defic Syndr* 2004;36:702-713.[PubMed]

64. Moore RD, Keruly JC. CD4$^+$ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis* 2007;44:441-446. [PubMed]

65. 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.**

66. Miro JM, Cofan F, Trullas JC, et al. Renal dysfunction in the setting of HIV/AIDS. *Curr HIV/AIDS Rep* 2012;9:187-199. [PubMed] **HIV-infected individuals commonly experience renal complications and have a high prevalence of risk factors, including HIV infection itself, that contribute to the development of kidney disease.**

67. Zaidan M, Lescure FX, Brochériou I, et al. Tubulointerstitial nephropathies in HIV-infected patients over the past 15 years: A clinico-pathological study. *Clin J Am Soc Nephrol* 2013;8:930-938. [PubMed] **Drug toxicity, infection, and syndromes associated with immunosuppression in the setting of HIV demonstrate the importance of monitoring kidney function HIV-infected patients.**

68. Laprise C, Baril JG, Dufresne S, et al. Association between tenofovir exposure and reduced kidney function in a cohort of HIV-positive patients: Results from 10 years of follow-up. *Clin Infect Dis*. 2013;56:567-575. [PubMed] **Tenofovir exposure significantly increased the risk of kidney dysfunction, but the loss in estimated glomerular filtration rate due to TDF was relatively mild over the long term.**

69. 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.

Classification of Antiretroviral Drugs

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Abacavir (ABC)
Didanosine (ddI)
Emtricitabine (FTC)
Lamivudine (3TC)
Stavudine (d4T)
Zidovudine (AZT, ZDV)

Nucleotide Reverse Transcriptase Inhibitor (NtRTI)

Tenofovir (TDF)

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Delavirdine (DLV)
Efavirenz (EFV)
Etravirine (ETR)
Nevirapine (NVP)
Rilpivirine (RPV)

Protease Inhibitors (PIs)

Atazanavir (ATV)
Darunavir (DRV)
Fosamprenavir (FPV)
Indinavir (IDV)
Lopinavir/Ritonavir (LPV/r)
Nelfinavir (NFV)
Ritonavir (RTV)
Saquinavir (SQV)
Tipranavir (TPV)

Fusion Inhibitor

Enfuvirtide (T-20)

CCR5 Co-receptor Antagonist

Maraviroc (MVC)

Integrase Strand Transfer Inhibitors (INSTIs)

Dolutegravir (DTG)
Elvitegravir (EVG)
Available only as a component of Stribild
Raltegravir (RAL)

Abacavir (ABC) *(Updated October 2012)*	[package insert]
Trade Name	Ziagen
Classification	Nucleoside Reverse Transcriptase Inhibitor
Form	300-mg tablets; 20-mg/mL oral solution Each Trizivir tablet contains ABC 300 mg, 3TC 150 mg, and ZDV 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, but clinical significance unknown
Food Effect	No known food interactions Alcohol ↑ ABC levels 41%; no effect on alcohol
Oral Bioavailability	83%
Serum Half-life	1.5 hours
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 exposure) during organogenesis; not seen in rabbits]
Black Box Warnings	Fatal hypersensitivity reactions reported [b]: • 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:** Tenofovir + lamivudine

[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)*	[package insert]
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 ≥60 kg — 200 mg once daily 10-29 — <60 kg — 100 mg once daily ≥60 kg — 125 mg once daily <10 — <60 kg — 75 mg once daily ≥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 ↓ 57% – 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 September 2012)*	[package insert]
Trade Name	Emtriva
Classification	Nucleoside Reverse Transcriptase Inhibitor
Form	200-mg capsules Each Truvada tablet contains FTC 200 mg and TDF 300 mg Each Atripla tablet contains EFV 600 mg, FTC 200 mg, and TDF 300 mg Each Complera tablet contains FTC 200 mg, RPV 25 mg, and TDF 300 mg Each Stribild tablet contains: EVG 150 mg, cobicistat 150 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 ***or*** with RPV 25 mg and TDF 300 mg as Complera, 1 once daily ***or*** with elvitegravir, cobicistat, and TDF as Stribild, 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 October 2012)* [package insert]

Trade Name	Epivir
Classification	Nucleoside Reverse Transcriptase Inhibitor
Form	150-, 300-mg tablets; 10-mg/mL oral solution Each Combivir tablet contains 3TC 150 mg and ZDV 300 mg Each Trizivir tablet contains ABC 300 mg, 3TC 150 mg, and ZDV 300 mg Each Epzicom tablet contains ABC 600 mg and 3TC 300 mg
Dosing Recommendations	150 mg twice daily or 300 mg once daily 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; consider dosing for CrCL<5mL/min. Dose after dialysis on day of dialysis
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 class adverse event, but is rare with lamivudine
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 December 2010)*	[package insert]
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; WHO recommends 30 mg twice daily in ≥60kg <60 kg: 30 mg twice daily
Hepatic Impairment Dosing	Use with close monitoring in patients with preexisting liver dysfunction; if liver disease worsens, consider discontinuing
Renal Impairment Dosing	**CrCl (mL/min)** — **Weight** — **Dose** 26-50 — <60 kg — 15 mg q12h >60 kg — 20 mg q12h 10-25 — <60 kg — 15 mg q24h >60 kg — 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	2.3 hours
Elimination	Renal excretion 40%
Adverse Events	Peripheral neuropathy (most common); discontinue drug if peripheral neuropathy develops, pancreatitis, lipoatrophy, lipodystrophy, rapidly progressive ascending neuromuscular weakness (rare) Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity; consider permanent discontinuation for patients with confirmed lactic acidosis Hepatotoxicity and hepatic failure, including fatal cases, have been reported. Fatal hepatic events reported most often in patients receiving hydroxyurea, didanosine, and stavudine. This combination should be avoided. Hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving ART and interferon and ribavirin. Monitor closely, consider dose reduction or discontinuation of interferon, ribavirin, or both if worsening clinical toxicities are observed, including hepatic decompensation (eg, Child-Pugh >6)
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 (antagonism)
Cautious Use or Dose Adjustment	
Antiretrovirals	**Didanosine:** Peripheral neuropathy, lactic acidosis, and pancreatitis have been reported with this combination – Avoid; use only if benefits clearly outweigh risks

Zidovudine (ZDV) *(Updated October 2012)*	[package insert]
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 3TC 150 mg and ZDV 300 mg Each Trizivir tablet contains ABC 300 mg, 3TC 150 mg, and ZDV 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 an uncommon 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 <11 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.

