Published in final edited form as:
Am J Health Syst Pharm. 2011 June 1; 68(11): 991–1001. doi:10.2146/ajhp100156.

A Review of Recommendations and Treatment Options Regarding the Management of HIV Infection

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Abstract

Purpose—This review focuses on the recommendations for when to initiate antiretroviral therapy and what regimen to use in treatment-naïve patients based on the January 2011 antiretroviral guidelines released by the Department of Health and Human Services (DHHS). The evolution of recommendations over the past decade, key data supporting recent changes, and information related to management of antiretroviral therapy are discussed.

Summary—Treatment guidelines are updated frequently because of ongoing emergence of data demonstrating the risks and benefits of antiretroviral therapy. The DHHS guidelines strongly recommend initiating therapy in patients with certain conditions regardless of CD4 cell count and in patients with CD4 cell counts <350 cells/mm^3. Although supporting data are less definitive, treatment is also recommended for patients with CD4 cell counts between 350–500 cells/mm^3. Treatment for patients with CD4 cell counts >500 cells/mm^3 is controversial. Although cumulative observational data and biological evidence support treatment at higher CD4 cell counts, randomized controlled trial data are not available, and the risk of antiretroviral toxicities, resistance, nonadherence, and cost should be considered in individual patients. The preferred regimens have been consolidated to four options, including a dual-nucleoside reverse transcriptase inhibitor backbone (tenofovir/emtricitabine) with a non-nucleoside reverse transcriptase inhibitor (efavirenz), a ritonavir-boosted protease inhibitor (atazanavir + ritonavir or darunavir + ritonavir), or an integrase strand transfer inhibitor (raltegravir). Regimens are classified as alternative or acceptable when they have potential safety or efficacy concerns, consist of higher pill burdens, or require more frequent dosing compared to preferred regimens.

Conclusion—The DHHS guidelines advocate earlier treatment initiation than recommended in recent years, yet recognize the limitations of the data supporting treatment at higher CD4 cell counts. Preferred regimens have been refined to maximize efficacy, safety, and quality of life for patients. The guidelines will continue to be updated as new data emerges.

Evidence to guide HIV-1 (hereafter referred to as HIV) treatment has been rapidly increasing for over a decade, particularly since the advent of combination antiretroviral therapy in 1996. The goals of antiretroviral therapy are to achieve and maintain viral suppression, prevent morbidity and mortality, restore and preserve immune function, and prevent HIV transmission.[1] HIV treatment is complex, lifelong, and usually requires a minimum of three antiretroviral drugs from at least two different drug classes to achieve long-term viral suppression. Given the availability of over twenty antiretroviral agents in six

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Disclosure:
Sarita D. Boyd serves as a non-voting observer on the DHHS Panel on Antiretroviral Guidelines for Antiretroviral Guidelines for Adults and Adolescents and has no potential financial conflicts of interest to report.

different drug classes today, numerous regimens can be created, each with potential advantages and disadvantages that need to be considered in the context of an individual patient. The decision about which regimen to initiate is not only based on safety and efficacy data from clinical trials but also on baseline drug resistance mutations, adherence-related factors, potential for drug-drug interactions, and other patient-specific factors.

The data supporting when to initiate antiretroviral therapy are less definitive than the evidence for which regimen to start. CD4 cell counts and HIV viral load are surrogate markers used to monitor HIV disease progression prior to starting therapy and to monitor antiretroviral efficacy after initiating therapy. Advanced HIV disease is associated with immune deterioration and increased risk of opportunistic infections and AIDS-defining illnesses, such as pneumocystis pneumonia (PCP), toxoplasmosis, cryptococcosis, etc. Low CD4 cell counts have typically been used as a surrogate marker for immunodeficiency, and thus used as a reference for when to start therapy. More recently, non-AIDS-related morbidity and mortality have been associated with higher CD4 cell counts,[2–4] suggesting treatment should be initiated earlier. The benefits and risks of starting or deferring antiretroviral therapy at various CD4 thresholds should be considered in each patient in order to optimize treatment goals.

First written in 1998 and since revised one to two times per year, the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents released by the Department of Health and Human Services[1] (hereafter referred to as the guidelines) contain detailed HIV treatment recommendations based on available data at the time of each revision. Among other topics, the guidelines address the goals of HIV treatment, when and what antiretroviral drugs to initiate, antiretroviral combinations to avoid, management of treatment-experienced patients, and overall therapeutic management of HIV patients. Guidelines for antiretroviral treatment in pregnant women[5] and pediatric patients[6] are available as separate, individual documents and are updated at varying intervals. Over the years, the recommendations for adults and adolescents have evolved based on the emergence of new data, particularly regarding initiation of antiretroviral therapy and selection of antiretroviral regimens.

When to start antiretroviral therapy in a treatment-naïve patient?

There has been a persistent debate about when to start antiretroviral therapy, particularly in asymptomatic treatment-naïve patients, and upon which CD4 cell count and/or viral load thresholds, if any, to base this decision. One consistent and concurrent recommendation throughout all guideline iterations has been to treat patients with an AIDS-defining condition[7] regardless of CD4 cell count or viral load. For other patients, the recommendations between 1998 and 2007 gradually shifted from treating early at higher CD4 cell counts (500 cells/mm^3 or less) and lower viral load thresholds (20,000 copies/mL or more) to deferring treatment until achievement of lower CD4 cell counts (less than 200 cells/mm^3) and higher viral loads (greater than 100,000 copies/mL). In 1998, combination therapy with three antiretroviral agents became standard of care, and the strategy was to treat early and aggressively with the theory of eradicating HIV.[8] However, it became clear that HIV eradication was not feasible with current treatment[9–10] and the regimens available at that time were associated with decreased quality of life for many patients. Given the high pill burdens, frequent dosing schedules, intolerable side effects, and moderate potency of the regimens along with data showing lower chance of progression to AIDS within a few years with higher CD4 cell counts,[11] treatment deferral became a strategy to prevent the development of drug resistance secondary to nonadherence and intolerance without causing rapid disease progression.

