Play It As It Lays

With drug resistance, every dose of meds is a crapshoot. Two new tests can maximize your odds.

January 1, 2000 By Maia Szalavitz

Drug resistance, distant thunder at the dawn of the antiretroviral era, is battering the structures and strategies of AIDS treatment like a tropical hurricane. While science is powerless to stop viral mutations that can lead to resistance, high-tech tests can at least identify all those “M184V”s and “G48V”s—and help you and your doctor figure out which drug in your combo has failed or which drug may never work. But there are numerous complexities and cautions regarding these costly tests, the correct interpretation of their data and the application of this information to sound medication choices. In addition, there are two types of resistance tests: genotypic and phenotypic, each with distinct pros and cons, but unfortunately, taking both doesn’t address every problem of either.

When is it time to test? Most HIV specialists see the red flag in a rising viral load and/or a falling CD4 count and/or an opportunistic infection—all possible signs of HAART failure. Several retrospective analyses of clinical data support the use of genotypic tests when viral load has increased. And two prospective trials correlating the results of genotypic testing with viral load changes found that the test correctly predicted medication response.

Results from studies using phenotypic tests are just starting to come in. One small study found that the test predicted response to a new HAART regimen after treatment failure; another achieved the same result for the nuke drug abacavir (Ziagen).

But with neither test in widespread use, doctors may read and use the results incorrectly. “It’s hard even for us who do it every day,” says Roger Pomerantz, MD, an HIV specialist at Thomas Jefferson University in Philadelphia. “The average practitioner needs to be very careful in interpreting these tests because he or she could throw a good drug away for no reason.”

Michelle Roland, MD, of the Positive Health Program at San Francisco General Hospital, is even more cautious: “The tests could be used in a dangerous way—they could make matters worse if the physicians don’t take into account the patient’s history [of antiretrovirals and responses to them]. Unfortunately, it’s not uncommon that a physician will look at a test and forget everything else.” One example of the complexities of interpretation would be a PWA with CD4s that are rising or stable at a good level, but also with an increasing viral load. The mutations uncovered by this person’s genotypic test might actually be reducing the ability of some of the viruses to do harm.

Complex computer programs are being developed to systematize interpretation of resistance data in the context of a specific medical history. Meantime, doctors can consult charts summarizing data on resistance patterns for each HIV drug, but the available charts differ and there is controversy about the meaning of many mutations.

Here are some expert tips to help you and your doc get the best from the test. Before choosing to take blood:

- Test only when you have a plan to respond to the results. Use the test to answer specific questions such as: Which drug in your current regimen is failing? Which drug that you might switch to is likely not to work?
- Test only before you stop your regimen. When the anti-HIV pressure of the drug is removed, the resistant strains have no reproduction advantage over the “wild type” and may soon fade away—leading to misleading results if resistance is measured down the line.
- Test only if viral load is above 1,000; below that, tests are not accurate.

When interpreting test results:

Bear in mind that the tests are useful to rule drugs out, not in. A “no resistance” result to a particular drug or class of drugs doesn’t mean that those drugs will work. There could be resistance below the test’s level of detection.

Conversely, mutations (found by genotypic tests) that are commonly linked to resistance may not actually create it in your body. Your own and the virus’ genetics, your particular drug combination and other factors could make a drug effective when the test predicts otherwise. Phenotypic tests can also yield imperfect data because it is not yet clear where to set the drug-concentration cutoff.

And note that tests from different labs may give different results. When all is said and done, resistance tests are only part of the equation—not the final word—in deciding on a particular treatment strategy. But used properly, the tests offer hope: HIV may be a confident and quick-charging hare of a virus, but the tortoise of AIDS research is evolving rapidly as well.

A PAIR OF ACES

Geno or pheno? What’s the difference? Which is better? Ask Mr. Science a question he can answer. Here’s what we know so far: A genotypic test, as its name suggests, identifies whether the genes of your HIV have mutated in a way that helps it elude a particular drug or combo, while a

phenotypic test measures how much of the drug or combo is required to keep your virus from replicating. If your viral load is high, your virus is rapidly evolving. One of HIV's tricks is to reproduce not only frequently but sloppily, constantly creating millions of mutations. Few of these cause problems, but some are adaptive—allowing the virus to reproduce in the presence of drugs that previously killed it.

Genotypic resistance testing pinpoints which, if any, mutant viruses a sample of HIV contains. This is done by comparing the genetic sequence of the viruses with sequences known to cause resistance. By contrast, phenotypic resistance testing determines the level of drug it takes to kill a virus: An HIV sample is exposed to various drugs in a lab medium, and if virus grows, that shows phenotypic resistance.

It might seem that phenotypic testing is more useful, since it tests actual virus against actual drugs, but it is less researched, more expensive and takes longer to obtain results (at least a month) than genotypic testing (10 days or less). On the other hand, genotypic results are harder for physicians to interpret because they require comparison with ever-expanding databases of known mutations.

So it's a toss-up: If you take both tests, you may find agreement that clearly directs you to drop one drug in favor of another. Or you may get confusing or conflicting results. But one thing is clear: With properly used info, more is better.
