



# Getting the Most from Available Antiretroviral Therapies

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**T**wo decades after the approval of the first antiretroviral drugs, combination HAART has dramatically lowered the risk of illness and death for people with HIV. The year 2007 was another milestone, witnessing the approval of the first agents in two new anti-HIV drug classes—CCR5 antagonists and integrase inhibitors—that provide new options for treatment-experienced patients.

Today, however, the anti-HIV drug pipeline is relatively sparse, with no blockbusters in the foreseeable future. While the first HIV maturation inhibitor, bevirimat, continues to slowly make its way through clinical trials, another once-promising agent that works by a completely novel mechanism, Koronis Pharmaceuticals' KP-1461, was recently put on hold after laboratory tests indicated that it did not demonstrate the expected antiviral activity.

At this juncture, it is useful to take stock of currently available antiretroviral therapies and how best to use them. Whether starting treatment for the first time or changing therapy, there are many factors to consider, including antiviral potency, tolerability, durability, and susceptibility to drug resistance.

This article reviews several recent studies looking at the relative merits of protease inhibitors (PIs) versus non-nucleoside reverse transcriptase inhibitors (NNRTIs), durability of antiretroviral regimens, and managing virological failure.

## PIs or NNRTIs for First-Line Therapy?

Despite countless studies to date, there is still no definitive answer to the question of whether PIs or NNRTIs are a better option for people starting antiretroviral therapy for the first time. Researchers continue to conduct clinical trials comparing these classes, looking at potency, drug-induced toxicities, and emergence of resistance mutations.

AIDS Clinical Trials Group (ACTG) study 5142 compared two commonly used traditional HAART regimens, one containing a ritonavir (Norvir)-boosted PI and the

other containing an NNRTI, both with two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). The investigators also included an NRTI-sparing regimen, since this drug class has been linked to metabolic and mitochondrial side effects, including lipoatrophy (peripheral fat loss). A total of 757 treatment-naïve participants were randomly assigned to start therapy with the NNRTI efavirenz (Sustiva) plus two NRTIs, the PI lopinavir/ritonavir (Kaletra) plus two NRTIs, or efavirenz plus lopinavir/ritonavir without NRTIs.

As reported in the May 15, 2008, *New England Journal of Medicine*, after about two years of follow-up, people in the efavirenz arm had a longer time before virological failure than those taking lopinavir/ritonavir; however, the time to failure was not significantly different for the NRTI-sparing arm compared with the other two groups. At 96 weeks, 89% of patients in the efavirenz arm had a viral load below 50 copies/mL, compared with 83% in the NRTI-sparing arm and 77% in the lopinavir/ritonavir arm. The groups did not differ significantly with regard to discontinuation due to toxicities. More people in the NRTI-sparing arm developed drug-resistance mutations, but the difference between the lopinavir/ritonavir and the efavirenz arms was not statistically significant.

In an accompanying editorial, Bernard Hirschel, MD, and Alexandra Calmy, MD, wrote that the results were “difficult to put in a nutshell.” Looking at HIV suppression, the efavirenz arm had the best results, closely followed by the NRTI-sparing and the lopinavir/ritonavir arms; when the regimens were ranked according to drug resistance, the winner was lopinavir/ritonavir, followed by efavirenz and the NRTI-sparing combination.

But other factors can also come into play, especially in developing countries where drug access may be limited. On the basis of this study, Drs. Hirschel and Calmy concluded, “it seems that efavirenz plus two NRTIs is hard to beat,” given that efavirenz has a lower pill burden and is less expensive. These findings, they added, “should challenge the 40% of clinicians who start antiretroviral treatment with a protease inhibitor and should reassure those who, in resource-limited settings, must use combinations of NRTIs and NNRTIs because they are cheaper.”

But another recent study, published in the July 1, 2008, *Journal of Infectious Diseases*, revealed that ritonavir-boosted PIs are less likely to permit the emergence of drug resistance, thereby allowing patients to remain on a regimen longer before they must switch due to virological failure.