Several years after treatment deferral became standard of care, antiretroviral regimens with low pill burdens (including combination drug products), once-daily dosing, better side effect profiles, and higher potency led to increased adherence and better success with early treatment. In 2007, the guidelines reverted back to recommending treatment at higher CD4 cell counts (350 cells/mm^3 and less) and eliminated the use of viral load as a criterion to start therapy.[12] In addition, treatment was recommended irrespective of CD4 cell count for patients who are pregnant or who have certain non-AIDS-defining conditions, such as HIV-associated nephropathy (HIVAN) or hepatitis B virus (HBV) co-infection if HBV treatment is indicated. In 2009, the guidelines recommended starting treatment at CD4 <500 cells/mm^3, similar to the first guidelines in 1998, and possibly treating patients with even higher CD4 cell counts; these recommendations remain unchanged in the 2011 guidelines (Table 1).

Treatment initiation in patients with CD4 <350 cells/mm^3 is strongly recommended and was initially based on mostly observational cohort data showing decreased risk of death, AIDS, and/or non-AIDS-defining conditions when initiating antiretroviral therapy at higher CD4 thresholds.[13–16] This recommendation was recently strengthened by randomized controlled trial data from the CIPRA-HT-001 trial conducted in Haiti in which antiretroviral-naïve patients with CD4 251–350 cells/mm^3 were randomized to immediate antiretroviral therapy versus deferred treatment until CD4 <200 cell/mm^3. Interim analysis of 816 patients by a data safety monitoring board (DSMB) showed a significantly higher mortality rate in the deferred treatment arm compared to the immediate treatment arm (HR 4.0, p=0.0011), resulting in early termination of the trial.[17] Starting antiretroviral therapy in patients with CD4 <350 cells/mm^3 is well established and is not generally disputed.

Conversely, recent recommendations to start treatment in patients with CD4 350–500 cells/mm^3 and CD4 >500 cells/mm^3 are controversial even among panel members as noted by the split in the strengths of these recommendations (Table 1). The rationale for earlier treatment is based on a collection of observational cohort studies that indicate a reduction in AIDS- and non-AIDS-related morbidity and mortality and prevention of sexual HIV transmission as a result of effective antiretroviral therapy. Arguments against starting antiretroviral therapy in patients with higher CD4 cell counts include the lack of prospective randomized controlled trials showing benefits of treatment as well as concerns about antiretroviral toxicities when used for decades, potential for selection of resistance mutations, nonadherence, and cost. The guidelines discuss both the benefits and concerns with early treatment and the evidence to support both arguments.

Two large, observational cohort studies, conducted primarily in Europe and North America, recently suggested treatment at higher CD4 cell counts lowers the risk of AIDS[18] and death.[2, 18] The first study showed a 28% increased risk of AIDS and death in patients who started treatment at CD4 251–350 cells/mm^3 compared to CD4 351–450 cells/mm^3 (HR 1.28, 95% confidence interval [1.04–1.57]), but no differences were seen in groups who started treatment at higher CD4 thresholds.[18] The causes of death in either arm were not defined. The second study showed a 69% increased risk of death in patients who started treatment at CD4 <350 cells/mm^3 compared to CD4 351–500 cells/mm^3 (RR 1.69, 95% confidence interval [1.26–2.26], p<0.001) and a 94% increased risk of death in patients who started treatment at CD4 <500 cells/mm^3 compared to >500 cells/mm^3 (RR 1.94, 95% confidence interval [1.37–2.79], p<0.001).[2] The causes of only 16% of deaths in both arms were provided, and the majority were non–AIDS-defining conditions, including hepatic, renal, and cardiovascular diseases and non–AIDS-defining cancers.[2]

Although these studies showed a significant and impressive increased relative risk of AIDS and/or death in patients who start treatment at lower CD4 cell counts, the absolute number

of events were low, and more importantly, they were not prospective, randomized controlled trials. These retrospective, observational studies attempted to adjust and control for potential confounding factors but could still have unmeasured bias, which would be more accurately accounted for in a prospective, randomized trial. The START study is an ongoing randomized controlled trial designed to determine whether antiretroviral initiation at CD4 >500 cells/mm^3 is superior to deferral until CD4 <350 cells/mm^3 in terms of AIDS- and non-AIDS-related morbidity and mortality.[19] This trial may also better address the concerns over potential limitations to early treatment, such as adverse effects and drug resistance, but results are not expected for several years.

Other studies have shown a positive association between untreated HIV infection and some non-AIDS-related morbidities such as HIVAN leading to chronic kidney disease and end-stage renal disease, HBV or hepatitis C (HCV) progression, cardiovascular disease, malignancies, and neurocognitive decline. The direct and indirect effects of HIV-associated inflammation and T-cell activation on particular end organs may be attenuated by initiating antiretroviral therapy and achieving suppressed viral loads. Suppressed viral load may halt the progression of or reverse renal dysfunction associated with HIVAN,[20–22] and the guidelines strongly recommend antiretroviral treatment for patients with HIVAN regardless of CD4 cell count. Patients with HBV co-infection should also start antiretroviral therapy regardless of CD4 cell count if HBV treatment is indicated, using antiretroviral agents with activities against both viruses (i.e. tenofovir + emtricitabine or lamivudine). HBV and HCV co-infected patients may also have a more rapid progression of liver disease,[23–24] but a decrease in cirrhosis, end-stage liver disease, hepatocellular carcinoma, and fatal hepatic failure as a result of HIV suppression has not been confirmed. Similarly, observational cohort data suggests a link between lower CD4 cell counts (<350–500 cells/mm^3) and AIDS- and non-AIDS-associated malignancies[3, 25] and HIV-associated dementia,[26] but definitive evidence is not available to strongly recommend antiretroviral therapy to prevent malignancies or neurocognitive decline.

