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**CLINICAL AND HEALTH AFFAIRS**

# Management of HIV: A Swing Back to the Future

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**Abstract**

During the last 15 years, there have been numerous advancements in the development of antiretroviral drug therapies for people with HIV/AIDS. More drugs and more classes of drugs are now available to treat the disease, and they have fewer side effects than older therapies. This article provides an overview of the current management guidelines for HIV infection in adults in the United States. It also highlights the rationale behind HIV treatment, including when to start it, what therapies to use, and details about key drugs and regimens.

After the first case of HIV/AIDS was identified in 1981, researchers embarked on a major effort to find suitable treatments for what was, if left unchecked, a deadly virus. In November 1995, when a similar article on managing HIV was published in this journal, five antiretroviral therapies (ARTs) were available —zidovudine, didanosine, zalcitabine, stavudine, and lamivudine.[1] Today, 30 antiretrovirals (ARVs) made up of 23 separate drugs are being used to control the virus. This growing armamentarium has changed the prospect of HIV/AIDS management for both patients and providers. Treatment has gone from temporizing in the face of a likely death sentence to management of HIV/AIDS as a chronic disease.

With the arrival of new antiretrovirals, our concept of when to treat HIV-infected individuals has changed as well. In fact, the pendulum has swung several times in the short history of this disease. Early on in HIV management, when ARVs first became available, many in the field advocated a “hit hard, hit early” philosophy, particularly when it was thought the virus could be eradicated if detected early. In fact, in 1996, the guidelines called for treating all HIV-infected patients with CD4+ cell counts below 500/mm3. Unfortunately, subsequent research indicated that viral eradication was not feasible. The available ARVs had a wide range of side effects, so the guidelines recommended treatment only when patients were moving toward the spectrum of T-cell immunity that brought about the greatest risk of opportunistic infections (CD4+ cell counts of 350 cells/mm3 or less). This approach protected patients from the toxicities of many drugs in the regimen. Now, the pendulum is swinging “back to the future.” Recent observational studies from both Europe and North America have begun to provide evidence that earlier treatment (CD4+ levels of 350 to 500) significantly reduces the risk of mortality. These findings have led many physicians to once again advocate earlier therapy for all HIV-infected patients.

With the plethora of ARVs, myriad potential drug-drug interactions, and the potential for multiple comorbidities, management of HIV patients has become a complex affair. In this article, we briefly touch on the major treatment modalities as well as some interesting complications associated with care.

## Testing

Testing is a necessity for HIV therapy and prevention. It is also a major challenge. The Centers for Disease Control and Prevention’s recommendation of universal “opt-out” screening for all patients in all health-care settings is rarely followed.[2] Because patients are often not screened, many pass through multiple portals in our health care system before they finally present with an AIDS-defining illness. In this day and age, with effective therapy that can prevent life-threatening and costly AIDS-related complications, missing an HIV diagnosis because patients are not being tested is unacceptable. This problem is not unique to the United States, as average CD4+ levels upon starting ART are low worldwide.[3] (The average in the United States is 187 cells/mm3; in southern Africa it is 90 cells/mm3; in western Europe, 200 cells/mm3; and in Russia, 160 cells/mm3). If we are to help those who need it most, we must test.

## When to Start Antiretroviral Therapy

According to the U.S. Department of Health and Human Services (DHHS), there are a number of goals for antiretroviral therapy. Currently, they are to reduce HIV-related morbidity and prolong survival, improve quality of life, restore and preserve immunologic function, maximally and durably suppress viral load, and prevent vertical HIV transmission. Emerging goals for ART and highly active antiretroviral therapy (HAART) are to decrease risk for immune reconstitution inflammatory syndrome, decrease

morbidity and mortality caused by non-AIDS-related diseases, achieve near-normal life expectancy, and decrease lifetime risk for HIV transmission to others.[4]

In deciding when and what to start for ART, all these goals should be kept in mind. In the United States, management of persons living with HIV/AIDS is guided by panels from two organizations—the U.S. Department of Health and Human Services (DHHS) and the International AIDS Society–United States (IAS-USA).[4,5] Both panels last updated their guidelines in 2008. Both sets of guidelines recommend ART for all asymptomatic individuals with a CD4+ count of less than 350 cells/mm3. In addition, they provide guidelines for identifying specific groups of patients for whom treatment is recommended (Table 1).

Evidence from NA-ACCORD4, an observational study combining 22 cohorts of HIV-infected patients in Canada and the United States, demonstrated a 70% higher risk of death in the group that deferred therapy (less than 350 cells/mm3) compared with the group that initiated therapy at higher CD4+ counts (350 to 500 cells/mm3). Another observational study, ART-CC5, reported similar results with patients having lower mortality when initiating ART at CD4+ counts above 350 cells/mm3, but not at CD4+ levels above 450 cells/mm3. There are a number of concerns regarding early treatment; these include the possibility of serious drug resistance, chronic side effects, increased high-risk sexual behavior caused by disinhibition, and the lack of data from randomized clinical trials. Yet, overall, it is becoming more difficult to justify holding off on starting ART (Table 2).

