Not My Type

Stephen Gendin's genotypic and phenotypic tests show resistance to most HIV meds.

February 1, 1999 By Lark Lands, PhD

Laboratory analyses of blood and other medical measurements, which help health practitioners make diagnoses and detect toxic effects of medication, can also help people with HIV track their health. Here, John Mellors, MD, professor of medicine at the University of Pittsburgh School of Medicine and director of the HIV/AIDS Program at the University of Pittsburgh Medical Center, analyzes the genotypic and phenotypic assay results of POZ *contributing editor Stephen Gendin.*

Stephen faces a dilemma common to many PWAs: Having already taken almost every available antiretroviral therapy, how do you decide if there are any drugs left that might work? Stephen stopped all anti-HIV meds in early April 1998—but with his very high viral load (most recently 690,000) and very low CD4s (below 20 for almost four years), there's strong motivation to find something useful. However, being heavily pretreated has left him a likely candidate for resistance to most drugs other than the nonnucleoside reverse transcriptase inhibitors (NNRTIs), which he has never taken.

With his physicians both encouraging him to consider an aggressive "kitchen-sink" regimen (see "Talk Therapy," this issue, and "Attack of the Monster Combo," *POZ*, November 1998), Stephen had genotypic and phenotypic resistance tests done in July to see if the results might help guide him toward an effective choice. A genotypic assay identifies mutations in HIV's protease and reverse transcriptase genes. Genotypic evidence of resistance means that exposure to a drug has resulted in viral mutations that may produce resistance and blunt the clinical response to that drug—and in some cases, to other drugs as well ("cross-resistance"). Phenotypic assays determine the ability of HIV to grow in the test tube despite exposure to a drug.

Clinical studies increasingly indicate that the results of genotypic and phenotypic assays can help forecast the response to a new regimen in already treated patients, but knowledge of how to optimally use these tests is still incomplete.

And the response to a new regimen may not always correlate with genotypic or phenotypic findings. This is because HIV resistance tests have several inherent limitations:

The significance of certain mutations (particularly relating to some of the newer drugs) seen with genotypic assays is poorly understood, as is the significance of certain combinations of

mutations.

Phenotypic assays may not detect small changes in drug susceptibility that do have clinical significance.

The degree of phenotypic resistance that is clinically meaningful varies among the different drugs, and the methodology for doing resistance tests has not been standardized, which can lead to variable results between laboratories.

The tests are not likely to be useful when the viral load is below 1,000, since that decreases the chance of detecting resistant species.

Neither assay may be able to detect drug resistance that has occurred in the past after the therapy has been stopped. This is because resistant viruses may drop to levels that are too low to be detected once the selective pressure of the drug is removed—but resistant viruses are likely to rapidly reappear if the drug is restarted. Thus, resistance tests are most useful in determining if resistance is present to the drugs a person is currently taking.

No resistance test has FDA approval, and insurance reimbursement is difficult. (Genotypic tests cost $450 [Virco/LabCorp] to $475 [Specialty Laboratories], and generally it takes one to two weeks to get results; the Virco/LabCorp phenotypic test costs $880 and takes four to six weeks.)

Stephen obtained genotypic tests from two different laboratories on blood samples obtained on the same day in July, approximately three months after stopping all his meds. Specialty Laboratories found resistance to AZT and possibly saquinavir. In contrast, the LabCorp genotype revealed evidence of resistance to AZT (mutations in reverse transcriptase at amino acids #41, #67, #210, #215), 3TC (#184), abacavir (AZT resistance mutations plus mutation at #184) and all four approved protease inhibitors (mutations at protease amino acids #10, #48, #71, #77, #82 and #90).

It’s worth noting that at amino acids 48 and 90 of protease, there was a mixture of mutant and wild-type (nonmutant) virus, with the mutant present as a minor species—a fact that helps to explain the phenotypic results (see next page). In addition, the LabCorp genotype showed possible cross-resistance to ddI (reverse transcriptase #184), ddC (#184) and the non-nucleoside RT inhibitors (#98), although the clinical significance of these mutations, particularly #98, is unclear. The marked differences in the results between the two labs probably reflect the lack of standardized methodology.