Tenofovir (TDF) *(Updated September 2012)*	[package insert]
Trade Name	Viread
Classification	Nucleotide Reverse Transcriptase Inhibitor
Form	150-, 200-, 250-, 300-mg tablets; 40 mg/1 g oral powder Each Truvada tablet contains FTC 200 mg and TDF 300 mg Each Atripla tablet contains EFV 600 mg, FTC 200 mg, and TDF 300 mg Each Complera tablet contains FTC 200 mg, RPV 25 mg, and TDF 300 mg Each Stribild tablet contains: EVG 150 mg, cobicistat 150 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 ***or*** with FTC 200 mg and RPV 25 mg as Complera, 1 once daily ***or*** with elvitegravir, cobicistat, and FTC as Stribild, 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% 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

Delavirdine (DLV) *(Updated October 2012)*	[package insert]
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 and inhibits cytochrome P450 3A4;,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 **Saquinavir**: SQV ↑ 5-fold – Monitor transaminase levels
Antacids	↓ **DLV** – Separate by at least 1 hour

Anticoagulants	**Warfarin**: ↑ warfarin – Monitor INR
Antifungals	**Voriconazole**: Potential for bi-directional inhibition – Monitor voriconazole concentrations for potential 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 with careful monitoring (consider pravastatin or rosuvastatin)

[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)*	[package insert]
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, RVP) 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% – ↑ EFV dose to 800 mg once daily in persons >50 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

Opioid Addiction Medications	**Buprenorphine:** ↓ buprenorphine AUC 50% - Monitor for withdrawal **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 February 2013)*	[package insert]
Trade Name	Intelence
Classification	Non-nucleoside Reverse Transcriptase Inhibitor
Form	25-, 100-, 200-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, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), and erythema multiforme. Etravirine should be discontinued for severe rash or if rash is accompanied by fever, hepatitis, and other systemic symptoms. Incidence of rash higher in females. 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
Antimalarials	**Artemether, lumefantrine:** ETR ↓ artemether, dihydroartemisinin, and lumefantrine concentrations by 38%, 25%, and 13%, respectively. Antimalarial efficacy may be ↓ with co-administration. ETR concentrations ↑ by 10%. Use with caution
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
Hepatitis C Protease Inhibitors (Boceprevir and Telaprevir)	**Boceprevir (BOC):** BOC AUC ↑ 10% (NS); ETR AUC ↓ 23%. Limited clinical data. Consider standard dose **Telaprevir (TVR): 25%** ↓ in TVR exposure. No change in ETR concentrations. Clinical significance unknown. Insufficient data to make a dosing recommendation for TVR
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 Strand Transfer Inhibitors	**Raltegravir:** No significant drug interactions
Synthetic Narcotics	**Methadone:** No significant interactions. Monitor for withdrawal symptoms and titrate dose to effect

Nevirapine (NVP) *(Updated November 2012)*	[package insert]
Trade Name	Viramune and Viramune XR
Classification	Non-nucleoside Reverse Transcriptase Inhibitor
Form	200-mg immediate-release tablets; 100-, 400-mg extended-release tablets; 50 mg/5 mL oral suspension
Dosing Recommendations	**For NVP-naïve patients:** one 200-mg immediate-release tablet daily for 14 days, then one 400-mg extended-release tablet daily with or without food **For patients transitioning from immediate-release NVP:** one 400-mg extended-release tablet daily *Note*: Patients must never take more than one form of NVP at the same time
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., DLV, EFV, ETR, RPV) Garlic supplements, ketoconazole, rifampin, rifapentine, St. John's wort
Cautious Use or Dose Adjustment	
Antiretrovirals	**Darunavir:** No data. Consider DRV/r 600/100 mg twice-daily with NVP co-administration **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 500/125 mg (3 tabs or 7.5 mL) twice daily with food **Maraviroc:** Use maraviroc 300 mg twice daily with standard NVP dose **Raltegravir:** No data. Interaction unlikely. Use standard dose **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:** May significantly ↑ NVP concentrations – Monitor for NVP-associated adverse effects **Itraconazole:** May ↓ itraconazole concentrations and ↑ NVP concentrations. Monitor itraconazole concentrations with co-administration **Voriconazole:** Potential for bi-directional inhibition; may significantly ↓ voriconazole and ↑ NVP concentrations – Monitor voriconazole serum concentrations and NVP 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.	

Rilpivirine (RPV) *(Updated December 2012)*	[package insert]
Trade Name	Edurant
Classification	Non-nucleoside Reverse Transcriptase Inhibitor
Form	25-mg tablet Each Complera tablet contains FTC 200 mg, RPV 25 mg, and TDF 300 mg
Dosing Recommendations	**For ART-naïve patients with HIV-1 RNA ≤100,000 copies/mL at start of therapy:** one 25-mg tablet once daily with a meal (≥550 calories) ***or*** with FTC 200 mg and TDF 300 mg as Complera, 1 once daily
Hepatic Impairment Dosing	No dose adjustment needed for mild to moderate (Child-Pugh A and B) hepatic impairment
Renal Impairment Dosing	Use standard dose with close monitoring in patients with ESRD. RPV unlikely to be removed during hemodialysis and peritoneal dialysis
Food Effect	Normal or high-fat meal improves RPV absorption. Fasted condition or high protein drink decreases RPV absorption by 40-50%. High protein binding 99.7%
Oral Bioavailability	Absolute bioavailability unknown, but food improves absorption
Serum Half-life	50 hrs
Elimination	Metabolized via CYP3A4. Not an inducer or inhibitor of CYP450 isoenzymes. Parent drug and metabolite are primarily excreted in the feces (85%) and urine (6.1%)
Adverse Events	Less CNS side effects compared to efavirenz (e.g., insomnia, headache, dizziness); severe depressive disorders have been reported; rash Hepatotoxicity has been reported in patients with underlying liver disease or in patients with elevated baseline transaminases. Monitor liver function tests before and during treatment with RPV Fat redistribution, immune reconstitution syndrome May prolong QTc interval. Rilpivirine should be used with caution when co-administered with a drug with a known risk of Torsade de Pointes Avoid rilpivirine co-administration with drugs that can significantly prolong QTc interval
FDA Pregnancy Category	B
Long-Term Animal Carcinogenicity Studies	At high concentrations in mice, rilpivirine induced hepatocellular neoplasms
Animal Teratogen Studies	Not teratogenic in animal studies. No human data
Black Box Warnings	None

Drugs to Avoid	**As part of the ARV regimen:** Any other NNRTIs (e.g., DLV, EFV, ETR, NVP) Carbamazepine, dexamethasone (long-term use), esomeprazole, lansoprazole, omeprazole, oxcarbazepine, pantoprazole, phenobarbital, phenytoin, rabeprazole, rifabutin, rifampin, rifapentine, St John's wort
Cautious Use or Dose Adjustment	
Antiretrovirals	**Darunavir:** DRV/r ↑ RPV AUC 130% - Use standard dose **Didanosine:** No significant interaction if ddI given 2 hours before RPV. RPV concentrations not affected **Lopinavir/ritonavir:** LPV/r ↑ RPV AUC 52% - Use standard dose **Tenofovir:** TDF AUC ↑ 23%. RPV concentrations not affected. Use standard dose
Antimycobacterials	Macrolide antibiotics (e.g., clarithromycin, erythromycin, telithromycin) may ↑ RPV concentrations. Monitor for QTc prolongation. Consider azithromycin with co-administration
Antifungals	**Ketoconazole:** Ketoconazole ↑ RPV AUC 49%; RPV ↓ ketoconazole AUC 24% Azole antifungal agents may ↑ RPV concentrations. Monitor for QTc prolongation and antifungal efficacy
Erectile Dysfunction Agents	**Sildenafil:** No significant interaction
H2 Receptor Antagonists	Use with caution. H2 blockers must be given 12 hrs before or 4 hrs after RPV. Antacids should also be administered >2 hrs before of 4 hrs after RPV
Lipid-Lowering Agents	**Atorvastatin:** ATO metabolites ↑ 23-39%; clinical significance unknown. Use stand dose atorvastatin
Oral Contraceptives	**Ethinyl estradiol:** AUC ↑ 14% **Norethindrone:** AUC ↓ 11% Clinical significance unknown – Use additional method of contraception
Synthetic Narcotics	**Methadone** (active R-isomer): AUC ↓ by 26%. Monitor for withdrawal symptoms
With CYP3A Inducers	Co-administration of RPV and drugs that induce CYP3A (e.g., carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifamycin antibiotic) may result in ↓ plasma concentrations of RPV and loss of virologic response and possible resistance
With CYP3A Inhibitors	Co-administration of RPV and drugs that inhibit CYP3A may result in ↑ plasma concentrations of RPV