Patients newly identified as HIV-positive should be referred to an HIV specialist for evaluation and treatment. Key baseline tests to order for the newly identified HIV-positive patient include plasma HIV levels, resistance testing, CD4+ cell count, numerous safety laboratory tests, and serologic studies for a number of pathogens to determine opportunistic infection prophylaxis and vaccination requirements.[4]

After these baseline investigations are completed, assuming no critical issues need to be addressed, a decision can be made as to when to begin ART. Determining a start date is complicated by multiple factors including the patient's age, comorbid conditions, psychological readiness, and access to care and services. Advanced age has been shown to speed up the rate at which HIV progresses and increase the risk of other HIV-related illnesses. Therefore, in older patients with HIV, it is reasonable to consider ART prior to their reaching the threshold CD4+ cell level. Other comorbid conditions such as heart disease, diabetes, or renal impairment as well as a patient's ability to transmit to others, either perinatally or through high-risk sexual behaviors, may also affect when to initiate ART. Perhaps the overriding determinant of when to start therapy is the patient's desire and ability to adhere to a regimen. Nonadherence not only makes it difficult to effectively manage HIV, it can also lead to HIV resistance. Therefore, the patient's frame of mind, in addition to his or her clinical and laboratory markers, plays a large role in determining a start date.

**What to Start**

In the mid-1990s, zidovudine combined with lamuvudine was believed to be the best combination for managing HIV, and it was only available under a compassionate-use protocol.[1] Since then, three more nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) have been developed—abacavir, emtricitabine, and tenofovir (production of zalcitabine has ceased). Several other new classes of drugs have been developed as well. The present guidelines recommend two NRTIs as a "backbone" of an ARV regimen. These are given along with either a "boosted" protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Such three-drug ARV combination therapies are commonly referred to as highly active antiretroviral therapy (HAART) or combination ART (cART). Table 3 outlines the preferred and alternative regimens suggested in the major HIV guidelines.

- **Nucleoside / Nucleotide Reverse Transcriptase Inhibitors**
  Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), sometimes referred to as "nukes," disrupt HIV's ability to replicate within healthy cells via the reverse transcriptase pathway. Tenofovir (Viread) is technically a nucleotide analogue, but it works in the same manner as other nucleoside analogs. Although there are several NRTIs, the most commonly used combinations involve coformulated fixed drug combinations.

  The DHHS guidelines list tenofovir/emtricitabine (Truvada) as the preferred nucleoside backbone. Abacavir/lamivudine (Epzicom) is considered an alternative combination. When choosing a NRTI backbone, the main criterion is whether to use tenofovir or abacavir. Each has several characteristics that should be evaluated when making this choice.

  Tenofovir/emtricitabine is usually taken once a day in pill form. It is generally well-tolerated. Side effects include rash, headache, pain, diarrhea, depression, weakness, and nausea. Caution must be used in patients with pre-existing renal disease, as it can worsen renal function.[6] The emtricitabine component of Truvada is associated with reversible hyperpigmentation of the

palms and soles of the feet, especially in dark-skinned individuals. Since the components of Truvada are both active against hepatitis B, it is the NRTI backbone of choice in patients with HIV and hepatitis B coinfection.

Abacavir/lamivudine is also routinely dosed as one pill once daily. In general, it is well-tolerated. There is a potential for hypersensitivity reaction in patients who are HLA-B*5701 positive; this can lead to serious complications including death. All patients for whom abacavir is a therapy option must have their HLA-B*5701 checked. If it is positive, they must never be prescribed abacavir. Also, recent studies have suggested an increased cardiovascular risk in patients taking abacavir.[7,8] In addition, one major study reported that patients with high entry viral loads (greater than 100,000 copies/mL) had earlier treatment failures on abacavir. Such concerns resulted in abacavir-based regimens being listed as an alternative to tenofovir-based treatments.[9]

- **Non-nucleoside Reverse Transcriptase Inhibitors**

  The non-nuceoside reverse transcriptase inhibitors (NNRTIs), also known as "non-nukes," work by preventing the conversion of RNA to DNA by attaching to reverse transcriptase to make it inactive. This class is made up of four drugs—nevirapine (Viramune), efavirenz (Sustiva), etravirine (Intelence), and delavirdine (Rescriptor). The only one preferred by both guideline panels is efavirenz. Currently, efavirenz, tenofovir, and emtricitabine are coformulated in one pill that is taken once a day. The long half-lives of the NNRTIs, especially efavirenz, make them forgiving of the occasional missed or delayed dose.

