Gathering Intelligence of the Resistance

Resistance tests can offer clues to whether antiretrovirals have stopped working

August 1, 1996 By Bob Lederer

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. ***Daniel Kuritzkes, M.D.****, is associate professor of medicine at the University of Colorado in Denver. He has done extensive research on AIDS drug resistance with the federal AIDS Clinical Trial Group. Kuritzkes analyzes the viral resistance test results of* POZ *founder Sean O. Strub.*

The most potent anti-HIV drug in the world can't help you if your body's virus has developed resistance to it. This reality is getting increasing attention from doctors and researchers as they realize that every antiretroviral on the market causes viral resistance sooner or later (see p. 52). That goes for both the first generation of these drugs -- AZT, ddI, ddC, 3TC and d4T -- which work by inhibiting the reverse transcriptase (RT) enzyme, and the newer batch -- saquinavir, ritonavir and indinavir -- which inhibit the protease enzyme.

If a drug causes mutations in the viral genes belonging to the targeted enzyme, the person's viral population may stop being sensitive to treatment with that particular drug. More troubling, if a PWA with these mutated viruses transmits them to someone else, that person may become drug-resistant before ever taking the first pill. The Centers for Disease Control and Prevention estimates that 10 to 15 percent of newly positive people have been infected with viral strains resistant to AZT.

For years, only expensive tests available to researchers could provide clues as to whether RT inhibitors had developed viral resistance. Now there are more modestly priced tests available to practicing doctors. (Such tests will soon also be available for protease inhibitors.)

There are two very different types of resistance assays (both are blood tests). Phenotypic assays measure the amount of a given drug needed to inhibit growth of a person's virus in a test tube; the need for a certain amount is said to show resistance. Yet not only are these tests time-consuming and expensive, but petri-dish measures of resistance don't always correlate with real-world drug activity.

By contrast, the genotypic assay -- the one Sean had done through his physician -- examines the genetic makeup of a person's virus to determine whether drug resistance mutations are present. This test is cheaper and quicker than the phenotypic variety, and can show specific mutations that may correlate with resistance to particular drugs. These are listed in the table at right with the headings Regimen and AA Pol Mutation -- which refers to the specific amino acid, or location, of the "Pol" gene corresponding to RT. (Note that ZDV refers to zidovudine, or AZT.) The genotypic test looks for mutations at all of these locations.

In Sean's case, only two -- HIV Gene Pol Amino Acid 135 and 184 -- were found, marked as Mutant. The table provided by the test company lists the 135 mutant as one of four associated with ddI Monotherapy. But in my view, the only mutation known to be clinically important for ddI resistance is 74. Since Sean lacks this mutant, it suggests his two months on ddI last year did not produce resistance. There's no disagreement that the 184 mutant indicates resistance to 3TC. In Sean's case, this is no surprise, since we know that viral resistance to 3TC emerges in nearly all PWAs within weeks of starting the drug. No other mutations were detected in Sean's test, suggesting that his two-month course of AZT a decade ago was not long enough to develop viral resistance.

The difference in interpretation of the 135 mutation points up one unresolved problem with genotypic tests -- HIV's high "natural" mutation rate can result in RT mutations completely unrelated to drug resistance. In addition, combinations of mutations may change their effect on drug resistance. For example, a patient with AZT-resistant virus who adds 3TC quickly shows a 184 mutant, but this may also reverse the effect of the AZT resistance mutations. Yet a genotypic test would still show the AZT mutation. Thus, accurate interpretation of individual mutations may call for an understanding of their effect on the virus phenotype, requiring a separate test.

In the meantime, can the HIV genotypic test offer at least one more useful element of the information mix for doctors and PWAs struggling to fine-tune their antiretroviral protocol? The jury is out, but the test is potentially useful in the following ways:

- HIV genotyping could tip off a positive person that he or she was infected with a particular drug-resistant strain, and thus help avoid starting with an ineffective drug.
- If the test is used while taking an antiretroviral, the results may indicate whether the virus has lost its susceptibility to that drug and which other drugs might still have some effect.
- Combination therapy is becoming more common, but adding a protease inhibitor to an RT inhibitor to which one has become resistant greatly reduces the duo's value. If a PWA can learn his or her resistances before deciding on a new regimen, that may help (along with other factors) to determine the optimal choice. Also, the test could be useful to a patient on a drug combination who wants to know which drug might be failing.

Since the genotypic test Sean used just became commercially available this year, it's not yet

standardized and it’s too early to be sure how to interpret it. Also, because the effects of certain mutations are controversial, PWAs and their doctors should discuss the results with someone knowledgable in the field before basing treatment decisions solely on this test.

Thus I think it’s premature to recommend routine resistance testing (though rapidly advancing technology might change that situation before long). Also bear in mind that no resistance test is yet covered by any insurance plan, private or governmental, so you should thoroughly discuss the pros and cons of this $275 test with your doctor before deciding to take it.

What should Sean do now? Luckily, his viral load -- indicated by the top line (HIV-1 RNA by PCR quant) to be 63,450 -- has gone down considerably from the 700,000 he registered in February (shortly after starting 3TC, but before adding ritonovir in March). That’s encouraging, but clinical trial results suggest he can get even better viral suppression.

Given that Sean has the resistance mutation for 3TC, it’s doubtful that drug is adding much to the activity of the ritonovir. One option he might consider would be to add AZT again, if he can tolerate it. Many patients taking an AZT-3TC combo seem to have a significant delay in the emergence of AZT resistance. An alternative would be to stop 3TC and substitute d4T, which Sean has never had and to which his virus should be sensitive. Whichever strategy Sean chooses, continued monitoring of his viral load will help guide his treatment decisions.

© 2026 Smart + Strong All Rights Reserved.
http://beta.docker.poz.com/article/Gathering-Intelligence-of-the-Resistance-13245-9769