Being Alive

Can You Make A Good Antiviral Cocktail Without a Protease Inhibitor?

Walt Senterfitt

July 5, 1997

Being Alive 1997 Jul 5: 5

In the media and in the hiv community vernacular, "protease inhibitors," "triple-drug cocktails" and "highly active antiretroviral therapy (HAART)" are used interchangeably. This is inaccurate and potentially misleading. It could lead positive people and less hiv-specialized physicians to assume that any drug regimen not including a protease inhibitor is inferior and inappropriate.

Effective suppression of hiv (as measured by reducing viral loads to undetectable levels) has been achieved with various other two- and three-drug regimens in at least some groups of people. Increasingly popular, especially for people who have not yet taken any antiviral drugs, are combinations containing NNRTIs.

What Are NNRTIs? NNRTIs are a class of drugs that have been under investigation for a long while but have just recently come into general use. The term is an acronym for a real mouthful: "non-nucleoside reverse transcriptase inhibitors." This means that its antiviral action comes by blocking the enzyme (reverse transcriptase) that allows hiv to translate its genetic material into a form that can merge into the core of a T-cell, to quietly lurk and one day turn the "host" T-cell into an hiv factory. This is the same target as the "nukes" (the nucleoside reverse transcriptase inhibitors like AZT, 3TC and the "d" drugs), but the NNRTIs work through a different mechanism.

The most widely used NNRTI is nevirapine (brand name Viramune). The FDA recently approved a second drug of the class, delavirdine (Rescriptor). Dupont Merck is currently conducting widespread clinical trials (with several sites in Los Angeles) of a third NNRTI, known for now as DMP266. DMP266, on the basis of preliminary studies, is thought to be considerably more active in blocking hiv than either of the first two.

How Good Are They? First thing to remember is that NNRTIs must only be used in combinations! Used alone, or with another drug to which your body has already become resistant, NNRTIs very rapidly lead to hiv resistance.

Viramune, in combinations with two nukes (say AZT plus 3TC, AZT plus ddI or ddI plus d4T) in people with intermediate or high T-cell counts (more than 200), has shown an antiviral effect comparable to that of combinations including a protease inhibitor. In one such study of 151 people, 70% of those taking AZT plus ddI plus Viramune achieved and maintained undetectable viral loads as of six months of treatment, compared to 40% of those on AZT plus ddI alone. In a larger study of people with more damaged immune systems (average T-cell count of 138) and with previous experience with nuke drugs alone or in combinations, the benefit was much slighter for combos with

Viramune. There was a sustained T-cell rise averaging 140 above baseline in the Viramune group after one year compared to the AZT plus ddI alone group (40), but there was not significantly better reduction in viral load or survival.

Later trials of combination therapy including nevirapine have failed to substantiate the duration of viral suppression found in the smaller trial mentioned above. In other words, viral load dropped as far as with proteases, but didn't last. For this reason, the new federal guidelines list Viramune-containing combinations as an alternative starting regimen to those containing protease, but an alternative with less evidence for its effectiveness over time.

Rescriptor (delavirdine) has shown less evidence of a significant effect in clinical trials so far, and its approval was somewhat controversial. The hiv treatment advocacy community's attitude is typified by the April/May 1997 issue of Treatment Issues; its cover story on Rescriptor's approval is entitled "Now There Are Eleven [FDA-approved antiretroviral drugs], But So What?" One study in people with no prior drug treatment (or less than six months of it), found that AZT plus ddI is virtually equal to AZT plus ddI plus delavirdine and ddI plus delavirdine. However, empirical data collected carefully by some physicians, Dr. Paul Bellman of New York in particular, found that a number of patients who were being failed by protease combinations started responding and improving again when delavirdine was added to their existing regimen. This may be due to a side effect of NNRTIs, increasing the bloodstream concentration of Crixivan. So approval came largely on the basis of providing one more alternative that may work for some people whom other combos are failing.

Side Effects And Interactions The most common side effect of NNRTIs is a rash, usually temporary and starting fairly soon after one begins the drug, but which may become quite severe and even life-threatening. The rash has occurred in about 22% of the people taking Viramune, and about 7% have had to stop taking their drug because of it. In unusual cases, this can escalate to a life-threatening allergic reaction known as Stevens-Johnson syndrome for which emergency treatment is necessary. If you or any one close to you ever starts having breathing problems or any other rapid-onset changes with a Viramune or Rescriptor rash, stop taking the drug immediately and get thee to an emergency room! Unlike say Bactrim, it is not recommended to re-start Viramune or Rescriptor after once stopping it because of the rash. What is now becoming standard practice is to start Viramune, at least, with a half dose for several days to two weeks before ramping up to full dose. Other side effects can include liver function abnormalities, fever and muscle soreness.

Drug interactions can be a big problem, at least if you need to take any of the other long list of drugs that are metabolized along the same liver-enzyme pathway as the NNRTIs. The pattern is similar to Norvir, but the list is constantly changing as more information accumulates from expanding use. Sometimes the interactions can be used to good effect, as was apparently done by Dr. Bellman in increasing Crixivan concentration to help those who can't absorb that drug well enough, but this should only be done under careful and expert medical monitoring. For the latest updates, call the Project Inform hotline (800.822.7422) or the manufacturer's special interaction information numbers (available on the package inserts or from your pharmacist or physician).

Recommendations The new draft federal guidelines rank Viramune plus two nukes as an inferior-grade alternative to proteases, but one which may be better or preferable for some people. The niche that the studies seem to indicate for NNRTIs is as a part of the starting combination for people with relatively high (over 200 anyway, some would say higher) T-cell counts who have not taken antiviral drugs previously. The virus is somewhat more forgiving of missed doses and other compliance problems with NNRTIs compared to protease inhibitors. This is another reason that many doctors and patients prefer to start with two nukes and an NNRTI, saving the protease inhibitors for later. You can learn how to be the "Compleat Compliant Pill Taker" and save a powerful backup for later, both at the same time! However, because of the lack of consistent evidence that the viral suppression benefits of NNRTIs are prolonged, many experts would recommend starting out directly with a protease-containing regimen, under the assumption that one wants optimal therapy from the beginning. This is an issue worth careful discussion with your provider.
The other usage is as a backup or "try-anything" drug for those who have run out of other choices. In the main, as with proteases, when changing therapies one should change as many as you can at the same time to give your body the best shot at knocking out virus resistant to your former drugs.
Access Both NNRTIs are on the MediCal and ADAP formularies. Manufacturers also have patient assistance programs to help people get drugs, even for free on a limited basis, if you have no other way to get them paid for. For Viramune, the number is 800.274.8651 and for Rescriptor it is 800.711.0807.

See the topic on aegis.org