Atazanavir (ATV) *(Updated January 2013)*	[package insert]
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 **For pregnant patients:** ATV should be administered with RTV. ATV can be used as an alternative to LPV/r in pregnancy. Increase to ATV 400 mg + RTV 100 mg once daily in the 2nd and 3rd trimester when ATV/r is co-administered with TDF ***or*** H-2 blockers
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 ↑ 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 Cases of lactic acidosis syndrome, sometimes fatal, and symptomatic hyperlactatemia have occurred in pregnant women using ATV in combination with nucleoside analogues. Lactic acidosis is associated with antiretroviral nucleoside analogues alone or in combination. Higher ATV exposures 2 months postpartum may occur; monitor for adverse events carefully Nephrolithiasis and/or cholelithiasis have been reported

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 (may increase risk of NVP toxicity) Tenofovir (when ATV is not combined with RTV) Tipranavir/ritonavir Alfuzosin, alprazolam, astemizole, bepridil, cisapride, ergot derivatives, garlic supplements, irinotecan, lovastatin, midazolam,[b] pimozide, pitavastatin, 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 (not recommended with ESRD or use with close orthostatic hypotension monitoring) **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 – Avoid. Consider monitoring concentrations
Anticoagulants	**Warfarin:** ↑ warfarin – Monitor INR closely
Anticonvulsants	**Carbamazepine:** May ↓ ATV when ATV not boosted with RTV **–** Avoid co-administration with unboosted ATV. With ATV boosted with RTV, RTV may ↑ **c**arbamazepine levels. Monitor carbamazepine concentrations in patients initiating RTV boosted ATV who are already receiving stable dose of carbamazepine. A carbamazepine dose reduction may be needed

	Phenobarbital, phenytoin: May ↓ ATV when ATV not boosted with RTV **–** Avoid co-administration. With ATV boosted with RTV, RTV may ↓ phenobarbital or phenytoin levels. Dose adjustment of **p**henobarbital or phenytoin may be required when co-administered with ATV boosted with RTV **Lamotrigine:** ATV boosted with RTV may ↓ lamotrigine – lamotrigine dose adjustment may be required. No lamotrigine dose adjustment required with unboosted ATV
Antidepressants	**Amitriptyline, imipramine:** ↑ tricyclics – Monitor tricyclic antidepressant concentrations. Avoid in patients with QTc prolongation
Antifungals	**Voriconazole:** Potential for bi-directional inhibition; when ATV boosted with RTV, may significantly ↓ voriconazole. Avoid co-administration unless benefit/risk to the patient justifies the use of voriconazole – With co-administration, monitor for toxicities and adverse events. Monitor ATV and voriconazole therapeutic drug levels.
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
Antimalarial Agents	**Atovaquone/proguanil:** ATV/r decreased atovaquone AUC 46% and proguanil AUC 41%. Consider an alternative agent for malaria prophylaxis. If Atovaquone is used for PCP prophylaxis, consider an alternative agent for PCP prophylaxis
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 once daily if patient also taking TDF or H2 blocker **For therapy-experienced pregnant patients in 2nd or 3rd trimester:** if ATV co-administered with TDF **or** H2 blocker, ATV 400 mg + RTV 100 mg once daily ↓ ATV concentrations – Give ATV 2 hours before or 10 hours after H2 blocker
Hepatitis C Protease Inhibitors (Boceprevir and Telaprevir)	**Boceprevir (BOC):** Concomitant administration of BOC and ATV/r resulted in 33% reduction in ATV AUC and 49% reduction in ATV Cmin. BOC Cmin ↓ 18%. Do not co-administer BOC with ATV/r **Telaprevir (TVR):** TVR AUC ↓ 20%; ATV AUC ↑ 17% (NS). Use standard dose TVR 750 mg q8h + ATV/r 300/100 mg once daily
Immunosuppressants	**Cyclosporine, sirolimus, tacrolimus:** significant ↑ immunosuppressants – Monitor immunosuppressant concentrations. Significant immunosuppressant dose needed
Lipid-Lowering Agents	**Atorvastatin:** May ↑ ATO substantially – Use lowest possible starting dose (10 mg) 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 alternative method of nonhormonal contraceptive. May ↑ progesterone exposure substantially
Opioid Addiction Medications	**Buprenorphine:** buprenorphine AUC ↑ 92% and 67% with ATV and ATV/r co-administration; may ↑ sedation. Do not co-administer buprenorphine with unboosted ATV **Methadone:** Not affected with unboosted ATV. With ATV/r, ↓ R-methadone levels 16%-18%. Monitor for withdrawal with ATV/r
Proton-pump Inhibitors	**Avoid PPI with ATV. If co-administration is needed:** **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. Limited clinical data, use with close monitoring. 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. Limited clinical data, use with close monitoring.

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 February 2013)*	[package insert]
Trade Name	Prezista
Classification	Protease Inhibitor
Form	75-, 150-, 400-, 600-, 800-mg tablets; 100 mg/mL oral suspension
Dosing Recommendations	Must be co-administered with ritonavir (RTV) – **For ARV-naïve patients or ARV-experienced patients without DRV resistance-associated mutations[a]:** DRV 800 mg + RTV 100 mg once daily with food, ***or*** Patients who have difficulty swallowing DRV tablets: 8 mL DRV + 1.25 mL RTV once daily with food (take DRV as two 4 mL administrations with the included oral dosing syringe) **For ARV-experienced patients:** With no darunavir resistance-associated substitutions[a]: DRV 800 mg + RTV 100 mg once daily with food ***or*** Patients who have difficulty swallowing DRV tablets: 8 mL DRV + 1.25 mL RTV once daily with food (take DRV as two 4 mL administrations with the included oral dosing syringe) With at least one darunavir-resistance associated substitution[a]: DRV 600 mg + RTV 100 mg twice daily with food[b] ***or*** Patients who have difficulty swallowing DRV tablets: 6 mL DRV + 1.25 mL RTV 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 DRV/r co-administration has a net CYP3A4 inhibitory effect)
Storage	Room temperature; do not refrigerate oral suspension
Adverse Events	Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with DRV/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 reactions, including erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis have been reported – Discontinue if severe skin reaction 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, 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, amiodarone, astemizole, cisapride, ergot derivatives, flecainide, lovastatin, midazolam, phenobarbital, phenytoin, pimozide, pitavastatin, propafenone, quinidine, ranolazine, rifampin, rifapentine, 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 800/100 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 ↑
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 ↓ at steady-state. 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
Antimalarials	**Artemether, lumefantrine:** Artemether concentrations ↓ 16% (NS); dihydroartemisinin concentration ↓ 18%; lumefantrine ↑ 175%; no change in DRV. Use standard dose. ↑ in lumefantrine may ↑ risk of QT prolongation; use with caution
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). For the treatment of TB: RFB 150 mg once daily. Consider monitoring rifabutin serum concentrations
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 (but dose-adjusted sildenafil can be considered for pulmonary hypertension) **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
Hepatitis C Protease Inhibitors (Boceprevir and Telaprevir)	**Boceprevir (BOC) and telaprevir (TVR):** Concomitant administration of DRV/r and hepatitis C protease inhibitors (i.e., BOC and TVR) resulted in reduced steady-state exposures to DRV, BOC, and TVR. Do not co-administer BOC or TVR with DRV/r

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. Limited clinical data. Monitor closely with co-administration. **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. Limited clinical data. Monitor closely with co-administration.
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

[a] V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.
[b] DRV 600 mg + RTV 100 mg twice daily recommended if no resistance testing obtained in patients previously treated with PIs and there is a high likelihood of PI-associated resistance.

