



## **Elements of Resistance Test Interpretation**

One of the most common reasons for failure of an antiretroviral (ARV) regimen is the development of viral resistance. Tests designed to determine the extent of this resistance in an individual patient are now available. The goal of these assays is to determine the resistance pattern of the patient's virus in order to choose the ARV regimen most likely to be successful. The precise role of these resistance assays in the clinical management of HIV patients is still not clearly defined, however a number of principles and indications have emerged to optimize their use.

There are two broad categories of commercially available resistance assays: genotype assays and phenotype assays. Genotype assays detect specific mutations in individual codons in the viral genome. These mutations have been associated with resistance to specific ARV medications in vitro. Phenotype assays determine the amount of drug necessary to inhibit HIV-1 replication in vitro. They compare this value to that of a wild type control and report the difference. The genotype test costs approximately \$350 – 500 and the results are usually available in 10 –14 days. The phenotype test costs approximately \$800 and has a turn around time of 14-28 days. Both assays require highly specialized labs and are therefore performed at only a small number of facilities. Both assays involve rapidly evolving technologies and standardization between labs is less than ideal.

These tests have certain limitations that need to be considered when interpreting them.

1. Both assays require a minimum HIV RNA level (viral load) to produce reliable results. This threshold is around 1000 for a genotype test and 500-1000 for a phenotype test. A test obtained on a patient with a viral load below this threshold may be inaccurate and should be avoided.
2. Both assays do not reliably detect strains of HIV that make up less than 20 –30% of the patients total viral population. A minority viral population with significant ARV resistance may exist within a patient and not be reported. This is particularly important with resistant strains that were once dominant but have waned off of therapy. This population is likely to become dominant when the selection pressure of an ARV regimen is reintroduced. Therefore:
  - Failure to detect resistance does not guarantee sensitivity.
  - Resistance assays should always be performed while a patient is on therapy
  - A resistance test should always be interpreted in the context of a patient's drug history.
3. Both resistance tests report resistance to individual agents while HIV patients are usually on combination therapies. The effect of drug interactions on viral resistance may be important and is not detected with these tests.
4. These tests are based on measurements made in vitro. The clinical correlation of any particular result is not fully known.
5. The ability of these tests to accurately report resistance to D4T (and probably DDI) is unclear. Rarely is significant resistance reported, yet clinical resistance clearly occurs.

6. It is unclear how multiple mutations on a genotype test interact with each other.
7. It may be possible to overcome low-level resistance (as measured on a phenotype test) with higher plasma levels of drugs. The tests do not make this determination.

The Department of Health and Human Services has generated recommendations for the use of ARV resistance testing. Resistance testing is recommended with virologic failure during HAART or during suboptimal viral load suppression after initiating therapy. Resistance testing should be considered during primary/acute HIV infection. Testing is not recommended for use in chronic HIV infection before the initiation of therapy. In addition, the International AIDS Society USA recommends resistance testing in HIV positive pregnant women.

There have been several prospective studies designed to determine the usefulness of resistance tests in clinical settings. In most of these studies, resistance testing improved short-term virologic outcomes in groups of patients who had failed at least one antiretroviral regimen. Some of these studies include expert consultation as part of the study design. One can obtain free, expert consultation on any HIV case by calling the Warmline at (800) 933-3413.