Reduction of HIV replication may also lower the risk of cardiovascular disease, which was observed as a secondary endpoint in the SMART study, where participants with CD4 >350 cells/mm^3 were randomized to continuous antiretroviral therapy or CD4-guided treatment interruptions. Treatment interruption was episodic and consisted of deferred antiretroviral therapy until occurrence of CD4 <250 cells/mm^3 followed by the use of antiretroviral therapy until CD4 increased back above 350 cells/mm^3. Compared to the continuous therapy arm, participants in the treatment interruption arm had a significantly greater incidence of cardiovascular events.[27] Additional data linking cardiac inflammatory markers and endothelial dysfunction with viremia also suggests earlier antiretroviral therapy may reduce the risk of cardiovascular disease.[28]

The recommendations for earlier treatment are also based on evidence that viral suppression can reduce the risk of HIV transmission. Use of antiretroviral therapy in pregnant women has decreased mother-to-child transmission rates from 20–30% to <2%,[29] and treatment of all pregnant women regardless of CD4 cell count is strongly recommended. Antiretroviral therapy to prevent sexual transmission is an emerging concept, and studies have shown reduced transmission rates between discordant heterosexual couples when viremia is suppressed in the HIV-infected partner.[30–31] Additional data are necessary to further support the concept of “treatment as prevention,” and concerns about nonadherence, incomplete viral suppression, and potential transmission of resistant HIV need to be addressed.

The totality of evidence generally supports initiation of antiretroviral therapy in patients with CD4 >350 cells/mm^3 to minimize progression to further immune deficiency, reduce AIDS- and non-AIDS-related morbidity and mortality, and prevent HIV transmission.

However, important limitations to early treatment remain, and deferral of antiretroviral therapy should be considered in some patients with higher CD4 cell counts. Deferral of therapy is reasonable in patients who have significant barriers to adherence or comorbidities that complicate or prohibit treatment, in patients who maintain plasma viral loads below the limit of standard detection in the absence of antiretroviral therapy (elite controllers), and in patients who sustain normal CD4 cell counts in the absence of antiretroviral therapy over 7–10 years (long-term nonprogressors). The benefit of antiretroviral therapy is not well-defined in elite controllers and long-term nonprogressors, which comprise a small subset of HIV-infected patients, 1% and 3–5%, respectively.[1]

Additional factors to consider when deciding whether or not to treat patients with higher CD4 cell counts are adherence, resistance, toxicities, and cost. Adherence to antiretroviral therapy remains critical to maintenance of viral suppression and prevention of drug resistance.[32–34] Despite lower pill burdens, less frequent dosing, and fewer side effects, adherence can be difficult for some patients depending on individual factors, including but not limited to uncontrolled psychiatric illnesses and active substance abuse. A major consequence of nonadherence is the development of drug resistance, which decreases treatment options and increases potential transmission of resistant HIV. Side effect profiles of antiretroviral therapy have greatly improved but have not been eliminated and can be major factor of nonadherence and decreased quality of life for some patients. Cost is also an important consideration, particularly for individual patients. Although overall healthcare costs of HIV may actually be reduced by initiating early treatment and preventing AIDS- and non-AIDS-related complications and transmission, costs to an individual may make it very difficult to initiate therapy in some patients. For these reasons, the guidelines recognize that providers need to assess barriers to treatment and patients need to understand the risks and benefits of treatment and need to commit to lifelong therapy with excellent adherence.

Which regimen to start in a treatment-naïve patient?

Combination antiretroviral therapy for treatment-naïve patients with no baseline resistance mutations traditionally consists of two nucleoside reverse transcriptase inhibitors (NRTI) as the backbone in combination with a third antiretroviral drug. The third component has been and continues to include either a ritonavir-boosted protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). More recently, antiretroviral agents in two additional drug classes, integrase strand transfer inhibitor (INSTI) and CCR5 antagonist, have been studied in combination with a dual-NRTI backbone and are approved for use in treatment-naïve patients. In 2009, an INSTI-based regimen with raltegravir was added as a third option to use with a dual-NRTI backbone, which represented an expansion of general options for the first time in almost a decade. Options were further advanced in 2011 when the CCR5 antagonist maraviroc with a dual-NRTI backbone was deemed an acceptable option. [1]

The recommendations for preferred and alternative first-line antiretroviral drugs have evolved considerably over the past twelve years based on factors including efficacy, safety, and convenience. Large, randomized, controlled efficacy trials generally compare a new regimen to what was considered a standard of care regimen at the time when the studies were designed. Many of these trials have demonstrated inferiority, non-inferiority, or superiority of newer regimens versus the comparator regimen, resulting in continual changes in the recommended preferred and alternative regimens. The changes also reflect significant progress from regimens with abundant adverse effects, extremely high pill burdens (10–23 pills per day), and inconvenient dosing (twice or thrice daily) to options with better tolerability, low pill burdens (1–4 pills per day), and more convenient dosing (many once daily). Although cost is an important consideration for patients and providers, the guidelines

do not address the issue of cost. Cost of antiretroviral drugs remains relatively high, with average wholesale price (AWP) from First DataBank ranging from approximately $21,000 to $30,000 per year for recommended first-line regimens (Table 2). The availability of fixed-dose combination antiretroviral drugs not only improved convenience but have lowered the overall cost for individual patients, particularly by reducing the number of copayments a patient may have to make. Efficacy, tolerability, convenience, and cost all weigh into the decision about which regimen to prescribe to each individual patient. The current preferred options include (1) NNRTI-based regimen: efavirenz/tenofovir/emtricitabine, (2) PI-based regimen: atazanavir + ritonavir + tenofovir/emtricitabine, (3) PI-based regimen: darunavir + ritonavir + tenofovir/emtricitabine, and (4) INSTI-based regimen: raltegravir + tenofovir/emtricitabine (Table 2 contains dosing, pill burden, and cost of each preferred regimen).