Fosamprenavir (FPV)* *(Updated April 2010)*	[package insert]
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 cannot 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, flecainide, garlic supplements, lovastatin, midazolam,[d] norethindrone, pimozide, pitavastatin, propafenone, 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)*	[package insert]
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 January 2013)*	[package insert]
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 or using an alternative PI (i.e., darunavir)
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.

	Rare: Hepatotoxicity, including some fatalities, has occurred. Monitor transaminase levels before and during therapy, especially in patients with underlying hepatic disease, including HBV and HCV, or marked transaminase elevations. 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, avanafil, cisapride, ergot derivatives, flecainide, fluticasone, garlic supplements, lovastatin, midazolam,[e] pimozide, pitavastatin, propafenone, ranolazine, rifampin,[f] rifapentine, high-dose sildenafil, salmeterol, simvastatin, St. John's wort, terfenadine, triazolam
Cautious Use or Dose Adjustment	
Antiretrovirals	**Atazanavir[g]:** 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[g]:** 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[g]:** ↑ IDV – ↓ IDV dose to 600 mg twice daily or 666 mg twice daily **Maraviroc:** ↑ MVC AUC – ↓ MVC dose to 150 mg twice daily **Nelfinavir[g]:** ↓ 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[g]:** SQV AUC and Cmin ↑ – Use SQV 1000 mg twice daily

Antiarrhythmics	**Amiodarone, bepridil, lidocaine (systemic), quinidine:** ↑ antiarrhythmics – Use with caution. Monitor concentrations of antiarrhythmics
Anticoagulants	**Rivaroxaban:** Rivaroxaban exposure ↑; possible increased bleeding. Avoid co-administration
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
Corticosteroids	**Budesonide, prednisone:** May ↑ steroid concentrations and ↓ serum cortisol concentrations. May ↑ risk for Cushing's syndrome and adrenal suppression. Consider alternatives for long-term use.

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
HCV-Protease Inhibitors	**Boceprevir:** Co-administration not recommended **Telaprevir:** Co-administration not recommended
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
Synthetic Narcotics	**Methadone:** ↓ methadone AUC 26%-53% – Monitor and titrate dose if needed
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.

[g] Dual boosted PIs are generally no longer recommended.

Nelfinavir (NFV) *(Updated October 2011)*	[package insert]
Trade Name	Viracept
Classification	Protease Inhibitor
Form	250-, 625-mg tablets
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

Anticoagulants	**Warfarin:** May ↑ warfarin concentration. Monitor INR closely with NFV co-administration
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)*	[package insert]
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, pitavastatin, 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)*	[package insert]
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, dofetilide, ergot derivatives, flecainide, garlic supplements (can be used with boosted SQV), lidocaine, lovastatin, midazolam,[d] pimozide, pitavastatin, propafenone, quinidine, ranolazine, rifabutin,[e] rifampin, rifapentine, high-dose sildenafil, simvastatin, St. John's wort, terfenadine, trazodone, 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)*	[package insert]
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, pitavastatin, propafenone, quinidine, ranolazine, rifampin, rifapentine, 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.
Opioid Addiction Medications	**Buprenorphine:** Compared to historical control, TPV AUC ↓ 26%; monitor for antiviral efficacy **Methadone:** Methadone ↓ 48% – Clinical significance unknown. May need to ↑ methadone dose

Enfuvirtide (T-20) *(Updated October 2012)*	[package insert]
Trade Name	Fuzeon
Classification	Fusion Inhibitor
Form	Injectable lyophilized 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)*	[package insert]
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	Rifapentine, 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.	

Dolutegravir (DTG)[a]	[package insert]
Trade Name	Tivicay
Classification	Integrase Strand Transfer Inhibitor (INSTI)
Form	50-mg tablet
Dosing Recommendations	**For ARV-naïve patients or ARV-experienced INSTI-naïve patients:** Dolutegravir 50 mg once daily **For INSTI-experienced patients** with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[a]: Dolutegravir 50 mg twice daily **When co-administered with EFV, FPV/r, TPV/r, or rifampin:** Dolutegravir 50 mg twice daily
Hepatic Impairment Dosing	Use not recommended in patients with severe hepatic impairment. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. Increased risk of hepatitis observed in patients with HBV or HCV co-infection.
Food Effect	High-fat meal increased dolutegravir AUC and Cmax 66% and 67%, respectively. Can be taken with or without food
Oral Bioavailability	Absolute bioavailability of dolutegravir has not been established
Serum Half-life	14 hours
Route of Metabolism	Eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway with some contribution from CYP3A. Excreted in feces and urine
Storage	Room temperature
Adverse Events	Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported. Discontinue immediately if signs or symptoms of hypersensitivity reactions develop. Patients co-infected with viral hepatitis B or C may be at increased risk for worsening or development of transaminase elevations. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with dolutegravir is recommended in patients with underlying hepatic disease such as hepatitis B or C. Risk of immune reconstitution syndrome similar to other ARVs. Dizziness, headache, nausea, diarrhea, insomnia.
FDA Pregnancy Category	B. No human data. Animal studies have revealed no evidence of impaired fertility or harm to the fetus
Black Box Warnings	None
Drugs to Avoid	**As part of the ARV regimen**: Nevirapine (may decrease dolutegravir concentrations) Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, St. John's wort (may decrease dolutegravir concentrations)

Cautious Use or Dose Adjustment	
Antiretrovirals	**Efavirenz**[b]: 57% ↓ DTG plasma concentration – ↑ DTG to 50 mg twice daily in ARV-naïve patients or ARV-experienced INSTI-naïve patients **Etravirine:** 71% ↓ DTG plasma concentration – DTG should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir **Fosamprenavir/ritonavir**[b]: 35% ↓ DTG plasma concentration – ↑ DTG to 50 mg twice daily in ARV-naïve patients or ARV-experienced INSTI-naïve patients **Tipranavir/ritonavir**[b]: 59% ↓ DTG plasma concentration – ↑ DTG to 50 mg twice daily in ARV-naïve patients or ARV-experienced INSTI-naïve patients
Antihyperglycemic agents	**Metformin:** May ↑ metformin concentration; monitor closely when starting or stopping DTG and metformin together. Metformin dose adjustment may be necessary
Antimycobacterials	**Rifampin**[b]**:** 54% ↓ DTG plasma concentration – ↑ DTG to 50 mg twice daily in ARV-naïve patients or ARV-experienced INSTI-naïve patients
Antiarrhythmics	May significantly ↑DTG serum concentrations and increase risk of cardiac arrhythmias. Do not co-administer with dofetilide
Polyvalent cation-containing agents (e.g., Mg, Al, Fe, or Ca)	Antacids, laxatives, sucralfate, oral iron supplements, oral calcium supplements, buffered medications: 74% ↓ DTG concentration – Avoid co-administration. Take DTG 2 hr before or 6 hr after taking medications containing polyvalent cations
Of note: No clinically significant change in dolutegravir concentrations was found with DRV/r, LPV/r, rilpivirine, TDF, boceprevir, telaprevir, prednisone, rifabutin, omeprazole.	

