When HIV Drugs Fail

Eight reasons why-and what you can do about it

December 1, 1997 By Rick Loftus

Here's a frighteningly common story these days: After staying in relatively stable health, your CD4 count plummets, your viral load skyrockets, and you start to feel crummy. Your doctor carefully outlines the pros and cons of each antiretroviral combination that applies to you, and after much thought, you begin one of them. But weeks later, your blood tests show little or no improvement, and you really don't feel much better. Or you do well on the cocktail for a while, and then the benefits just start to melt away.

WHY DO ANTIRETROVIRAL DRUGS FAIL?

Robert Grant, MD, a researcher at San Francisco's Gladstone Institute of Virology and Immunology, and Project Inform, a leading HIV treatment information center, have outlined eight major reasons why HIV viral load levels remain detectable in the face of treatment:

The virus becomes resistant to one or more drugs. People for whom combination therapy fails are often those who added a new drug to an already failing combo-which means they were effectively taking the new drug alone-or who took drugs one at a time. In either case, the potent combination necessary to fully suppress the virus wasn't present. This allows the virus to reproduce and mutate, leading to resistance and drug failure. Viral loads then rise, making it necessary to switch to new drugs. Unfortunately, there is also the problem of "cross-resistance"-HIV that resists one drug may be able to resist others in the same class. This may be a reason why people who have failed one protease inhibitor do less well on follow-up drugs.

You aren't taking the drugs regularly. Obviously, the drugs can't attack the virus if they're not getting into your body. Taking them only occasionally is far worse over the long term than not taking them at all. Stanford University researchers have found that missing saquinavir doses for only two days results in rapid increases in viral load and, possibly, an increased chance of developing resistance. Many of these combos require taking 20 or more pills a day at inconvenient intervals-a tough challenge for even the most enthusiastic drug-taker. Yet some PWAs report that their doctors never warned them about the importance of taking meds on schedule, much less offered helpful hints on how to do so.

Your body has problems absorbing the drugs. Even if you take the drugs regularly, you may

not absorb them because of problems with your gut. The biggest worries are diarrhea and malabsorption, both very common in people with HIV. There are various causes, including infections, medications (such as antibiotics or other anti-HIV drugs like nelfinavir [Viracept]) or just plain HIV. Chances are, you're not absorbing your antiretrovirals, either. Take every step to diagnose and treat diarrhea and malabsorption. Nutritional supplements available at health-food stores, such as L-glutamine (key for maintaing the small intestine's absorption capacity) or extra digestive enzymes taken with meals, may help here. The stomach may also have problems. A study appearing in *Clinical Infectious Diseases* in December 1995 found that at laest 60 percent of PWAs had lowered stomach acid. This may undermine absorbing drugs, such as Crixivan or delavirdine (Rescriptor), that need acidic conditions. If your stomach acid is found to be low, taking such drugs with hydrochloric acid supplements may be helpful.

How you take drugs can also affect absorption. Many doctors give their Crixivan patients antacids because taking the pills on an empty stomach gives them heartburn, while other Crixivan patients mistakenly take their drug with ddI, whch contains a buffer that reduces stomach acid. These antacids can interfere with absorption. Switching drugs or drug schedules, or taking drugs like Crixivan with a light, fat-free snack, may eliminate these problems without impairing absorption.

Another drug you're taking decreases the antiviral's effectiveness. Many other drugs interact with protease inhibitors, sometimes in ways that reduce their blood levels. The antiretroviral nevirapine (Viramune), antibiotics like rifampin and rifabutin, and many antiseizure medicines can bring down protease-inhibitor blood levels. Fortunately, this interaction works both ways: Anti-HIV drugs can be combined to *increase* their blood levels (check with your doctor or the sources below for details).

The drug's not going everywhere it needs to. Drugs that reach the blood or lymph nodes may not get into other places HIV reproduces, such as the central nervous system (CNS), including the brain. None of the protease inhibitors show good CNS penetration, and data suggest that only AZT, d4T and nevirapine can reliably penetrate the brain and bring down CNS HIV levels. (Data on delavirdine are unclear.) Therefore, someone with HIV-related dementia or neurological problems should discuss with their doctor whether to include one of the older drugs in a combination.