NRTI backbone of regimens

The recommended preferred NRTI backbone for many years included options such as stavudine, didanosine, and zidovudine. Today, stavudine is no longer recommended and didanosine and zidovudine are considered acceptable or alternative NRTI options due to a higher potential for mitochondrial toxicities compared to newer NRTIs, such as abacavir and tenofovir. Lamivudine or its longer acting, fluorinated analog, emtricitabine continue to be part of most NRTI backbones because of excellent efficacy when combined with other NRTIs, minimal toxicity, and convenience. Either lamivudine or emtricitabine is part of every NRTI-containing fixed-dose combination pill, and the decision of which one to use is generally based on whether tenofovir, abacavir, or zidovudine is selected for use in the backbone. Didanosine is not part of any fixed-dosed combination, and although less frequently used today, it is acceptable to use in combination with either lamivudine or emtricitabine.

Abacavir/lamivudine was briefly included as a preferred NRTI backbone after a relationship was established between abacavir-associated hypersensitivity reaction and patients with the HLA- B*5701 allele. Screening for HLA B*5701 has become standard, and abacavir is only recommended in patients who test negative since they are unlikely to develop hypersensitivity reaction. Despite the ability to lower the incidence of hypersensitivity reaction, abacavir/lamivudine was changed from preferred to alternative status after specific, potential efficacy and safety concerns. An abacavir/lamivudine-based regimen compared to a tenofovir/emtricitabine-based regimen in a large randomized trial resulted in inferior virologic efficacy in patients with baseline viral load >100,000 copies/mL[35] and similar virologic efficacy in patients with baseline viral load <100,000 copies/mL,[36] while a subgroup analysis of another study demonstrated similar efficacy regardless of baseline viral load.[37] Safety concerns were raised after data showed a potential increased risk of myocardial infarction with recent or current use of abacavir, especially in patients with high underlying risk for cardiovascular events.[38–40] The relationship between abacavir and cardiovascular events remains controversial because not all studies have supported this association.[41–42] Although abacavir/lamivudine is recommended as an alternative NRTI-backbone, it may be preferable in some patients who are HLA-B*5701 negative, have low risk factors for cardiovascular disease, and have risk factors for or presence of renal insufficiency where tenofovir use may not be desirable.

Tenofovir/emtricitabine has been a preferred NRTI-backbone since 2003 and has now been studied with many different combinations. Not only has tenofovir/emtricitabine shown non-inferior or superior virologic efficacy compared to abacavir/lamivudine,[36–38] it has also shown superior virologic efficacy compared to zidovudine/lamivudine[43] and stavudine/lamivudine.[44] Furthermore, tenofovir/emtricitabine has demonstrated potent virologic activity in combination with all other components of preferred regimens[44–47] and is available in a one-pill, once daily fixed-dose combination with efavirenz. Tenofovir/

emtricitabine (or tenofovir + lamivudine) is also a potent treatment for hepatitis B and is preferred for patients with HIV/HBV co-infection since monotherapy with emtricitabine or lamivudine for HBV treatment is not recommended. Although uncommon, tenofovir can cause renal impairment, ranging from glomerular filtration rate decline to acute tubular necrosis; serum creatinine, electrolytes, and urinalysis should be routinely monitored in patients taking tenofovir.[48–49] Currently, tenofovir/emtricitabine is the preferred NRTI backbone as part of all four preferred regimens.

PI-based regimens

Protease inhibitors are another example of significant change since the first version of the guidelines in 1998 at which time low-dose ritonavir was not commonly used to pharmacokinetically enhance PIs and unboosted PIs dominated the preferred list. The earlier PIs (saquinavir, ritonavir, indinavir, nelfinavir, and amprenavir) had poor bioavailability, requiring large pill burdens and frequent dosing schedules. Since PIs are cytochrome P450 3A4 (CYP3A4) substrates and ritonavir is a potent CYP3A4 inhibitor, low-dose ritonavir improves bioavailability and prolongs the half-life of PIs, allowing for lower pill burdens and less frequent dosing. A tablet formulation of ritonavir was recently approved eliminating any need for refrigeration as was required with the original, capsule formulation. Although more ritonavir-boosted PIs gradually made their way onto the preferred list, unboosted PIs continued to remain as a preferred option until lopinavir/ritonavir was shown to have superior virologic efficacy compared to nelfinavir.[50] Soon after, all unboosted PIs and older ritonavir-boosted PIs such as indinavir + ritonavir and saquinavir + ritonavir were demoted from the preferred list, and lopinavir/ritonavir became the gold standard PI-based regimen.

Lopinavir/ritonavir remained the only preferred PI for many years until it was challenged by multiple ritonavir-boosted PI-based regimens, including atazanavir + ritonavir,[45] fosamprenavir + ritonavir,[51] saquinavir + ritonavir,[52] and darunavir + ritonavir,[53] all of which were shown to have non-inferior efficacy in achieving viral load <50 copies/mL at 48 weeks (Figure 1). At 96 weeks, darunavir + ritonavir once daily was shown to have superior virologic efficacy compared to lopinavir/ritonavir once or twice daily in the ARTEMIS trial, an open-label, randomized non-inferiority trial in treatment-naïve patients. In the intent-to-treat analysis at 96 weeks, 79% of 343 subjects in the darunavir + ritonavir arm versus 71% of 346 subjects in the lopinavir/ritonavir arm achieved a viral load <50 copies/mL, resulting in a difference of 8.3%, 95% confidence interval (CI): 1.8 to 14.7. Overall, darunavir + ritonavir was well tolerated, and patients in this arm experienced significantly less diarrhea and less increases in total cholesterol and triglycerides compared to patients in the lopinavir/ritonavir arm.[46]

Although darunavir once daily, atazanavir once daily, and fosamprenavir twice daily, each with the appropriate ritonavir boosting dose, have all demonstrated superior or non-inferior virologic efficacy compared to lopinavir/ritonavir with at least 48-week published data, the preferred options have been simplified to atazanavir + ritonavir and darunavir + ritonavir once daily based on good tolerability, once-daily dosing, low pill burden, and lowest ritonavir boosting dose (100mg per day).[1] Lopinavir/ritonavir and fosamprenavir + ritonavir are now recommended as alternative options and can be excellent options for some patients. Of note, twice daily lopinavir/ritonavir remains the preferred PI to start in pregnant women.