[a] Consider prior to initiating treatment with dolutegravir: Poor virologic response was observed in subjects treated with dolutegravir 50 mg twice daily with an INSTI-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions, including L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R.
[b] The lower DTG exposures observed in INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance) with co-administration of potent inducers may result in loss of therapeutic effect and development of resistance to DTG or other co-administered ARVs.

Elvitegravir (EVG)* **Elvitegravir is available only as a component of the combination pill Stribild* **Stribild** (elvitegravir/cobicistat/emtricitabine/tenofovir) [Stribild package insert]	
Trade Name	Stribild
Classification	Combination of 1 integrase strand transfer inhibitor (elvitegravir), 1 pharmacokinetic enhancer (cobicistat), and 2 nucleos(t)ide analog HIV-1 reverse transcriptase inhibitors (emtricitabine/tenofovir)
Form	Tablet (elvitegravir 150 mg, cobicistat 150 mg, tenofovir 300 mg, emtricitabine 200 mg)
Dosing Recommendations	**For ART-naïve patients:** 1 tablet once daily with food
Renal Impairment Dosing	• CrCl >70 mL/min: Use standard dose • Avoid use in patients with CrCl <70 mL/min at the start of treatment • Discontinue treatment in patients with CrCl <50 mL/min
Food Effect	Must be taken with food
Storage	Room temperature
Adverse Events	Nausea (16%), diarrhea (12%), vomiting, flatulence (2%); nausea more common compared to EFV/FTC/TDF, but comparable to ATV/r + FTC/TDF Rash is less common compared to EFV/FTC/TDF (15%) and ATV/r + FTC/TDF (6%) Central nervous system (CNS): Somnolence (1%), headache (7%), dizziness (3%), insomnia (3%), abnormal dreams (9%); CNS adverse drug reaction lower compared to EFV/FTC/TDF and comparable to ATV/r + FTC/TDF Patients with underlying renal insufficiency or other conditions predisposing to renal insufficiency may be at increased risk for nephrotoxicity Decreased bone mineral density Acute exacerbation of hepatitis B upon discontinuation of FTC/TDF Skin hyperpigmentation associated with emtricitabine Lactic acidosis and hepatic steatosis are rare. Causal relationship not established. *In vitro*, TDF is one of the NRTIs least associated with mitochondrial toxicity. In a clinical trial, d4T resulted in significantly more hyperlactatemia (>2.2 mmol/L) compared to TDF (27% vs. 4%, p <.0001). Hepatitis Burkitt's lymphoma No effect on cholesterol and lower triglyceride elevation compared to ATV/r + FTC/TDF
FDA Pregnancy Category	B (not teratogenic in animal studies; no human data)
Black Box Warnings	None

Drugs to Avoid	Stribild should not be co-administered with other ART agents; Stribild is a fully potent ART regimen Stribild should not be co-administered with adefovir
Cautious Use or Dose Adjustment	See: • Drug-Drug Interactions for Elvitegravir and Cobicistat table below • *Antiretroviral Therapy*: Appendix A: Tenofovir table • *Antiretroviral Therapy*: Appendix A: Emtricitabine table

DRUG-DRUG INTERACTIONS FOR ELVITEGRAVIR (EVG) AND COBICISTAT (COBI) *(EVG and COBI are currently approved only as components of the combination pill Stribild; for additional prescribing considerations, see the Stribild package insert)*		
Drug Class	**Effect of Interaction**	**Recommendations/Comments**
α-Blocker - Alfuzosin	May increase alfuzosin serum concentrations	o Contraindicated due to potential for hypotension; avoid concurrent use o Consider doxazosin and terazosin for benign prostatic hyperplasia (with close monitoring)
β-Blockers - Metoprolol - Timolol	Some β-blocker concentrations may be increased	Use low dose β-blocker with slow titration; may consider atenolol
Acid-reducing agents - PPIs - H_2 receptor blockers	No change in EVG when co-administered with famotidine or omeprazole	Use standard dose
Antiarrhythmics - Amiodarone - Bepridil - Disopyramide - Flecainide - Lidocaine (systemic) - Mexiletine - Propafenone - Quinidine	COBI may increase serum concentrations of antiarrhythmics	Use with caution; monitor antiarrhythmic concentrations with dose adjustment
Antacids	EVG AUC decreased 15-20% when antacid administered 2 hours before or 2 hours after EVG	Administer EVG at least 2 hours before or after antacid
Antianginal - Ranolazine	May significantly increase ranolazine serum concentrations	o Avoid co-administration o May increase risk of QTc prolongation
Antibiotic - Trimethoprim	Similar to COBI, high-dose trimethoprim may inhibit tubular secretion of creatinine resulting in an additive increase in serum creatinine	o Co-administration may result in an additive increase in serum creatinine o Unless direct measurement of GFR (i.e., iohexol) can be performed, discontinuation is recommended with a serum creatinine elevation of >0.4 mg/dL

Anticoagulant - Warfarin	Warfarin concentrations may be increased or decreased due to CYP3A inhibition and CYP2C9 induction	Monitor INR closely and adjust warfarin dose accordingly
Anticonvulsants		
- Carbamazepine - Oxcarbazepine	o Carbamazepine concentrations may be increased o COBI and EVG concentrations may be decreased	o Avoid co-administration o Consider valproic acid or levetiracetam
- Ethosuximide	COBI may increase ethosuximide concentrations	Use with close monitoring
- Phenobarbital - Phenytoin	May significantly decrease COBI and EVG concentrations	o Avoid co-administration o Consider valproic acid or levetiracetam
Antidepressants		
- SSRIs (e.g., paroxetine)	COBI may increase SSRI concentrations	Start with low dose then titrate SSRI to therapeutic effect
- St John's wort (*Hypericum perforatum*)	May significantly decrease COBI and EVG serum concentration	Contraindicated due to potential loss of therapeutic effect; avoid concurrent use
- Trazodone	COBI may increase serum concentration of trazodone	Initiate with lowest dose of trazodone and titrate dose of trazodone carefully
- Tricyclics (TCAs; e.g., desipramine, amitriptyline, imipramine, nortriptyline)	o Desipramine AUC increased 65% o Other TCA concentrations may also be increased	o Start with low-dose TCA and monitor for adverse drug reactions o SSRI may be preferred due to better safety profile
Antifungals		
- Itraconazole	COBI may increase serum concentration of itraconazole, and itraconazole may increase COBI and EVG concentrations	o Avoid itraconazole >200 mg/day o Monitor itraconazole serum concentrations (target >1-2 μg/mL) with co-administration
- Ketoconazole	COBI may increase serum concentrations of ketoconazole	Do not exceed ketoconazole 200 mg once daily
- Posaconazole	COBI may increase serum concentrations of posaconazole	Monitor posaconazole serum concentrations with co-administration
- Voriconazole	COBI may increase or decrease voriconazole serum concentration due to CYP3A4 inhibition and CYP2C9 induction, and voriconazole may increase COBI and EVG concentrations	Monitor voriconazole serum concentration (target Cmin >2 μg/mL) with co-administration
Antigout agent - Colchicine	COBI may significantly increase colchicine concentrations	o No data o Dose for patients with normal renal and hepatic function: colchicine one dose of 0.6 mg, followed by 0.3 mg 1 hour later for acute gout flare; treatment course may be repeated no earlier than 3 days o For gout prophylaxis, use 25% of the original dose

