reason for hope

Help on the way

by the AIDS Writers Group
Special to Q-Notes

The news of the past year has been good for most people with HIV disease, but the new drug cocktails do not work for everyone. New antivirals are in the pipeline. Some are new versions of old drugs and others are drugs that stop the virus in completely new ways. These new drugs may help many having trouble with their existing regimens or who have failed all available therapies; however, all may not be effective in people whose virus is now resistant to current antivirals.

Trial and error

There are now 11 HIV antivirals at your pharmacy. They are divided into three different types of drugs, "nuke" and "non-nuke" RT inhibitors and protease inhibitors, which attack the virus at two different places in its life cycle. It has been found that combinations of these drugs set up blockades that are far more effective in stopping the virus than if any one drug is used alone. It has taken doctors over two years of trial and error to better understand ways to use these new antiviral combinations. Unfortunately, for those who took the drugs before it was known how best to use them, some, or all, of the current antivirals no longer work. Their virus has developed "resistance."

In addition, because of side effects, some people have been unable to tolerate many of the available therapies. Other people have been unable to keep to the complicated schedules that some drugs require. So the need continues for potent, more tolerable antivirals which are convenient to take. The good news is that such drugs may be on the way; several should be FDA-approved this year. Others will take a while longer before they become available.

Coming attractions

There are three experimental antivirals now in clinical trials which are likely to be approved by the FDA this year: abacavir, Sustiva and adefovir. Two are improvements on types of drugs already available. One belongs to a new class altogether. For those who have used up their antiviral options and cannot afford to wait until these drugs are approved, there are expanded access programs making them available for some people now.

A new nuke

One of the promising newcomers is called *abacavir* (the drug formerly known as 1592-U89). Abacavir is a nucleoside analog reverse transcriptase inhibitor or "nuke" RT inhibitor like DDI or AZT. This type of drug slows down HIV by interfering with its ability to teach your cells how to make more HIV. But unlike the old nukes, like AZT which only suppresses HIV by about 70 percent in patients who have never used antivirals, abacavir was able to suppresses the virus by as much as 99 percent. This is as good as any other drug now available.

One problem with HIV antivirals is that if you failed one drug, a similar antiviral you have never used may not work. This is called cross-resistance. The good news about abacavir is that even if a person has already failed D4T (Zerit) and possibly DDI (Videx), abacavir may still help. When tested in such people, it brought the amount of virus down by 97 percent. Unfortunately, there is some evidence that abacavir may be of less benefit to those who have failed AZT-3TC.

The major side effect of abacavir is nausea, although there have been some reports of a serious allergic reaction to the drug in a few people.

A new non-nuke

DMP-266 is a non-nucleoside reverse transcriptase inhibitor or "non-nuke" RT inhibitor. The brand name for DMP-266 is *Sustiva*. Non-nukes like Sustiva stop the virus at the same point in the viral life cycle as the nukes but in a different way. Data shows that Sustiva can drop the amount of virus by 97 percent.

Sustiva has been testing in combination with the protease inhibitor, crixivan. Together they can drop the amount of virus in the body by 99.8 percent. Studies are now being done with the drug in combination with other protease inhibitors. Unfortunately, Sustiva may not work if you have failed either of the other available non-nukes, nevirapine (Viramune) and delavirdine (Rescriptor). Sustiva is easier to use than other drugs because it requires just once-a day-dosing. Side effects of Sustiva include rash, headache, dizziness and nausea.

A new kind of drug

The drug adefovir (or PMEA) is one of a whole new class of antivirals called nucleo R inhibitors. Adefovir also blocks the virus at the same point as the nuke and non-nuke RT inhibitors, but, as a Nucleotide, it needs less processing by the body for the drug to change into its active form than the others do.

Adefovir does not seem to be very powerful at suppressing HIV, dropping the amount of virus by only about 80 percent, but it has several advantages over current antivirals: Adefovir is slower to develop resistance than current drugs so it can successfully suppress HIV for longer periods of time. Adefovir is a broad-spectrum antiviral that suppresses herpes and other viruses that may contribute to HIV disease progression. It is also possible that adefovir will still work in people that have already used up all the drugs now available. Like Sustiva, adefovir only needs to be taken once a day. Adefovir depletes the body's supply of the amino acid L-carnitine, so a person taking it will also have to take an amino acid supplement. An additional potentially serious side effect of adefovir is kidney toxicity. Regular blood tests will be required to monitor the drug's effects on the kidneys.

Further down the road

Other promising experimental drugs which can be accessed through clinical trials are in the pipeline.

PMPA is a chemical cousin of adefovir, but looks a lot more powerful. In its first clinical trial it dropped the amount of HIV by 99 percent. Like adefovir, PMPA may also work for those who have failed other drugs although its too early to tell for sure. Also, more has to be learned about PMPA's side effects.

Also in early testing is the drug known as T-20. T-20 is one of a new class of antivirals called "Fusion Inhibitors." Fusion Inhibitors do something that none of the current antivirals do; it stops HIV from getting into t-cells, which keeps the virus from reproducing. In its first trial, T-20 also dropped the amount of virus by 99 percent.

T-20 could be a major breakthrough in HIV antivirals adding an additional barrier, along with the RT Inhibitors and the protease inhibitors, in blocking the virus. Because T-20 stops the virus before it infects the cells where all the other antivirals work, it should be effective for those who have failed any other drugs. Unfortunately, because the body gets rid of T-20 so quickly, the drug may have to be put into your body constantly by a small portable pump similar to that used by diabetics. So far, T-20 appears safe and fairly well tolerated, but more data is needed to determine if this will be true over the long term.

Amprenavir is a new protease inhibitor from Glaxo-Wellcome and Vertex. There have been recent reports of impressive results with amprenavir in combination with several of the current protease inhibitors resulting in 99.9 percent decreases in virus. This is similar to the results of the saquinavir (Fortovase) plus ritonavir (Norvir) combination. These are the most powerful combinations of antivirals yet tested. Test tube studies suggest that amprenavir may be useful to people who have used up the benefit of other protease inhibitors, but it remains to be proven if this is true.

In time, more will be known about these drugs and there are still others to keep an eye on such as zinc finger inhibitors, antisense drugs and integrase inhibitors. To find out about clinical trials for experimental HIV antivirals, call the AIDS Clinical Trials Information Service at 1-800-874-2572.

In the Meantime

While waiting for these new therapies, there are actions you can take to protect your health and your antiviral options: Plan a treatment strategy using a doctor who is experienced in HIV care. With your provider, select antivirals carefully, so as not to limit your options later if the combination fails. Choose the most powerful antiviral regimen you can tolerate. If possible, choose a regimen that is likely to suppress HIV completely, preventing drug resistance. If you have no or limited antiviral options, make sure you have a doctor who is giving you the care you need, one who is aware of the most effective treatments for opportunistic infections. ▼