  Efavirenz is the most active ARV, according to data from the AIDS Clinical Trial Group (ACTG 5142) study.[10] Results showed superior virological suppression with efavirenz compared with a boosted protease inhibitor (lopinavir/ritonavir), and it is the current standard for all other studies comparing ARVs. Simplicity is the hallmark of regimens using efavirenz, since taking one pill on a daily basis has much appeal. Efavirenz does have a number of neuropsychiatric side effects such as strange dreams, dizziness, drowsiness, or a general sense of "fogginess" characterized by difficulty concentrating. These side effects are usually self-limiting and generally diminish within one month. For that reason, patients are advised to take their dose in the evening, prior to going to bed. Other patients may complain of worsening of baseline depression or aggression. Uncontrolled psychiatric conditions can be a relative contraindication to use of efavirenz. Interestingly, use of efavirenz has been noted to cause false-positive toxicology tests for marijuana.

  Efavirenz has been shown to efficiently suppress the virus compared with most other ARVs.[11] However, it should not be used in pregnant women, as it is teratogenic (Category D). In patients for whom adherence may be an issue, the long half-life becomes a driving factor for increased risk of virologic resistance if treatment is interrupted for long periods. The long half-life results in nonadherent patients having low serum levels over a long period of time, which leads to point mutations in the HIV genome, such as K103N—an example of the "low genetic barrier to resistance" phenomenon.

- **Protease Inhibitors**

  Protease inhibitors (PIs) work by blocking the protease enzyme within the cell, which stops HIV from replicating since there are no functional new HIV particles. In essence, PIs stop HIV after it has already entered cells and integrated with their DNA. Four PIs are currently recommended under the DHHS guidelines. All preferred PI-based regimens involve the use of a ritonavir-boosted PI, with unboosted atazanavir and unboosted fosamprenavir listed as alternative regimens. "Boosting" is done with low-dose ritonavir (a cytochrome PA34 [CYP3A4] inhibitor). It results in significant increases in the plasma level of the other PIs; hence the term "boosted PIs." Taking PIs with ritonavir has led to a reduction in the number of pills in the regimen, less-frequent dosing, and improved viral potency compared with the regimens used prior to 2001. Many boosted-PI regimens, namely darunavir, atazanavir, fosamprenavir, and lopinavir, can be taken once daily; saquinavir is taken twice daily.

  Unlike the NNRTIs, boosted PIs have a high barrier to resistance. Even when regimens fail, functional resistance is rare. The lack of resistance leads to what can be called a "forgiveness factor," whereby patients can miss multiple doses with a low risk for developing resistance. PIs are associated with gastrointestinal toxicity, diarrhea, nausea, and abdominal pain, as well as dyslipidemia. Patients may also experience lipodystrophy with increased fat around the abdomen, breasts, and back of the neck. The newer PIs such as darunavir and atazanavir have fewer lipid effects than lopinavir/ritonavir. Multiple studies have demonstrated superior T-cell (CD4+) reconstitution on PI regimens.[12-15]

Ritonavir (Norvir) was initially used at high doses but poorly tolerated. It is a strong CYP3A4 inhibitor, which at greatly reduced doses increases serum levels of other PIs. It is administered in 100 mg daily doses (one pill) when used with atazanavir, darunavir, and fosamprenavir, and 200 mg daily doses when coformulated with lopinavir. Physicians must exercise care when evaluating for other serious drug-drug interactions.

Lopinavir/ritonavir (Kaletra) can be taken daily or twice a day. It has long been considered the "gold standard" with which all other PIs are compared in drug trials. It is frequently associated with a worse lipid profile (increased total and LDL cholesterol and triglycerides) when compared with other boosted PIs. Lopinavir/ritonavir often has more gastrointestinal side effects than the other recommended boosted PIs.

Atazanavir (Reyataz) can cause hyperbilirubinemia because of increased unconjugated bilirubin (similar to Gilbert's syndrome). It requires stomach acid for adequate absorption so concurrent potent acid suppressive drugs need to be avoided or used with caution.

Darunavir (Prezista) has shown impressive viral suppression with excellent T-cell response. A major study noted a superior overall treatment effect when compared with lopinavir.[15] Its side-effect profile has been favorable, with better lipid response compared with lopinavir/ritonavir. Darunavir is a sulfa-containing drug that should be used with caution in patients with a known sulfa allergy.

Fosamprenavir (Lexiva), when combined with ritonavir in a 700/100 mg twice-daily dose, has no clear advantage over coformulated lopinavir/ritonavir. The 1,400/100 mg once-daily dose has less comparative data and no clear advantage over either once-daily atazanavir/ritonavir or once-daily darunavir/ritonavir.

Saquinavir (Invirase) is given as three pills twice a day (two saquinavir plus one ritonavir); this makes it a more burdensome regimen compared with the other boosted PIs.