		o Monitor closely for bone marrow suppression
Anti-hepatitis B agent - Entecavir	Interaction unlikely	Use standard dose
Anti-hepatitis C agents - Boceprevir - Telaprevir	No data	Do not co-administer
Antihistamines - Astemizole - Terfenadine	COBI may significantly increase serum concentration of astemizole and terfenadine	Contraindicated due to the potential for cardiac arrhythmia; avoid concurrent use
Antimycobacterials		
- Clarithromycin	Clarithromycin, COBI, and EVG concentrations may be increased	o Dose: adjust clarithromycin dose according to renal function - CrCl ≥60 mL/min: use standard dose - CrCl <50-60 mL/min: 50% of clarithromycin dose o Avoid with QTc prolongation o Consider using azithromycin
- Rifabutin	o EVG AUC and Cmin decreased by 21% and 67%, respectively o Rifabutin active metabolite (25-*O*-desacetyl rifabutin) AUC increased 6.25-fold	o Avoid co-administration o Consider an alternative antimycobacterial agent (e.g., fluoroquinolone)
- Rifampin	Rifampin may significantly decrease COBI and EVG concentrations	o Contraindicated due to potential loss of therapeutic effect; avoid concurrent use o Consider an alternative antimycobacterial agent (e.g., fluoroquinolone)
- Rifapentine	Rifapentine may significantly decrease COBI and EVG concentrations	o Avoid co-administration o Consider an alternative antimycobacterial agent (e.g., fluoroquinolone)
Antipsychotic - Pimozide	COBI may significantly increase serum concentration of pimozide	Contraindicated due to potential for QTc prolongation and cardiac arrhythmias; avoid concurrent use
Antivirals - Famciclovir - Ribavirin	Interaction unlikely	Use standard dose
Anxiolytic - Buspirone	COBI may increase buspirone concentrations	Buspirone dose may need to be decreased; monitor for adverse drug reactions (i.e. dizziness, drowsiness)
ART agents		o Elvitegravir and cobicistat are currently approved only as components of the combination pill Stribild, which is designed as a fully potent ART

		o Stribild should not be co-administered with other ART agents
Benzodiazepines - Alprazolam - Chlordiazepoxide - Clonazepam - Clorazepate - Diazepam - Estazolam - Flurazepam - Midazolam (oral) - Triazolam	COBI may increase plasma concentrations of benzodiazepines that are 3A4 substrates	o Oral midazolam is contraindicated o Use IV midazolam with very close monitoring o Avoid triazolam co-administration o Benzodiazepine dose adjustment may be needed o Consider using lorazepam, temazepam, or oxazepam
Bronchodilator - Salmeterol (inhaled)	COBI may increase salmeterol serum concentrations	o Avoid co-administration o Consider formoterol
Calcium channel blockers - Amlodipine - Diltiazem - Felodipine - Nifedipine - Verapamil - Nicardipine	COBI may increase serum concentration of all calcium channel blockers	Use with close monitoring
Cardiac glycoside - Digoxin	Digoxin Cmax increased 41%; digoxin AUC not significantly affected	Use with caution; monitor antiarrhythmic concentrations with dose adjustment
Corticosteroids		
- Dexamethasone	Dexamethasone (at steady state) may decrease COBI and EVG concentrations	Consider alternative corticosteroid (prednisone or methylprednisolone)
- Fluticasone (inhaled/intranasal)	COBI may increase serum concentration of fluticasone	o Avoid co-administration o Concurrent use of fluticasone and RTV might lead to increased fluticasone plasma concentrations and decreased cortisol, resulting in Cushing's syndrome o Consider beclomethasone
- Prednisone	COBI may increase serum concentration of prednisone	o Concurrent use of prednisone and COBI may lead to increased prednisolone plasma concentrations o May require a lower prednisone dose with long-term co-administration
Erectile dysfunction agents		
- Sildenafil	COBI may significantly increase sildenafil concentrations	o Contraindicated when used for pulmonary arterial hypertension due to increased risk for significant sildenafil adverse effects o Avoid high-dose sildenafil; for erectile dysfunction, do not exceed 25 mg in 48 h
- Tadalafil	COBI may significantly increase tadalafil concentrations	o Dose adjustment for erectile dysfunction; do not exceed tadalafil 10 mg q72h

		o Dose adjustment pulmonary hypertension: once COBI is at steady state (1 week), initiate tadalafil 20 mg/day once daily, then titrate to 40 mg/day
- Vardenafil	COBI may significantly increase vardenafil concentrations	o Avoid high dose vardenafil o Dose adjustment for erectile dysfunction, do not exceed vardenafil 2.5 mg q 72h
Ergot derivative - Ergot alkaloid	COBI may significantly increase serum concentration of ergot alkaloid	o Contraindicated due to the potential for acute ergotism; avoid concurrent use
Gastroprokinetic agent - Cisapride	COBI may significantly increase serum concentration of cisapride	Contraindicated due to the potential for cardiac arrhythmia; avoid concurrent use
Immunosuppressive agents		
- Cyclosporine	COBI may significantly increase serum concentration of cyclosporine	Use with dose adjustment and close monitoring of cyclosporine serum concentrations
- Sirolimus	COBI may significantly increase serum concentration of sirolimus	Avoid or use with dose adjustment and close monitoring of sirolimus serum concentrations
- Tacrolimus	COBI may significantly increase serum concentration of tacrolimus	Use with dose adjustment and close monitoring of tacrolimus serum concentration
Ketolide antibiotic - Telithromycin	Telithromycin and COBI concentrations may be increased	Monitor for hepatitis
Lipid-lowering agents		
- Atorvastatin	COBI may increase atorvastatin concentrations	Dose: Start with low-dose atorvastatin and titrate slowly; avoid doses >40 mg/day
- Lovastatin	COBI may significantly increase lovastatin serum concentration	o Contraindicated due to potential for myopathy/rhabdomyolysis; avoid concurrent use o Consider alternative statin (pravastatin, atorvastatin, and rosuvastatin)
- Pravastatin	Pravastatin concentrations may be increased	o No data o Consider starting with 10 mg once-daily and titrate slowly
- Rosuvastatin	o Rosuvastatin AUC increased 38% o No change in EVG concentrations	Initiate with low dose rosuvastatin (5 mg) with co-administration
- Simvastatin	COBI may significantly increase simvastatin serum concentration	o Contraindicated due to potential for myopathy/rhabdomyolysis; avoid concurrent use o Consider alternative statin (pravastatin, atorvastatin, and rosuvastatin or pitavastatin)

