

## Bloodwork: part 3

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In the last two issues, we looked at the common laboratory tests that most people with HIV have from time to time — CD4 count, [viral load](#) [1]A measurement of the quantity of HIV RNA in the blood. Viral load blood test results are expressed as the number of copies (of HIV) per milliliter of blood plasma., and the various biochemistry tests. In this conclusion to our three part series on blood tests, we look at a couple of tests which, which still fairly exotic, we think you'll soon be hearing more and more about.

We're getting better all the time. From the early days when HIV treatment essentially consisted of toxic doses of not-very-effective drugs, crossed fingers and palliative care, modern HIV medicine is more sophisticated than ever before.

Not only do we have more drugs in our anti-HIV arsenal, we're getting better at using those drugs. There are still plenty of challenges, especially dealing with long-term side effects and drug resistance, but we're gradually getting there.

Resistance testing and therapeutic drug monitoring (TDM) are two of our newest weapons against HIV, and while they aren't widely available right now, they promise to become essential tools in managing HIV treatment.

### Resistance testing

The development of drug resistance continues to be a major issue in HIV medicine. It's an unfortunate fact of life that, even with treatment, HIV can still multiply and mutate inside our bodies and, given enough time, resistance will eventually develop. We've learned a lot about resistance (and how to avoid it) over the last few years but it remains a problem that most of us will, at some time or other, have to deal with.

The first line of defence against resistance is careful adherence to antiretroviral drug dosing schedules. Missed doses open a chink in our defences against the virus, and like a crack in a dam wall, that can soon turn into a viral flood. Even with meticulous adherence, sometimes resistance, and treatment failure, just happens. If it does, what we do next becomes critically important.

Resistance testing provides a way for doctors to determine exactly which drug(s) in your current combination your has become [resistant](#) [2]HIV which has mutated and is less susceptible to the effects of one or more anti-HIV drugs is said to be resistant. to, and which drug combination is most likely to bring the virus back under control.

There are two different types of resistance tests. Each has its advantages and disadvantages, and there's no clear consensus yet on which is best.

Genotypic tests work by mapping the genetic makeup of the virus in the test sample. They don't produce an entire genetic blueprint (genome) for the virus, but instead they look for mutations at specific locations in HIV's genetic code (RNA) by comparing the sample to the genetic code for 'wild-type' virus.

Wild-type virus is the natural, dominant or 'wild' form of HIV, without any of the mutations which can occur as a result of being exposed to [antiretrovirals](#) [3]A medication or other substance which is active against retroviruses such as HIV..

There are more than 60 locations (codons) where HIV RNA mutations are known to cause drug resistance. In most cases, mutations have to occur at several different codons before drug resistance develops — different combinations of mutations lead to resistance to different drugs.

The results of this test are reported as a series of code numbers. For example, the code 'K70R' means that at codon 70, the genetic code has changed from 'K' to 'R'. (K70R is one of several mutations associated with resistance to AZT and, to a lesser extent, d4T and abacavir).

Genotypic tests are cheaper and faster than phenotypic tests, and they're easier to do, making them available at more laboratories.

The disadvantage is that they are quite complex to interpret — it's not simply a matter of 'this code means you're resistant to that drug'. Most forms of antiviral resistance require several mutations to be present, and some mutations are more significant than others in creating resistance. In most cases, resistance is not simply a matter of black and white: even with some resistant virus, viral suppression can take place. Taking account of all the variables means that interpreting this test is very complex.

Phenotypic tests take a different approach. Small samples of the virus are grown in the laboratory and different antiviral drugs are added; one to each of the samples. The rate at which the virus multiplies is then measured and compared with wild-type virus grown in the same conditions. The rate of resistance to that drug is then reported as 'folds' — e.g. '10-fold resistance' means the virus multiplies 10 times faster than the wild type when exposed to that drug.

Phenotypic tests require more complex lab equipment and take a lot longer than genotypic tests, making them more expensive. But they are a more direct measurement of resistance to specific drugs, and they're relatively easy to interpret.

Both types of resistance test have limitations — they cannot be done at viral load levels below about 1000 copies, and they may not detect resistance if the resistant virus makes up only a small portion of the [viruses](#) [4]A small infective organism which is incapable of reproducing outside a host cell. in the sample.

Medicare doesn't cover resistance tests yet, and the tests are quite expensive. The Medical Services Advisory Committee, which advises the government on funding medical services including laboratory tests, is currently considering genotypic resistance tests and is expected to make a recommendation soon.

In the meantime, resistance testing is available on a limited basis through some hospital clinics.

## Therapeutic Drug Monitoring

Resistance testing promises to be an extremely useful and valuable tool, but it is mostly useful to people who have already developed resistance and experienced treatment failure. Another emerging technology, Therapeutic Drug Monitoring, promises to help prevent resistance occurring in the first place.

Getting the dose of antiviral drugs right is the key to effective treatment. If the dose is too low, the drug may not suppress HIV replication sufficiently to keep it under control. Too high, and you run the risk of severe side effects.

Like Goldilocks in the three bears' house, the idea is to find the level that's 'just right'.

The recommended doses for HIV [antivirals](#) [5]A medication or substance which is active against one or more viruses. May include anti-HIV drugs, but these are more accurately termed antiretrovirals. and for all drugs are standard amounts which work effectively for almost everyone. Because people come in different sizes, genders, races and ages, the standard dose for a given drug may not be exactly the same as the ideal dose for every individual. Some people have higher metabolic rates than others; some have medical conditions such as hepatitis that make drugs stay in the body longer; some people are taking other medications which interact with their anti-HIV drugs.

Doctors do take account of these differences when prescribing drugs, but doing so is an inexact science. That's where TDM comes in.

The idea behind TDM is that by testing the actual levels of antiviral drugs in the bloodstream after they are taken, doctors can detect whether the dose is too low or too high for that person, and adjust it if necessary.

At the moment, TDM is not in widespread use anywhere in the world, and tests are still being developed. But several recent studies of TDM have produced promising results. In a 2003 study involving 147 people starting treatment for the first time, patients in one group had their doses adjusted using TDM while the other group had standard management. The TDM group had fewer treatment failures than the others, and fewer people

discontinued treatment due to side effects in the TDM group. Several other small studies have also produced encouraging results.

Because of the different ways that different drugs are absorbed, TDM tests can currently measure levels of protease inhibitors and non-nucleosides, but not nucleoside drugs like AZT, 3TC, D4T and abacavir. Even for the drugs which can be measured, there is still no standard on what constitutes the right drug level or the right way to measure it.

It's important to stress that, despite the obvious promise of this technology, there is no universal agreement on the usefulness of TDM. The technology is still in the early stages of development and is not in widespread [clinical](#) [6] use anywhere in the world. Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science.

Finally, while TDM promises to help reduce the likelihood of resistance and side effects, it will never replace good adherence.

**Links:**

[1] <http://www.napwa.org.au/glossary/term/416>

[2] <http://www.napwa.org.au/glossary/term/109>

[3] <http://www.napwa.org.au/glossary/term/122>

[4] <http://www.napwa.org.au/glossary/term/125>

[5] <http://www.napwa.org.au/glossary/term/123>

[6] <http://www.napwa.org.au/glossary/term/475>