- **Integrase Inhibitors**
  Raltegravir (Isentress) is the first integrase inhibitor to be approved by the Food and Drug Administration. It is unique in that it blocks HIV prior to viral integration with cellular DNA. Another integrase inhibitor, elvitegravir, is currently in phase III trials. Raltegravir was initially approved for HIV treatment-experienced patients but, on June 8, 2009, was approved for use in treatment-naïve individuals after results of the STARTMRK study were released.[16] Raltegravir was equivalent to efavirenz in terms of time of viral suppression. It also had minimal lipid side effects. Raltegravir achieves viral suppression quickly compared with other ARVs, although this is of unknown significance. Raltegravir is presently prescribed as a twice-daily regimen. The QDMRK trial is attempting to determine if taking the drug once a day is acceptable.

**Future Concerns**

As HIV-positive patients survive long-term, the risk for standard health problems associated with aging (ie, cardiovascular disease and cancer) increases. There is an additional concern that chronic HIV infection is associated with high levels of immune activation, which can further contribute to risk for cardiovascular disease and cancer. In addition, there is a possibility that HIV drugs may contribute further to cardiovascular disease and metabolic disturbances. And increased rates of osteopenia/osteoporosis, liver disease, kidney disease, and fragility contribute to worry about premature aging in people who have been HIV positive for a long time.

**Conclusion**

The HIV/AIDS epidemic has been around for nearly 30 years. Researchers have made amazing progress in developing HIV therapeutics during the last 15 years. People with HIV are living longer and experiencing fewer side effects from their treatment than in the past. Still, there is a long way to go. Testing for HIV must become integrated into routine health care. Such an approach is needed to identify the majority of patients who are HIV positive and enroll them in treatment as early as possible.

As HIV patients continue to live longer because of improved virologic suppression and immunologic reconstitution, managing HIV in conjunction with the diseases of aging will become a major focus. Preventive health measures such as screening for cardiovascular risk factors, renal disease, and bone disease and administering necessary immunizations are important to reducing non-AIDS-related complications. Furthermore, there is hope that one day we will make headway toward a functional cure by possibly eradicating HIV from reservoir sites. Enormous strides have been made, but making these advances accessible to all HIV-positive patients remains a major challenge that requires involvement of all sectors of society. **MM**

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References

1. Henry K. Management of HIV infection: A 1995-96 overview for the clinician. Minn Med. 1995;78(11):17-24.
2. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep. 2006;55(14):1-17.
3. Egger M. Outcomes of ART in Resource-limited and Industrialized Countries. Available at: www.retroconference.org/2007/Abstracts/30600.htm. Accessed September 16, 2009.
4. 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; 2008:1-139. Available at: www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed September 8, 2009.
5. Hammer SM, Eron JJ, Reiss P, et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. JAMA. 2008;300(5):555-70.
6. Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. Clin Infect Dis. 2005;40(8):1194-8.
7. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med. 2003;349(21):1993-2003.
8. Strategies for Management of Anti-Retroviral Therapy/INSIGHT; DAD Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. AIDS. 2008;22(14):F17-24.
9. Sax P, Tierney C, Collier A. ACTG 5202: shorter time to virologic failure (VF) with abacavir/lamivudine (ABC/3TC) than tenofovir/emtricitabine (TDF/FTC) as part of combination therapy in treatment-naive subjects with screening HIV RNA >100,000 c/mL. In: 17th International AIDS Conference. Mexico City, Mexico. August 3-8, 2008.
10. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med. 2008;358(20):2095-106.
11. Maggiolo F, Ravasio L, Ripamonti D, et al. Similar adherence rates favor different virologic outcomes for patients treated with non-nucleoside analogues or protease inhibitors. Clin Infect Dis. 2005;40(1):158-63.
12. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Atazanavir/ritonavir vs lopinavir/ritonavir in antiretroviral-naïve HIV-1-infected patients: CASTLE 96 Week Efficacy and Safety. 2008. Available at: www.natap.org/2008/ICAAC/ICAAC_14.htm. Accessed September 8, 2009.
13. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. Lancet. 2008;372(9639):646-55.
14. Ortiz R, DeJesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. AIDS. 2008;22(12):1389-97.
15. Mills A, Nelson M, Jayaweera D, et al. Efficacy and safety of darunavir/ritonavir 800/100mg once-daily versus lopinavir/ritonavir in treatment-naïve, HIV-1-infected patients at 96 weeks: ARTEMIS (TMC114-C211). 2008. Available at: www.natap.org/2008/ICAAC/ICAAC_17.htm. Accessed September 8, 2009.
16. Lennox J, DeJesus E, Lazzarin A, others. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive HIV-1 infected patients: STARTMRK protocol 021 [abstract no. H-896a]. In: 48th Annual ICAAC/IDSA Meeting; 2008:25-28.