Neuroleptics - Aripiprazole - Fluphenazine - Haloperidol - Perphenazine - Quetiapine - Risperidone - Thioridazine - Ziprasidone	COBI may increase neuroleptic concentrations	o A lower dose of the neuroleptic may be required o Monitor for adverse drug reactions
Oral contraceptives (e.g., norgestimate/ethinyl estradiol)	o Norgestimate AUC increased 126% o Ethinyl estradiol AUC decreased 25%	o Monitor for potential increased progestational effect o An additional form of contraception can be considered
Pulmonary hypertension agent - Bosentan	May significantly increase bosentan serum concentrations	o No data o Recommendation based on RTV co-administration o Co-administer bosentan only after COBI dosing has reached steady state o In patients on COBI >10 days: start bosentan at 62.5 mg once daily or every other day o In patients already receiving bosentan: discontinue bosentan for ≥36 hours prior to initiation of COBI and restart bosentan at 62.5 mg once daily or every other day after COBI has reached steady state (after 10 days) o Consider ambrisentan for pulmonary hypertension
Sedative-hypnotic - Zolpidem	COBI may increase zolpidem serum concentrations	Zolpidem dose may need to be decreased
Synthetic opioids		
- Buprenorphine	Buprenorphine serum concentrations may be increased	Monitor for possible increased sedation
- Methadone	No significant effect	No dosage adjustment necessary

Raltegravir (RAL) *(Updated December 2011)*	[package insert]
Trade Name	Isentress
Classification	Integrase Strand Transfer Inhibitor (INSTI)
Form	25-mg chewable tablet, 100-mg chewable tablet, 400-mg film-coated tablets Formulations are not bioequivalent – do not substitute chewable tablets for the 400-mg film-coated tablet
Dosing Recommendations	One film-coated 400 mg tablet 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	Severe, potentially life-threatening, and fatal skin reactions have been reported, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Discontinue immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop. 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 (2013)*	DHHS Recommendations (2013)†	IAS-USA Recommendations (2012)‡
1. Evaluation for initiation of ART is recommended for *all* patients with chronic HIV infection, regardless of CD4 count. (AII) **2. The highest risk patients, in whom timely ART initiation is most important, continues to include those who**: • have an AIDS-defining condition (AI) • are pregnant (AI) • are symptomatic from HIV (AI), regardless of CD4 count, including any of the following: o HIV-associated neurocognitive disorder (HAND) (AII) o Severe thrombocytopenia (AII) o HIV-associated nephropathy (AII) o HIV-related malignancies (AII) • have chronic hepatitis B or C infection (AII) • have two successive measurements of CD4 counts ≤500 cells/mm^3 (AII) • are age 50 or older (AII) • have rapidly declining CD4 counts (>100 cells/mm^3 per year) (AIII) **3. Patients with seronegative partners should be counseled about the reduction of HIV transmission risk when effective ART is initiated; ART is strongly recommended in these patients.** (AI)	**1. ART is recommended for all HIV-infected individuals. The strength and evidence for this recommendation varies on the basis of pretreatment CD4 cell count:** • CD4 count <350 cells/mm^3 (AI) • CD4 count 350 to 500 cells/mm^3 (AII) • CD4 count >500 cells/mm^3 (BIII) **2. ART is recommended for HIV-infected individuals for the prevention of transmission of HIV. The strength and evidence for this recommendation vary by transmission risk:** • Perinatal transmission (AI) • Heterosexual transmission (AI) • Other transmission groups (AIII) **3. Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence** (AIII)**. Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.**	**ART is recommended and should be offered regardless of CD4 count. The strength of the recommendation increases as CD4 count decreases and in the presence of the following conditions:** • Pregnant women • Chronic hepatitis B virus co-infection • Hepatitis C virus co-infection • Age >60 years • HIV-associated nephropathy • Acute phase of primary HIV infection, regardless of symptoms

* See Table 3.

† 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. February 12, 2013. Available at: www.aidsinfo.nih.gov

‡ Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International AIDS Society--USA Panel. *JAMA* 2012;308:387-402.

APPENDIX C: EVIDENCE BASE FOR RECOMMENDATIONS TO INITIATE ART

EVIDENCE BASE FOR RECOMMENDATIONS TO INITIATE ART	
Evaluation of all chronically infected patients for initiation of ART	(AII) Refs 1-6
Patients who are symptomatic	(AI) Refs 5-7
Patients who are pregnant	(AI) Ref 8
Patients with CD4 count ≤500 cells/mm^3	(AII) Refs 1, 4-6,9,10
Patients with HIV-related conditions	
o HIV-associated neurocognitive disorder	(AII) Ref 11-14
o Severe thrombocytopenia	(AII) Refs 15-17
o HIV-associated nephropathy	(AII) Refs 5-7,18-20
o HIV-related malignancies	(AII) Refs 21-25
Patients with chronic HBV	(AII) Refs 5,6,9,26,27
Patients with chronic HCV	(AII) Refs 6,7,26,28,29
Patients 50 years of age or older	(AII) Refs 1,9,30-33
Patients with rapid decline in CD4 count, defined as >100 cells/mm^3 per year	(AIII) Ref 5
Partner serodiscordance	(AI) Refs 34-37

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. Writing Committee for the CASCADE Collaboration. Timing of HAART initiation and clinical outcomes in human immunodeficiency virus type 1 seroconverters. *Arch Intern Med* 2011;171:1560-1569. [PubMed]

3. Marin B, Thiébaut R, Bucher HC, et al. Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy. *AIDS* 2009;23:1743-1753. [PubMed]

4. 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.**

5. 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. February 12, 2013. Available at: www.aidsinfo.nih.gov. **Recommends treatment for all HIV-infected patients to reduce disease progression with strength and evidence varying by pretreatment CD4 count. ART also recommended to prevent transmission of HIV.**

6. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International AIDS Society -- USA Panel. *JAMA* 2012;308:387-402. [PubMed] **ART is recommended and should be offered regardless of CD4 count. Strength of the recommendation increases as CD4 cell count decreases and in the setting of pregnancy, chronic HBV or HCV co-infection, age >60 years, HIV-associated nephropathy, acute phase of primary HIV infection.**

7. European AIDS Clinical Society (EACS). Guidelines for the clinical management and treatment of HIV-infected adults in Europe, version 6. October 2011. Available at: http://www.europeanaidsclinicalsociety.org/. **Recommends treatment for patients with any of the following: symptomatic HIV disease, HIV-associated kidney disease, HIV-associated neurocognitive impairment, Hodgkin's lymphoma, HPV-associated cancers, HBV requiring treatment, active HCV co-infection with CD4 <500 cells/mm^3.**

8. Centers for Disease Control and Prevention. Achievements in public health. Reduction in perinatal transmission of HIV infection--United States, 1985-2005. *MMWR Morb Mortal Wkly Rep* 2006;55:592-597. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5521a3.htm

9. 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.**

10. 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.**

11. 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.**

12. Ellis RJ, Badiee J, Vaida F, et al. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. *AIDS* 2011;25:1747-1751. [PubMed] **Initiation of ART as early as possible may reduce the risk of developing HAND.**

