



When HIV changes

Resistance explained

by Dr. Cécile Tremblay

You've been on antiretrovirals for years. They're working well, your CD4 counts are high and viral load: undetectable. Great. Then out of nowhere, after a regular checkup, your test results come back and your viral load is detectable. Same thing next time. And it's rising. What happened? It's possible HIV has become resistant to your meds.

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Highly Active Antiretroviral Therapy (HAART) has transformed what it means to live with HIV. Powerful antiretrovirals (ARVs) now make it possible to treat HIV as a chronic illness, allowing people to lead a near-normal lifestyle and pursue their goals. But the emergence of ARV-resistant strains of HIV — the ARVs that once kept your viral load down, no longer do — represents the biggest threat to the durability of treatment. There are a growing number of people developing drug-resistant viruses and some are resistant to more than one class of ARVs, like the man from New York who made headlines last winter. His situation is rela-

tively rare, but it's estimated that an average of 12% of new HIV infections are with strains that are resistant to at least one ARV.

Is my virus resistant?

Every time you see your doctor, blood samples are taken to test your viral load — how much virus is in your blood. If your ARV treatment is effective, it will suppress the virus (keep it from reproducing), and your viral load will become undetectable within a few months. Resistance is suspected when **a)** a formerly undetectable viral load suddenly increases, or **b)** the viral load never becomes undetectable in the first place. Occasional minor 'blips' in the viral load are not uncommon. For example, the viral load can rise to 200 copies/mL one week and become undetectable again the next. This is not a cause for concern. But if the viral load is detectable over two consecutive blood tests, it's possible the virus is developing

resistance to your ARVs. On the other hand, if your viral load never went down to undetectable levels, even 12 or more weeks after starting treatment, you may be dealing with a virus that's already resistant. In this case, your doctor will order a genotyping test that examines the genetic make-up of the virus and identifies mutations that enable it to resist ARVs.

How resistance develops

Unlike human cells, whose genetic material is composed of DNA, HIV's genetic makeup — called a genome — consists of RNA. It contains about 10,000 nucleotides, which are the building blocks of genetic material. In order for HIV to multiply, it must copy itself within human cells. This is achieved with enzymes like reverse transcriptase, which converts HIV's RNA into DNA, ultimately to become part of the cellular genome, or genetic makeup of the human cell. Reverse transcriptase is not perfect: it makes errors in copying the viral genome, so it will eventually produce millions of new viruses, each a little different from one another. These small changes are called mutations.

Some mutations don't affect HIV's ability to replicate or its sensitivity to drugs. But others occur in the genes that code for (describe how to build) reverse transcriptase and protease, the enzymes that ARVs target. These mutations lead to drug resistance.

The story continues

Over time, HIV continues to replicate, resulting in a viral population that's far from identical and possibly contains — albeit in very small quantities — drug resistant mutations. Once you've started on a therapy powerful enough to suppress the viral load to undetectable levels, HIV's replication is slowed down so much that it's prevented from mutating any further. These traces of mutant virus begin to disappear. But if the treatment is not powerful, for example a monotherapy (one ARV) or dual therapy (two ARVs), HIV can still replicate. Consequently, any newly produced viruses susceptible to antiretrovirals are quickly eliminated, while those with drug-resistant mutations survive, not unlike Darwin's survival of the fittest concept. In this case, ARV-resistant HIV is much more "fit" allowing it to survive.

Factors in resistance

For some drugs, a single mutation in HIV's genome is enough to allow resistance to occur. This is called having a low genetic barrier to resistance. If taken with other drugs, the virus and mutations

can still be kept from replicating, but if administered alone, resistance occurs quite rapidly.

With other ARVs, resistance builds up gradually after a series of mutations, as is the case with zidovudine (AZT) and some protease inhibitors (PIs). When a virus mutates to become ARV-resistant, it can get weaker and become less capable of replicating itself efficiently. It must then mutate in other areas of its genome to recover. This triggers a series of mutations, resulting in a drug-resistant virus whose ability to replicate may be either decreased (making it a "less fit" virus) or increased (a "more fit" or stronger virus). If its ability to replicate is increased and it is ARV-resistant, it becomes very difficult to treat.