Viviane Lima, PhD, from the British Columbia Centre for Excellence in HIV/AIDS and colleagues looked at the emergence of drug-resistance mutations among 2,350 individuals who started first-line antiretroviral therapy between 1996 and 2004. After five years, people who started with a boosted PI were nearly 2.5 times less likely to develop resistance mutations than those who took combination regimens containing either non-boosted PIs or NNRTIs. Furthermore, patients who started HAART more recently (2002–2004) were about 60% less likely to develop resistance than those who started in 1996–1998.

## Durability of HAART Regimens

Along with drug resistance, side effects are another common reason for changing therapy; regimens that cause fewer toxicities, therefore, are likely to be more durable over the long term. As reported in the May 31, 2008, issue of *AIDS*, Rebecca Lodwick and colleagues studied 508 HIV patients attending the Royal Free Hospital in London who started antiretroviral therapy between 2000 and 2005, achieved viral load suppression below 50 copies/mL within six months, and never experienced virological failure.

Study participants started on 3TC (lamivudine; Epivir) or emtricitabine (FTC; Emtriva) plus a second NRTI and either a PI (usually boosted) or an NNRTI. During 912 person-years of follow-up, there were 357 total treatment modifications, of which half were due to drug-related toxicities.

The most common side effects leading to regimen changes were central nervous system (CNS) symptoms (22.9%) and lipodystrophy (19.4%); while CNS side effects, such as depression, anxiety, and unusual dreams, are com-

monly caused by efavirenz, body shape changes are more often attributed to PIs. Other reasons for changing therapy were patient choice (17.6%) and poor adherence (3.6%).

Older individuals and those taking d4T (stavudine; Zerit) as opposed to AZT (zidovudine; Retrovir), or lopinavir/ritonavir as opposed to efavirenz, were more likely to change therapy. Conversely, those taking tenofovir (Viread) as opposed to AZT, or atazanavir (Reyataz) as opposed to efavirenz, were less likely to switch.

“In patients who have never experienced virological failure, the rate of treatment change due to toxicities is low, and certain regimens are associated with an even lower rate of change,” the investigators concluded. “If virological failure is avoided, some regimens are so far proving to be sufficiently stable to suggest that very long-term use is potentially feasible.”

In contrast, an analysis of the Swiss HIV Cohort (reported in the June 15, 2008, *Journal of Infectious Diseases*) found that about 45% of treatment-naïve patients modified their initial regimen within one year, and this proportion did not change much between 2000–2001 (48.8%) and 2004–2005 (44.3%). Here, too, the most common reason for switching was side effects (51.1%), followed by patient choice (15.4%), physician decision (14.8%), and virological failure (7.1%). Despite the high rate of regimen modification, however, outcomes improved over time, with a higher proportion of patients achieving undetectable viral load during 2000–2001 compared with 2004–2005 (84.5% vs 92.7%, respectively).

## Managing Virological Failure

While durability is an important feature of a successful HAART regimen, it is important to consider changing therapy when treatment begins to fail. In a poster presentation at the 15<sup>th</sup> Conference on Retroviruses and Opportunistic Infections this past February, Maya Petersen and colleagues reported on an analysis of 982 patients in two U.S. cohorts, looking at the effects of delayed regimen modification following a first virological failure.

Most first-time HAART failures (76%) occurred among patients taking at least one PI, including 32% among those taking a boosted PI. After controlling for such factors as viral load, CD4 cell count, and treatment experience, people who delayed modification of a failing NNRTI-based regimen had a higher risk of disease progression and death. Delaying modification of a failing PI-based regimen, however, did not have the same deleterious effect.

Another study presented at the conference looked at virological failure of a second HAART regimen. Steven Deeks, MD, and colleagues with the North American AIDS Cohort Collaboration on Research and Design analyzed more than 33,000 participants starting HAART in the U.S. and Canada. Within this group, 15,457 people experienced a first virological failure; 9,337 of these modified the non-

NRTI component of their regimen (for example, switching from an NNRTI to a PI, or vice versa), and 5,057 subsequently experienced a second virological failure.