Although ritonavir-boosted PI-based regimens are more expensive than other preferred first-line regimens (Table 2), development of PI resistance mutations with first-line failure is unlikely. Gastrointestinal side effects, mainly diarrhea, are the main side effects of all ritonavir-boosted PIs, including atazanavir + ritonavir and darunavir + ritonavir; long-term class-wide adverse effects, such as dyslipidemia, insulin resistance, and hepatotoxicity, are also possible. Indirect hyperbilirubinemia is the major laboratory abnormality associated

with atazanavir + ritonavir, but it is generally not associated with concomitant hepatic transaminase elevations. In addition, cases of nephrolithiasis with atazanavir + ritonavir have been reported.[54] Drug interactions are also a concern with all ritonavir-boosted PIs since ritonavir is a potent inhibitor of CYP3A4 and all PIs are substrates of CYP3A4. As a result, a number of undesirable bi-directional drug-drug interactions with concomitant medications are possible, and in some cases, co-administration of some drug combinations is not recommended or dosage adjustments may be necessary. The guidelines provide recommendations in the drug interaction tables to guide clinicians on appropriate use of these interacting drugs.[1] Atazanavir + ritonavir is not only subject to interactions secondary to CYP3A4, but it is also susceptible to interactions with acid-reducing drugs since atazanavir requires an acidic environment for absorption. Despite the cost, side effect profiles, and drug interaction potential of atazanavir + ritonavir and darunavir + ritonavir, they remain potent, efficacious once daily preferred options with relatively low risk for development of PI resistance with first-line failure. Furthermore, the side effect profiles are considerably better than with older PIs.

NNRTI-based regimens

In contrast to PIs, NNRTI recommendations have remained unchanged since efavirenz was added to the preferred list in late 1998. Since then, efavirenz has maintained its placement on the preferred list based on its virologic potency demonstrated in several, large pivotal studies[47, 55–56] and has had the longest running tenure on the preferred list where it remains today. Other available NNRTIs, nevirapine, delavirdine, and etravirine have not earned preferred status for different reasons. Nevirapine can cause serious skin reactions, including Stevens-Johnson syndrome and symptomatic hepatitis, associated with CD4 >250 cells/mm^3 in women and CD4>400 cells/mm^3 in men, and remains on the alternative list of first-line regimens. Delavirdine is no longer used because it may be the least potent NNRTI, and it is dosed three times daily when all currently used antiretroviral drugs are dosed once or twice daily. Etravirine was the latest NNRTI approved in 2008 for treatment-experienced patients and has yet to be studied in treatment-naïve patients in a large, randomized trial.

Efavirenz is available in a fixed-dose combination with tenofovir and emtricitabine and administered once daily, making it the simplest and least expensive regimen on the preferred list. A major disadvantage of an efavirenz-based regimen is the low genetic barrier to resistance since one mutation can render both efavirenz and nevirapine resistant, and resistance to both NNRTIs and NRTIs is common upon failure. The main adverse effects of efavirenz are rash and central nervous system side effects, such as dizziness and vivid dreams, and are transient and manageable in most patients. Similar to PIs, hepatotoxicity is also a potential concern with efavirenz. A major limitation of efavirenz is its teratogenic potential, which precludes its use during the first trimester of pregnancy, in women trying to conceive, and in women not taking proper precautions to prevent conception. Like PIs, NNRTIs are subject to bi-directional drug-drug interactions, which are included in the drug interaction tables in the guidelines; efavirenz is a CYP3A4 and CYP2B6 substrate, CYP3A4 mixed inducer/inhibitor, and CYP2B6 inducer. Most of the drawbacks of efavirenz can be overcome or avoided, and the advantages outweigh the disadvantages in many patients.

INSTI-based regimen

Raltegravir, the first in the INSTI class, was originally approved for management of patients with multiple drug class resistance. In 2009, it received an indication for use in treatment-naïve patients and earned a spot on the guidelines' preferred list, expanding the basic options to include an INSTI-based regimen. In the STARTMRK trial, a double-blind, randomized controlled non-inferiority trial in treatment-naïve patients, raltegravir was compared to efavirenz, each in combination with tenofovir/emtricitabine. In the intent-to-treat analysis

over 48 weeks, 86.1% of 280 subjects in the raltegravir arm versus 81.9% of 281 subjects in the efavirenz arm achieved a viral load <50 copies/mL, resulting in a difference of 4.2%, 95% CI −1.9 to 10.3, establishing noninferiority. Overall, raltegravir was very well tolerated, and patients in the raltegravir arm experienced significantly less dizziness, rash, and increases in all lipid parameters compared to efavirenz.[47] When compared to an efavirenz-based regimen, a raltegravir-based regimen was equally efficacious and tolerable at 48 weeks.