Some mutations can lead to resistance to one or two drugs. Others cause resistance to an entire class of drugs. This is called cross-resistance and is bad news because it limits your treatment options. For example: a K103N mutation. K103N is the 'address' of the place on the genome (also called a codon) where the mutation occurs. This mutation results in resistance to all non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), while an

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M184V mutation results only in resistance to 3TC[®], and to a lesser extent, abacavir (Ziagen[®]). For protease inhibitors, a D30N mutation results in resistance to nelfinavir (Viracept[®]) only, while mutations



to different areas (codons 82, 84 and 90) generally impart resistance to all PIs.

How to prevent resistance?

The development of resistance can be prevented. The best way is through treatment that suppresses the viral load completely. This depends on several factors:

Choice of treatment

The first treatment you're exposed to is crucial in determining how HIV will evolve over the years. If your first drug regimen is powerful and renders the viral load undetectable, the likelihood of resistance is minimal. Current guidelines suggest several types of HAART regimens that can effectively suppress the viral load. (See combos article page 4). Unfortunately, many people started taking ARVs before the advent of HAART, receiving AZT (zidovudine) monotherapy for several years, or in

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other cases, dual therapy. It's very likely that by now, their virus already carries mutations that are resistant to these drugs. However, there are often treatment alternatives for people who have developed resistance.

If you experience virologic failure (meaning your HAART regimen is not bringing your viral load down to undetectable levels), prompt re-evaluation of your treatment is essential. The longer the wait to deal with treatment failure, the greater the accumulation of mutations. This can render HIV resistant to not only one drug, but possibly to an entire class of ARVs. Discuss this with your doctor. He or she will order a genotyping test that will provide you with a genetic portrait of the virus and identify the drugs that will no longer work. Combined with a history of the ARVs you've already tried, this genetic portrait will help pinpoint a new treatment that will be effective.

Adherence to treatment

ARV therapy only succeeds in keeping viral replication in check if taken regularly, without skipping any doses. Taking medication regularly, several times a day can be problematic for some people due to work schedules or lifestyle. It's not uncommon,

after several years of taking medication diligently, to tire of the schedule and feel like there's no end in sight. Sometimes side effects like nausea and diarrhea force people to skip a dose here and there. Whatever the reason, failure to continuously take one's medication as prescribed can have dramatic consequences, especially with drugs that have a low genetic barrier to resistance.

Poor absorption

Every person's metabolism is unique. Medication is absorbed through the intestine and in most people, the quantity that finds its way into the bloodstream is enough to block a virus. But a small number of people have difficulty absorbing medication, sometimes temporarily (due to problems like diarrhea), sometimes permanently. Other drugs (natural, pharmaceutical and over-the-counter [OTC]) can also lower the level of ARVs that make it into the bloodstream. This topic, known as drug interactions, is covered in depth on page seven. In these cases, viral reproduction is not completely suppressed and resistant strains of the virus emerge. If you suspect poor absorption, see your doctor. Therapeutic drug monitoring, or TDM, is a valuable tool that measures blood medication levels to determine if poor absorption exists. Unfortunately, it's not available everywhere in Canada. Many physician groups and people living with HIV are campaigning to have TDM included as part of our HIV treatment resources.

Stopping treatment safely

The length of time a drug stays in your bloodstream is different for each ARV. Described by the drug's half-life, it refers to how quickly it leaves your bloodstream. If you intend to stop treatment, consult your doctor, because drugs with a longer half-life must be stopped earlier than others. Otherwise you might end up inadvertently receiving a monotherapy.

Resisting resistance

These measures are the keys to preventing the development of resistance. For people with a virus already resistant to several ARVs, the advent of different classes of drugs aimed at new targets presents an interesting option, because there's no evidence yet of cross-resistance between new and old classes of drugs. If you're just starting treatment, discuss your options with your doctor in careful detail, so you can choose a treatment that reflects your lifestyle and your concerns, and one that you'll be able to adhere to diligently over a long period of time. **R**