The rate of second virological failure declined over time, from 114 cases per 100 person-years during the early HAART era (1996–1997), to 42 cases during 2000–2001, to just 15 cases during 2004–2005. Higher viral load, lower CD4 cell count, and clinical AIDS at the time of the second treatment failure were associated with an increased risk of death; however, treatment experience (for example, NRTI monotherapy) prior to combination HAART, time since starting the first HAART regimen, total number of HAART regimens ever used, and pre-HAART viral load and CD4 count had no impact.

Based on these findings, the investigators concluded that the risk of second episodes of virological failure had “declined dramatically over the past decade,” but added that “mortality after second HAART failure has not improved over time.” They recommended that individuals at greatest risk of death should be managed as soon as possible after treatment failure, and emphasized the need for access to newer drugs for people who experience treatment failure in resource-limited settings.

## Conclusion

While much remains to be learned about optimizing antiretroviral therapy, improved drugs and a better understanding of how to use them have benefited HIV positive people as a group, regardless of which specific regimen they choose.

With more than 20 antiretroviral agents now available, patients have more options than ever, and therefore better prospects for constructing an individually tailored regimen that works best for them.

“It’s generally scrambled eggs now,” observed Eric Goosby, MD, Chief Medical Officer of Pangaea Global AIDS Foundation. “Your treatment regimen should be determined by personal considerations such as your drug resistance profile, what medications you’re allergic to, what organs work or don’t work, and your family history with cardiovascular disease and diabetes.”

Most experts today would agree that NNRTIs and second-generation PIs—especially when boosted with ritonavir—both offer very good efficacy against HIV, and that most people starting treatment for the first time have excellent odds of achieving full viral suppression. Furthermore, treatment-experienced patients with extensive drug resistance also have a high likelihood of achieving undetectable viral load, especially given the availability of new drugs in novel classes. According to the current U.S. treatment guidelines, full virological suppression should be the goal of therapy for all patients.

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## Drug Resistance Testing: Genotypic vs Phenotypic

Two forms of drug resistance testing—genotypic and phenotypic—are used to predict how particular strains of HIV will respond to antiretroviral therapy.

Genotypic resistance testing screens HIV from an individual’s blood for mutations known to be associated with resistance to various antiretroviral drugs. Phenotypic resistance testing exposes a patient’s HIV to various drugs in the laboratory to see how it responds to those drugs.

Although specific resistance mutations—changes in the viral genetic material—are known to reduce susceptibility to anti-HIV drugs, these mutations may not be “expressed” in the viral phenotype, and thus may not alter the virus’s response to treatment.

Genotypic testing alone, therefore, may provide an incomplete picture of an individual’s range of viable treatment options. As Dr. Goosby explained, some patients show multiple mutations associated with resistance to specific drugs on genotypic test results, but still fare well on those drugs. “If you looked at their genotype, you’d say, ‘That’s it, there’s nothing I can do for them,’” he says. “But put them on four or five drugs and their viral load goes from 200,000 down to 30 [copies/mL] and stays there.”

### Selected Sources

Deeks, S. and others. Trends in second virologic failure and predictors of subsequent mortality among ART-experienced patients: North American experience. 15<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (15<sup>th</sup> CROI). Boston, MA. February 3–6, 2008. Abstract 41.

Hirschel, B. and A. Calmy. Initial treatment for HIV infection—an embarrassment of riches. *New England Journal of Medicine* 358(20):2170–2072. May 15, 2008.

Lima, V. and others. Increased resilience to the development of drug resistance with modern boosted protease inhibitor-based highly active antiretroviral therapy. *Journal of Infectious Diseases* 198(1):51–58. July 1, 2008.

Lodwick, R. and others. Stability of antiretroviral regimens in patients with viral suppression. *AIDS* 22(9):1039–1046. May 31, 2008.

Petersen, M. and others. Long-term consequences of the delay between virologic failure of HAART and regimen modification: a prospective cohort study. 15<sup>th</sup> CROI. Abstract 798.

Riddler, S. and others. Class-sparing regimens for initial treatment of HIV-1 infection. *New England Journal of Medicine* 358(20):2095–2106. May 15, 2008.

Vo, T. and others. Durability and outcome of initial antiretroviral treatments received during 2000–2005 by patients in the Swiss HIV Cohort Study. *Journal of Infectious Diseases* 197(12):1685–94. June 15, 2008.