One major disadvantage of a raltegravir-based regimen is that it is dosed twice daily, whereas the other preferred options are dosed once daily. A major advantage of raltegravir compared to NNRTIs and PIs is the lack of CYP450-related drug interactions since raltegravir is metabolized via UDP-glucuronosyltransferase 1A1 (UGT1A1)-mediated glucuronidation and does not affect CYP450 enzymes. The cost of a raltegravir-based regimen is between that of an efavirenz-based and a ritonavir-boosted PI-based regimen (Table 2). Information is still emerging about the development of resistance mutations upon failure of a raltegravir-based regimen, although resistance appears to develop more rapidly than with ritonavir-boosted PIs. The addition of an INSTI-based regimen with raltegravir to the preferred list allows for preservation of other classes and avoidance of NNRTI- and PI-related drug interactions.

Categories of regimens other than preferred

The guidelines have always recommended “preferred regimens” and “alternative regimens,” and recently added new “acceptable regimen” categories (Table 3). The alternative regimen list (Table 3) continues to include effective and tolerable options but which have potential disadvantages compared to preferred regimens. For some patients, based on individual factors, an alternative regimen can be a preferred option. The advantages and disadvantages of each component of each regimen can be found in a table format in the guidelines.[1]

The acceptable list includes third-line regimens that can be selected but are not as satisfactory as preferred or alternative options. For example, unboosted atazanavir combined with either abacavir/lamivudine or zidovudine/lamivudine is recommended as acceptable, but ritonavir-boosted atazanavir is preferred. If a patient has maintained a suppressed viral load on unboosted atazanavir and is not at risk for drug interactions that may reduce atazanavir levels (e.g. tenofovir or acid-reducing drugs), continuation of that regimen is acceptable. Maraviroc with zidovudine/lamivudine was added as an acceptable regimen in the 2011 guidelines for use in patients with only CCR5-tropic virus. Disadvantages of maraviroc include the requirement for and the high cost of tropism testing as well as twice daily dosing.

Some regimens are listed as acceptable because of a lack of sufficient data required for placement into a higher category. Raltegravir as well as darunavir + ritonavir were studied in combination with tenofovir/emtricitabine[46–47] and maraviroc in combination with zidovudine/lamivudine[55] in treatment-naïve patients. Combining raltegravir or darunavir + ritonavir with alternative NRTI backbones such as abacavir/lamivudine or zidovudine/lamivudine and using maraviroc with tenofovir/emtricitabine or abacavir/lamivudine may be safe and effective, but these specific combinations have not been studied.

Some acceptable regimens have shown virologic efficacy but should be used with caution because of safety, resistance, or efficacy concerns. For example, unboosted fosamprenavir, upon virologic failure, can select for darunavir-associated resistance mutations, potentially compromising future use of darunavir twice daily for salvage therapy. Abacavir and nevirapine can both cause hypersensitivity reactions, although using abacavir only in HLA-B*5701 negative patients and using nevirapine only in women with CD4 <250 cells/mm^3

and men with CD4 <400 cells/mm^3 can limit the incidence of both hypersensitivity reactions. Although the incidence is reduced in these patients, hypersensitivity reaction is possible,[57–59] and therefore, abacavir and nevirapine should be used together with caution. Saquinavir + ritonavir was recently demoted from the alternative list to this acceptable category because of product label changes noting significant prolongation of PR and QT intervals in healthy volunteer studies and rare post-marketing reports of torsades de pointes and complete heart block.[1]

Antiretroviral regimens or combinations to avoid

Over time, information has accumulated about which antiretroviral drugs should not be used in combination due to suboptimal efficacy or drug interactions that result in heightened toxicities or other unwanted effects. Mono-, dual-, or triple-therapy with NRTIs is not recommended because of suboptimal efficacy, and dual-NNRTI-containing regimens should not be used because of an increased risk of adverse effects with the combination of efavirenz and nevirapine.[60] Etravirine, recommended only for treatment-experienced patients, should not be combined with other NNRTIs, unboosted PIs, or ritonavir-boosted atazanavir, fosamprenavir, or tipranavir because of potential or established drug interactions leading to suboptimal drug levels of the PI or etravirine. Darunavir, saquinavir, and tipranavir when used without ritonavir have inadequate bioavailability and should never be used as unboosted PIs. Tipranavir + ritonavir is also only recommended for treatment-experienced patients. Additional antiretroviral components to avoid can be found in the guidelines.

In summary, numerous antiretroviral regimens can be constructed for a treatment-naïve patient who lacks baseline drug resistance mutations. The guidelines have categorized regimens according to efficacy, safety, and convenience and have simplified the preferred recommendations to four options, including NNRTI-, ritonavir-boosted PI-, and INSTI-based regimens in combination with two NRTIs. A CCR5 antagonist-based regimen with two NRTIs has been added as an acceptable option for patients with only CCR5-tropic virus.. The selection of a regimen for an individual patient is based on various considerations, which can include side effects, drug interactions, pill burden, dosing schedule, food effects, resistance potential, ease of adherence, and cost. Ultimately, patients need an antiretroviral regimen that produces long-term viral suppression and minimal toxicities and which they can adhere to long-term.

Other Sections of the Guidelines

The treatment guidelines contain a wealth of information not only about when and what to start in treatment-naïve patients but also how to manage treatment-experienced patients. The same considerations when selecting a regimen in treatment-naïve patients apply to treatment-experienced patients. In cases where patients have failed antiretroviral therapy, possible reasons for failure should be addressed and thorough antiretroviral history and cumulative drug resistance testing results should be used to design a subsequent regimen. In some cases, patients who are virologically suppressed may be simplified to a regimen that is more convenient and/or better tolerated. The guidelines address the specifics of these topics based on available data, and the goals in treatment-experienced patients are the same as for treatment-naïve patients.