When genotypic results (unlike Stephen’s) show resistance to only one protease inhibitor, experience suggests that this may prime the pump for resistance—and thus a less impressive response—to a second protease inhibitor.

The LabCorp phenotype performed on the same blood sample showed resistance to AZT (Retrovir) and 3TC (Epivir—not detected by the Specialty genotype), and intermediate resistance (4-10 fold

decrease in drug sensitivity) to nelfinavir (Viracept) and ritonavir (Norvir). (The clinical significance of an intermediate resistance finding has not yet been determined for most drugs, but for ritonavir or saquinavir, such a result has been associated with a poor response to those drugs.) The absence of resistance to saquinavir, despite the 48 and 90 mutations detected with the genotypic test, is probably a consequence of the mutants being present only as minor species. Unlike the LabCorp genotype, the phenotype showed no evidence of ddI (Videx) or ddC (Hivid) cross-resistance, and the entire class of NNRTIs would appear to be favorable options—all are reported as sensitive. Stephen's results are a good example of how the genotype and phenotype results do not always match completely but may provide complementary information.

[Ed. note: Although not available at the time of Stephen's tests, LabCorp—but not Specialty—now also includes on its genotype a search for the presence of the Q151M complex and the 69SSS as indicators of resistance to multiple nucleoside analogues (see "The No-Nukes Movement").]

It's very important to remember that resistance testing results should always be interpreted in the context of a thorough treatment history. Although resistance was detected to several drugs months after they were discontinued, phenotypic and genotypic assays may not always detect the remaining small quantities of virus that at one time mutated and became resistant to a drug later discontinued. The fact that the assays don't find them and, thus, don't show resistance doesn't mean that this resistant species won't resurface if the drug is re-used. Since Stephen had been off all the antiretroviral drugs for four months prior to these assays, he may have other minority species with resistance to additional drugs.

In general, clinical studies have shown that if these assays show resistance to a drug, there's little chance that it will be able to provide a significant or sustained antiretroviral effect. On the other hand, the fact that assays indicate no resistance to a particular drug is not a guarantee that it will be successful. Thus, we can use the tests to exclude drugs, but not to guarantee their anti-HIV activity.

These assays' greatest value right now is, as previously stated, in determining whether there's resistance to drugs a patient is currently taking. If the drugs appear to be failing, this may help determine whether the cause is resistance or other factors, such as adherence or how the body handles the drug. Since failure may occur with resistance to only one member of a combination, identifying early on which drug is problematic might help to guide a therapy change that could save the entire combo from failing.

Because of Stephen's very low CD4s and high viral load, my feeling would be that he doesn't have time to wait for new drugs to appear. Based on his treatment history, combined with these results, I would construct an aggressive six- to seven-drug regimen, including d4T (since we don't usually see resistance to it and didn't find it in the tests), ddI (since he might still be sensitive to it) and hydroxyurea (Hydrea; to possibly reverse any resistance to ddI). To these I would add efavirenz (Sustiva; the most potent NNRTI), two protease inhibitors (although some resistance is expected to these based on the resistance tests), and adefovir (an experimental nucleotide analog), since adefovir appears to have activity against viruses with AZT and 3TC resistance mutations.

Then I would monitor Stephen's viral load weekly. I'd want to see it drop continuously, preferably with a one-log (10-fold) reduction every 7 to 14 days until it reaches undetectable levels with an ultrasensitive assay. If it didn't get to undetectable—preferably by 8 to 10 weeks and no later than 12 to 16 weeks—or if the response to the regimen was unimpressive, I would recommend discontinuing the regimen (to help prevent development of resistance to efavirenzor adefovir), and going back to waiting for newer agents.

This recommendation for aggressive therapy is reasonable, although I am the first to admit that there is very limited data supporting such a multi-drug combination—and there is a risk of developing resistance to the NNRTI class.

If Stephen were to prefer waiting for the possibility of some new drugs becoming available that have potential activity against resistant viruses, such as "second-generation" protease inhibitors (Abbott's ABT-378), new nucleotide analogs (Gilead's PMPA) and a fusion inhibitor like Trimeris' T-20 (pentafuside), to combine with efavirenz or another NNRTI, then I would respect his stance, but these new drugs will probably not become available for multi-drug combinations in experienced patients for at least a year.

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