At the End of Your Rope?

A guide to your antiretroviral options when all else fails

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In Year Two of the protease inhibitor era, it's common knowledge that some PWAs never see the lowered viral loads and improved symptoms associated with the "miracle drugs" -- or see such benefits only briefly. Take Jeff Cipcic of Grand Rapids, Michigan. After ritonavir (Norvir) was approved in March 1996, Cipcic added it to his previous combination of AZT and 3TC. His CD4 cells climbed from 48 to 210, but Cipcic found the drug hard to take. "The side effects kept getting worse," he says. "I was nauseated beyond belief."

In July, Cipcic switched to a second cocktail: ddI, d4T and Crixivan (indinavir). His viral load plummeted from 152,000 to 682, but by this past April, it had returned to 36,000. Third at bat: A combination of ritonavir and saquinavir (Invirase). "It failed miserably. Within four weeks my viral load doubled, and then doubled again." At a medical conference, Cipcic compared notes with PWAs from the West Coast. "They were doing completely different combinations, like three nukes with two proteases," he says. He returned to his doctor asking to try more unusual combinations, but complains, "He's very conservative. I said, 'Look, I'm not your typical patient. I'm more advanced. I'm at the end of my rope.'"

Estimates on how many people are dangling at the "end of the rope" are tough to come by. "We have no data," cautions Steven Deeks, MD, assistant clinical professor of medicine at the University of California, San Francisco. "But it appears that about a third of the patients in our public AIDS clinic here at San Francisco General Hospital have failed on protease inhibitor-containing combinations." Deeks has begun a formal review of patient charts to learn the true rate of protease combination treatment failures. Meanwhile, 7,000 people failing the older three protease inhibitors sought access to nelfinavir (Viracept) last year. Thus, it is estimated that the number of people currently failing combination therapy is at least this large and possibly much larger.

The reasons for combination failures are complex. Managing the problem is difficult and demands creativity and sophistication on the part of PWAs and their doctors.

Building effective combinations depends on marshaling all the antiretrovirals at your disposal. Members of the "end of the rope" club may be willing to try therapies often overlooked, some of which are presented below. A warning: There is little or no data on safety or long-term activity of novel drug combinations. Always carefully discuss such options with your doctor before trying

them. Among the possibilities:

NNRTIs. The nonnucleoside reverse-transcriptase inhibitors include nevirapine (Viramune) and delavirdine (Rescriptor). Research has shown some modest viral-load decreases and mild CD4 boosts when these drugs are used with double nucleoside combinations (for example, AZT/ddI). Since both nevirapine and delavirdine cross the blood-brain barrier, they are of particular interest to those with neurological complications who are resistant to, or intolerant of, AZT and d4T (the other drugs commonly used to help protect the brain). Unfortunately, in the combinations so far studied, NNRTIs have not been proved to prolong health or survival. For those who choose to use NNRTIs with nucleoside analogs, it is best to use them with ones that haven't been used before.

It is possible that better results might be seen with at least some NNRTIs if used with protease inhibitors. For example, delavirdine boosts blood levels of saquinavir 2- to 14-fold. Delavirdine also increases Crixivan levels 2.5- to 5-fold. Paul Bellman, MD, an HIV specialist in New York City, has been adding delavirdine to Crixivan combinations that did not fully suppress HIV. After six months, about 20 percent of the patients had undetectable viral loads. Another 40 percent had "markedly lower" viral loads. The rest had brief or no responses. Bellman says, "This represents an extraordinary result, given that all of these patients were extensively treatment-experienced, including protease inhibitor therapy, with high and usually rising viral loads prior to delavirdine therapy." However, not all NNRTIs increase protease effectiveness, and for many drugs the impact of interactions is not yet known. We do know that nevirapine lowers Crixivan and saquinavir blood levels.

Be aware that trials of combos containing nevirapine or delavirdine have found 20 percent to 40 percent of PWAs experienced rash; with nevirapine, eight percent of rashes were life-threatening. (Rash can often be avoided by beginning with lower doses for a very limited time period.) Another concern is that if NNRTI-based combinations don't completely suppress the virus, HIV may quickly develop very strong resistance. Since more powerful drugs in this class are in the pipeline (Dupont-Merck's DMP-266, for example) and are likely to be cross-resistant, the resistance risk should be weighed carefully before using these drugs.

Dual protease combinations. It is now widely recognized that ritonavir can be used to boost levels of the poorly absorbed saquinavir. However, data presented at the Retrovirus Conference last January suggest other synergistic protease duos. For example, nelfinavir can boost levels of either saquinavir or Crixivan. Not all protease duets are harmonious, however. For example, test-tube studies show that saquinavir and Crixivan antagonize each other.

Hydroxyurea. This prescription anticancer drug attacks HIV in a completely different way than any approved antiretroviral: It inhibits cellular enzymes necessary for viral replication, rather than acting on the virus itself. It works especially well with ddI. Researcher Franco Lori of the Research Institute for Genetic and Human Therapy in Gaithersburg, Maryland has shown that hydroxyurea can allow ddI to work even against virus that has developed mutations against ddI. After a year of treatment, all 40 of his patients are still responding well. In a study of drug-experienced patients, ddI/d4T/hydroxyurea yielded viral-load decreases of 30- to 300-fold, and an average CD4 increase

of 84. Advantages of this drug include good brain penetration, and activity against HIV in macrophages, cells thought to be an important viral reservoir untouched by most drugs. The biggest worry with hydroxyurea is that it suppresses bone-marrow function, and so is not a choice for people with pre-existing low blood counts or on bone marrow-suppressive drugs such as ganciclovir.

Herbal compounds. Members of the New York-based buyers club Direct AIDS Alternative Information Resources (DAAIR) have been experimenting with a four-compound herbal regimen of SPV-30 (boxwood extract), bitter melon, glycyrrhizin (licorice extract) and curcumin -- at a total monthly cost of about $120. Of four people who tried the combination, three had viral-load decreases of 1.5 log (30-fold) after four months, while one person's viral load continued to increase. DAAIR director Fred Bingham cautions that such scant information is impossible to interpret, but adds, "For end-of-the-ropers, it's a what-the-hell therapy -- particularly because of these herbs' usually minimal toxicity. So far, in the people who respond, the results are impressive." Bingham selected these agents because each has shown anti-HIV activity, at least in the test tube. Only SPV-30, however, has been in large randomized clinical studies (in France), where it seems to show a mild anti-HIV effect.

Meanwhile, some PWAs in San Francisco continue to use Compound Q, an extract of Chinese cucumber root that has shown activity against HIV in macrophages. Treatment advocates note that there are hundreds of herbal compounds whose antiretroviral activity has been shown in test-tube research, but funding has rarely been made available for clinical trials.

New antiretrovirals. Drugs in the pipeline that may enter clinical trials or expanded-access programs (see p. 92, "Expanding Your Access") in the next year include Glaxo's 1592 (abacavir), Gilead's bis-POM PMEA (adefovir dipivoxil), the Glaxo protease inhibitor 141W94 (formerly Vertex's VX478), and ABT-378, a second-generation protease inhibitor from Abbott Labs.

Cipcic says he plans to continue aggressively pursuing the latest research results. "Something I've figured out is that on the West Coast and in New York City, the doctors have to keep abreast because the patients are reading and sucking up this information, and going to them with it. I'm on my fifth doctor now -- I fired them all." For Cipcic and many other PWAs in the "end of the rope" club, aggressively seeking cutting-edge information and then using one or more of these "overlooked options" may provide hope -- and a bridge to the next generation of therapies.