13. Borjabad A, Morgello S, Chao W, et al. Significant effects of antiretroviral therapy on global gene expression in brain tissues of patients with HIV-1-associated neurocognitive disorders. *PLoS Pathog* 2011;7:e1002213. [PubMed] **ART can be broadly effective in reducing pathophysiological changes in the brain associated with HAND.**

14. Heaton RK, Franklin DR, Ellis RJ, et al. HIV-associated neurocognitive disorders before and after the era of combination antiretroviral therapy: Differences in rates, nature, and predictors. *J Neurovirol* 2011;17:3-16. [PubMed] **Consistent association of neurocognitive impairment with nadir CD4 count in both the pre- and post-ART era suggests that earlier treatment may help to prevent HAND.**

15. 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.**

16. 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.**

17. 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.**

18. Wearne N, Swanepoel CR, Boulle A, et al. The spectrum of renal histologies seen in HIV with outcomes, prognostic indicators and clinical correlations. *Nephrol Dial Transplant* 2012;27:4109-4118. Epub ahead of print. [PubMed] **ART reduced mortality in patients with HIVAN. Patients with HIVAN alone were followed for 2 years on ART and showed stable GFR and a trend toward decreased proteinuria.**

19. Lescure F-X, Flateau C, Pacanowski J, et al. HIV-associated kidney glomerular diseases: Changes with time and HAART. *Nephrol Dial Transplant* 2012;27:2349-2355. Epub ahead of print. [PubMed] **Marked reduction in HIVAN in recent years as more patients are receiving ART.**

20. Wyatt CM, Meliambro K, Klotman PE. Recent progress in HIV-associated nephropathy. *Annu Rev Med* 2012;63:147-159. [PubMed] **Review investigating the role of HIV in HIVAN pathogenesis. Establishes HIVAN as a direct result of HIV infection and as indication for ART.**

21. Silverberg MJ, Chun C, Leyden W, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. *Cancer Epidemiol Biomarkers Prev* 2011;20:2551-2559. [PubMed] **Immunodeficiency was positively associated with the following non-HIV-related malignancies: lung cancer, colorectal cancer, and melanoma compared with HIV-uninfected individuals. Earlier ART initiation to maintain high CD4 levels might reduce the risk of cancer.**

22. 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.**

23. 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.**

24. 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.**

25. 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.**

26. 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.**

27. Matthews GV, Avihingsanon A, Lewin SR, et al. A randomized trial of combination hepatitis B therapy in HIV/HBV coinfected antiretroviral naïve individuals in Thailand. *Hepatology* 2008;48:1062-1069. [PubMed]

28. 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.**

29. 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.**

30. Sabin CA, Smith CJ, d'Arminio Monforte A, et al., Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Study Group. Response to combination antiretroviral therapy: Variation by age. *AIDS* 2008;22:1463-1473. [PubMed] **Better virologic response but lower immunologic response in individuals 55 and older.**

31. van Lelyveld SF, Gras L, Kesselring A, et al., on behalf of the ATHENA national observational cohort study. Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort. *AIDS* 2012;26:465-474. [PubMed] **Poor immunological recovery despite virological successful ART is associated with a higher risk for overall morbidity and mortality, underscoring the importance of starting ART at higher CD4 cell counts, particularly in older patients.**

32. 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**.

33. Li X, Margolick JB, Jamieson BD, et al. CD4 T-cell counts and plasma HIV-1 RNA levels beyond 5 years of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2011;57:421-428. [PubMed] **Men >50 years of age who start ART with CD4 counts between 351-500 cells/mm^3 could achieve the same immunologic response as younger men who started with lower CD4 counts.**

34. Cohen MS, Chen YQ, McCauley M, et al., HPTN 052 Study Team Prevention of HIV-infection with early antiretroviral therapy. *N Engl J Med* 2011;365:493-505. [PubMed]

35. 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.**

36. 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.**

37. 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.**

APPENDIX D. NEW YORK STATE ADHERENCE SERVICES CONTACT LIST

January 2010

Albany Medical College
Joseph Kerwin
AIDS Program Administrator
47 New Scotland Avenue
Albany, NY 12208
(518) 262-4432

Bellevue Hospital Center
Lucy Grugett
Assistant Director, Grants Management
462 First Avenue, 12 E 12
New York, NY 10016
(212) 562-5201
lucy.grugett@bellevue.nychhc.org

Community Health Network
Danita Djelosk
Treatment Adherence Program Coordinator
87 North Clinton Avenue, 4th Floor
Rochester, NY 14604
(585) 244-9000, Ext. 247
ddjeloski@achcrochester.org

Erie County Medical Center, Corp.
Kathleen Walsh MSW, CSW
AIDS Program Administrator
462 Grider Street
Buffalo, NY 14215
(716) 898-4481
kwalsh@ecmc.edu

Greenwich House, Inc.
Gerri Matusewitch
Assistant Executive Director
224 West 30 Street, 3rd Floor
New York, NY 10001
(212) 991-0003, Ext. 202
gmatusewitch@greenwichhouse.org

Harlem Hospital Center
Trustees of Columbia University in the City of New York
Sharon Mannheimer, MD
Program Director
506 Lenox Avenue, Room 3101A
New York, NY 10037
(212) 939-2948
sbm20@columbia.edu

Kings County Hospital Center
John Krevitt, MPH
Associate Director
451 Clarkson Avenue
Brooklyn, NY 11203
(718) 245-2821
krevittj@nychhc.org

Montefiore Medical Center
Jorge Rodriguez
Administrative Director
111 East 210th Street
Bronx, NY 10467
(718) 920-2199
jorrodri@montefiore.org

Nassau Health Care, Corp.
Hamid Reza Pahlevan, MD
Adherence Counselor
2201 Hempstead Turnpike
Mailbox 73
East Meadow, NY 11554
(516) 572-1319
hpahleva@numc.edu

New York Presbyterian Medical Center
Paula Merrick-Lewis
Coordinator, Education and Outreach
Partnership for Family Health
Alice Higgins
Program Administrator
Columbia University Medical Center
180 Fort Washington Avenue, #624
New York, NY 10032
(212) 305-8925
pam9069@nyp.org

Promesa, Inc.
Lisa Garay
CEO
1776 Clay Avenue
Bronx, NY 10457
(718) 960-7601
lgaray@promesa.org

St. John's Riverside Hospital
Diane Anderson LCSW-R, CASAC
Assistant Director - HOPE Center
2 Park Avenue
Yonkers, NY 10703
(914) 964-7551
danderson@riversidehealth.org

SUNY Brooklyn/Downstate Medical Research Foundation
Jayashree Ravishankar, MD
Medical Director
PO Box 1240
450 Clarkson Avenue
Brooklyn, NY 11203
(718) 270-4180
jayashree.ravishankar@downstate.edu

SUNY Upstate Medical University Hospital Research Foundation
Judith Rees, ACRN, NP
Program Director
Crouse Physicians Office Building
725 Irving Avenue, Suite 211
Syracuse, NY 13210
(315) 464-5533
reesj@upstate.edu

Westchester County Health Care Corporation
Claire Brazil, RN
Coordinator
BHC-S022
Valhalla, NY 10595
(914) 493-7905
brazilc@wcmc.com

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

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).

Continues on next page…

[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