Another infection creates more active virus. Any other infection-whether chronic (like the herpes infections that most people carry, which can wax and wane), acute (a cold, flu or other short-term illness) or opportunistic (any of the serious infections PWAs may get)-will activate the immune system. This may increase HIV replication and dramatically elevate viral load-which then increases the chance of viral mutations and, thus, resistance to drugs.

You switched viral load tests. The two major viral load tests are from Roche ("PCR") and Chiron ("bDNA"). PCR may give higher viral load readings on a sample than does bDNA. If you've started tracking your viral load with one test, it's best to stick with it.

Remember, too, that your "true" viral load may be up to five times higher or lower than the result on your viral load report. So if your viral load doubles, it may simply reflect variations in the lab,

rather than in your blood. Any change you detect in your viral load should be checked with a repeat test within a few weeks, before you switch your therapy.

None of the above. Scientists theorize that the low but persistent viral loads sometimes seen in people on combos may come from HIV reproduction in infected cells where the drugs don't work. Which cells, how they may do this trick, and whether this virus activity can lead to drug resistance are subjects of intensive study. Meanwhile, this may explain why some people's drug combos fail when none of the other explanations apply.

WHAT YOU CAN DO

For people who have already used up one or more combinations, it's a challenge to put together a new drug cocktail that can maximally suppress HIV levels for more than a few weeks or months. Cutting-edge physicians and treatment activists offer the following advice:

Use drugs you haven't used before. Project Inform recommends "changing at least two elements of the combination therapy at the same time," preferably choosing drugs never used before. You may think you have tried 'em all, but there could be some "overlooked options" still available to you, including still-experimental drugs (see "At the End of Your Rope?", *POZ*, October 1997). In particular, consider using drugs shown by researchers to enhance each other's effectiveness. Examples are ddI-hydroxyurea, delavirdine-indinavir, delavirdine-saquinavir, ritonavir-saquinavir, nelfinavir-saquinavir and nelfinavir-indinavir.

Try to select drugs to which you are less resistant. Even if they include some new drugs, most folks with lots of drug experience will still have to use drugs they've tried before. Thus, the issue is picking those drugs to which your HIV has the least resistance. In general, this is likely to mean the drugs you've used the least and/or which you've used in combos with some degree of effectiveness. In addition, some PWAs are now rushing to do drug resistance tests. There are two types: Genotypic, which looks at the genetic code of a person's strain of HIV, and phenotypic, in which his or her virus is actually grown in a test tube and then exposed to various drugs. Results from these tests *might* provide useful information, especially when they seem to correlate with viral load and CD4 counts. But the ultimate usefulness is still uncertain. For example, many anecdotal reports indicate that the presence or absence of mutations found with genotypic testing (the cheaper and more widely used method) may *not* always correlate with viral loads. People with high viral loads don't always show the viral mutations that would explain resistance to the drugs they're taking. Conversely, people whose virus does have resistance-associated mutations may still have undetectable viral loads. Currently, most experts recommend against using these tests as a major determinant of therapy choice.

Make sure the drugs are getting into your blood. See the points on adherence, absorption and drug interactions, above.

Bring the load down hard and fast. Research from Dr. Dale Kempf and colleagues at Abbott Labs suggests that the time period antiretrovirals keep working depends on just how low the viral

load goes after starting treatment. Some researchers also believe that a fast decraese in virus levels is preferable to a long, slow decline. If your viral load has not decreased by at least 10-fold (one log) within four weeks of starting therapy, discuss with your doctor the idea of adding another drug to the combination, at least until the load comes down to lower (hopefully undetectable) levels. If you have a long history of using single drugs, consider starting treatment with a four- or five-drug combination.

When your drug combo fails, the first step is researching all the possible options and discussing them with your physician. Once you clearly understand why drugs fail-and how to create the best possible new combo-you can greatly improve your chances of finding an effective treatment approach.

For more information on antiretroviral failure and alternative combos, contact Project Inform at 800.822.7422 (website: www.projinf.org), or visit the Critical Path AIDS Project website at www.critpath.org. To report protease inhibitor failure, contact the Protease Inhibitor Response Project at www.netcom.com/~protease.

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http://beta.docker.poz.com/article/drugs-arv-fail-12883-4745