Additional sections of the guidelines of particular interest to pharmacists include therapeutic drug monitoring, adherence, adverse effects, drug interactions, and antiretroviral characteristics. Drug levels, although not routinely recommended, can help assess adherence or determine correct dosing in patients who may have subtherapeutic levels because of drug interactions, malabsorption, altered metabolism, or pregnancy. Suggested minimum target trough concentrations are specified and assist with analysis of drug levels. Assessment and

optimization of adherence, prevention and management of adverse effects and drug interactions, and correct dosing in cases of renal or hepatic dysfunction are inter-related and crucial for complete virologic suppression, safety, and prevention of drug resistance. Various tables in the guidelines contain detailed information about each of these considerations.

Conclusion

The DHHS antiretroviral treatment guidelines have assisted practitioners evaluate, treat, and monitor HIV patients for many years, and the evolution of the recommendations for when to start antiretroviral therapy and which antiretroviral regimen to start is based on continually emerging data and individual patient factors. When making treatment decisions in an individual patient, adherence and resistance potentials remain a focus of determining when and what to start. Recognition and management of antiretroviral drug interactions, toxicities, inaccessibility, and dosing complexities help improve adherence and prevent resistance. Recommendations have shifted toward treatment at higher CD4 cell counts (< 500 cells/mm^3 and perhaps >500 cells/mm^3) with simpler, better tolerated, and more potent regimens that not only include NNRTI- and PI-based regimens but also an INSTI-based regimen and in some cases a CCR5-based regimen, all with a dual-NRTI backbone. Modification of treatment recommendations will continue as new data emerges.

Acknowledgments

I thank Dr. Alice Pau for her critical review of this manuscript. This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

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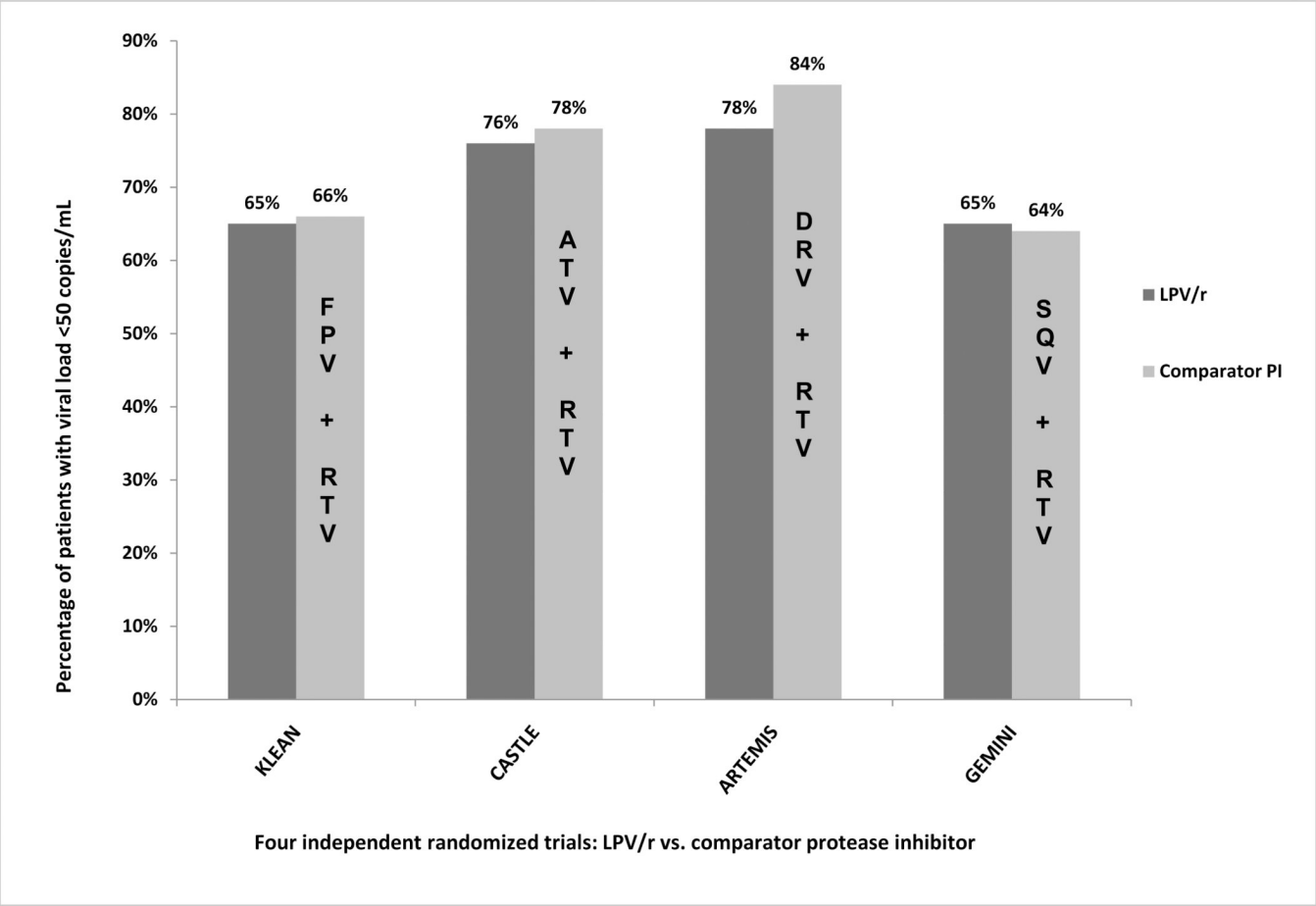

Figure 1.

Lopinavir/ritonavir vs. comparator protease inhibitors: percentage of patients achieving viral load <50 copies/mL at 48 weeks in four independent randomized trials in treatment-naïve patients.[43, 49–51]

Total number of patients in both arms (randomized 1:1) of each study: KLEAN: n=878, CASTLE: n=883, ARTEMIS: n=689, GEMINI n=337. Different dual-NRTI backbones were used in each trial. Some trials allowed the use of LPV/r capsules or tablets. All trials used twice daily LPV/r, except for ARTEMIS, where once daily LPV/r was allowed.

Abbreviations: LPV/r = lopinavir/ritonavir, PI = protease inhibitor, FPV = fosamprenavir, RTV = low-dose ritonavir, ATV = atazanavir, DRV = darunavir, SQV = saquinavir

Table 1

When to start antiretroviral therapy in treatment-naïve patients based on the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, January 10, 2011[1]

CD4 cell count	Recommendation
Any	ART should be initiated in patients with the following clinical conditions: • History of AIDS-defining illness (AI) • Pregnancy (AI) • HIV-associated nephropathy (AII) • HBV coinfection if treating HBV (AIII)
<350 cells/mm^3	ART should be initiated (AI)
350–500 cells/mm^3	ART is strongly recommended by 55% of the panel and moderately recommended by 45% of the panel (A/B-II)
>500 cells/mm^3	ART is moderately recommended by 50% of the panel, and ART is optional as stated by 50% of the panel (B/C-III)
Patients initiating should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence. Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.	

Recommendation Rating: A = strong, B = moderate, C = optional

Evidence Rating: I = data from randomized controlled trials, II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes, III = expert opinion

Table 2

Relative cost per month and daily pill burden of the 2011 DHHS guidelines' preferred antiretroviral regimens for treatment-naive patients

	# pills/day	AWP[a] for 30-day supply
NNRTI-based regimen EFV/TDF/FTC 600mg/300mg/200mg once daily	1	$ 1755.55
PI-based regimen ATV 300mg + RTV 100mg + TDF/FTC 300mg/200mg – all once daily	3	$ 2503.82
PI-based regimen DRV 800mg + RTV 100mg + TDF/FTC 300mg/200mg – all once daily	4	$ 2528.80
INSTI-based regimen RAL 400mg BID + TDF/FTC 300/200mg once daily	3	$ 2192.64

[a] First DataBank, January 2010

Abbreviations: AWP = average wholesale price, ATV = atazanavir, DRV = darunavir, EFV = efavirenz, FTC = emtricitabine, RTV = ritonavir, RAL = raltegravir, TDF = tenofovir

Table 3

Alternative and Acceptable Regimens and respective daily pill burden based on the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolscents, January 10, 2011.[1] Note: 3TC and FTC are interchangeable in all regimens but may affect daily pill burden.

Alternative Regimens (Regimens that are effective and tolerable but have potential disadvantages compared with preferred regimens. An alternative regimen may be the preferred regimen for some patients.)	**# pills/day**
NNRTI-based regimens	
EFV 600mg once daily + (ABC/3TC 600mg/300mg once daily or ZDV/3TC 300mg/150mg twice daily)	2–3
NVP 200mg twice daily (after induction dosing) + ZDV/3TC 300mg/150mg twice daily	4
PI-based regimens	
ATV 300mg once daily + RTV 100mg once daily + (ABC/3TC 600mg/300mg once daily or ZDV/3TC 300mg/150mg twice daily)	3–4
[(FPV 700mg + RTV 100mg twice daily) or (FPV 1,400mg + RTV 100-200mg once daily)] + (ABC/3TC 600mg/300mg once daily or TDF/FTC 300mg/200mg once daily or ZDV/3TC 300mg/150mg twice daily)	4–6
LPV/r (800/200mg once daily or 400mg/100mg twice daily) + (ABC/3TC 600mg/300mg once daily or TDF/FTC 300mg/200mg once daily or ZDV/3TC 300mg/150mg twice daily)	5–6
Acceptable Regimens (Regimens that may be selected for some patients but are less satisfactory than preferred or alternative regimens.) and **Regimens that May be Acceptable but More Definitive Data are Needed**	
NNRTI-based regimen	
EFV 600mg + ddI (weight-based dosing) + (3TC 300mg or FTC 200mg) – all once daily	3
PI-based regimens	
ATV 400mg once daily (unboosted) + (ABC/3TC 600mg/300mg once daily or ZDV/3TC 300mg/150mg twice daily)	3–4
DRV 800mg once daily + RTV 100mg once daily + (ABC/3TC 600mg/300mg once daily or ZDV/3TC 300mg/150mg twice daily)	4–5
INSTI-based regimen	
RAL 400mg twice daily + (ABC/3TC 600mg/300mg once daily or ZDV/3TC 300mg/150mg twice daily)	3–4
CCR5-based regimen	
MVC 300mg twice daily + (ABC/3TC 600mg/300mg once daily or TDF/FTC 300mg/200mg once daily or ZDV/3TC 300mg/150mg twice daily)	3–4
Regimens that May be Acceptable but Should be Used with Caution (Regimens that have demonstrated virologic efficacy in some studies but have safety, resistance, or efficacy concerns.)	
NNRTI-based regimen	
NVP 200mg twice daily (after induction dosing) + (ABC/3TC 600mg/300mg once daily or TDF/FTC 300mg/200mg once daily)	3
PI-based regimens	
FPV 1,400mg twice daily (unboosted) + (ABC/3TC 600mg/300mg once daily or TDF/FTC 300mg/200mg once daily or ZDV/3TC 300mg/150mg twice daily)	5–6
SQV 1,000mg twice daily + RTV 100mg twice daily + (ABC/3TC 600mg/300mg once daily or TDF/FTC 300mg/200mg once daily or ZDV/3TC 300mg/150mg twice daily)	7–8

Abbreviations: ABC = abacavir, ATV = atazanavir, ddI = didanosine, DRV = darunavir, EFV = efavirenz, FPV = fosamprenavir, FTC = emtricitabine, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NVP = nevirapine, RTV = low-dose ritonavir, RAL = raltegravir, SQV = saquinavir, TDF = tenofovir, ZDV = zidovudine, 3TC = lamivudine