

# ANTIRETROVIRAL DRUG RESISTANCE: A GUIDE FOR THE SOUTHERN AFRICAN CLINICIAN

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Both private and public sector see a bewildering clinical array of patients taking failing antiretroviral (ARV) regimens. We intend this article to provide a practical guide to help clinicians understand and manage ARV drug resistance in an African context.

ARV resistance is a rapidly evolving field, requiring expertise in dealing with a wide range of situations. Much of the information we have on ARV resistance is from populations in the developed world where clade B is the biggest problem, while in most of Africa clade C is the commonest infection.

Southern Africa is faced with the daunting prospect of putting several hundred thousand people on ARV therapy (ART) in the next few years.<sup>1</sup> ART is the only effective option available to people with advanced HIV disease, and is remarkably effective in improving quality of life, increasing lifespan, dramatically decreasing the burden of opportunistic disease, and returning people to productive life.<sup>2</sup>

The levels of adherence demanded by ARV regimens are extremely high relative to any other chronic disease. The South African government's Comprehensive Care for HIV/AIDS in the Public Health Sector<sup>3,4</sup> programme has a 'second-line' ARV regimen (Fig. 1), specifically as a safety net for people failing the first-line regimen. Other countries do not have this luxury. The SA second-line regimen is more difficult to take, has greater toxicity, and is more expensive than the first-line treatment.

ARV resistance often compromises future treatment options. The choice of regimens in the SA programme maximises the use of available drugs in this country.

Our experience of private practitioners in South Africa is that they use a range of drug regimens other than those recommended in the government guidelines. There is no effective mechanism to enforce use of the government's recommended drug regimens, but we feel that they are the most rational use of drugs currently available in SA and that deviation from guidelines in routine use should be discouraged, unless alternative options exist. AZT/3TC is still a popular combination, and there are excellent data to support its use as the nucleoside reverse transcriptase inhibitor (NRTI) backbone in first-line therapy, but the alternatives available when resistance to this option develops (i.e. d4T with ddI) are very toxic. In other countries, alternative regimens may be more appropriate.

While we have focused on adult ARV choices in this article, the same principles generally hold for children, although choice of drugs is currently different. Again, we recommend the use of the SA guidelines, published in the November 2005 *Journal*.

### CLINICIAN'S GUIDE TO PATHOGENESIS OF ARV RESISTANCE

The HIV reverse transcriptase enzyme lacks a proof-reading capability. This is the key to both the virus's rapid evolution, causing highly effective and continued evasion of the immune system, and the rapid development of drug resistance.

Depending on the stage of the disease, up to 10 billion HIV virions are produced in HIV-positive people every day. Each virion has a half-life of about 30 minutes. The viral swarm consumes huge numbers of lymphocytes every day.

The genetic strand that codes for the virus is 10 000 nucleic acid base pairs long, and a mistake occurs, on average, approximately every 10 000 translations. The absence of the

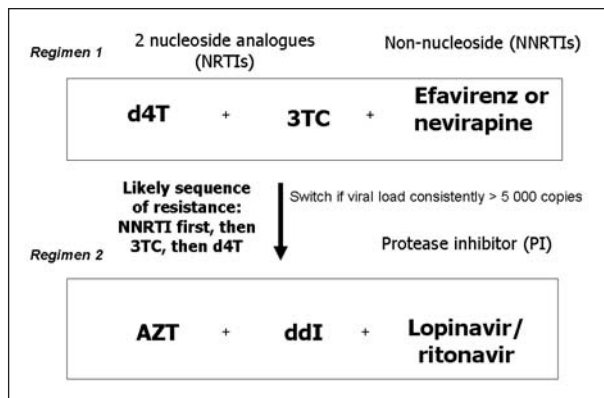


Fig. 1. South African government 2004 recommendation for sequencing of ARVs; nevirapine use for women wanting/at risk of pregnancy.

proof-reading function means that, on average, there is a nucleic acid mutation in every single copy of the virus. It is estimated that every known mutation occurs 10 000 to 100 000 times in every person with untreated HIV every single day.

Mutation rates accelerate when there is accelerated viral replication – i.e. the faster the virus is produced (e.g. when someone has tuberculosis), the more mistakes are made. Some mutations are useful to the virus, allowing it to duck and dive away from the antiviral properties of the immune system and ARV drugs. Other mutations (in fact, most) are harmful, making it more susceptible to both the immune system and/or ARVs. These weakened forms are rapidly outcompeted, as the fittest version exercises its replicative advantage and outgrows the competitors.

Of course, some progeny will have no mutations while others will have multiple changes, but the massive replication means that selection for more virulent strains is inevitable: what has been termed a 'predetermined agenda'. This leads to the development of quasispecies, HIV 'gangs' competing against each other for the same turf in the human host. The term 'wild type' refers to the most effective gang that exists in the absence of ARVs and the absence of significant ARV mutations. 'Fitness' reflects how much replicative ability the virus has. The 'fittest' wild type will prevail, unless something comes along that changes the natural order of things – like an ARV drug.

It has been estimated that untreated HIV-positive people have every known ARV resistance mutation somewhere in their bodies at any given moment, despite *never having been exposed to ARVs!* This occurs by pure chance – the 'predetermined agenda'. However, in the absence of ARV selection pressure, these quasispecies cannot out-compete the wild-type strain.

### WHAT IS ARCHIVING?

At each step, replicatively effective viral DNA is 'archived', or integrated into non-replicating or slowly replicating cells throughout the body (e.g. memory T cells and macrophages).

This means that the body houses a memory bank of all effective virus quasispecies it has witnessed within its tissues. If a potent selection pressure inhibits the 'wild-type' virus, and the 'archived drug-resistant virus' starts to replicate, it can rapidly spread and become the predominant quasispecies. It seems that resistance mutations to some drugs are 'remembered' (archived) in the host human DNA better than others, but, disastrously, ARV drug resistance can be uncovered after many years of effective viral suppression.

So why do the ARVs work at all, given all this mutagenic ability? Many mutations (but not all) interfere with the virus's replicative and infectious ability. A virus with several mutations to exposed drugs may be so crippled that it is unable to be viable (Fig. 2).

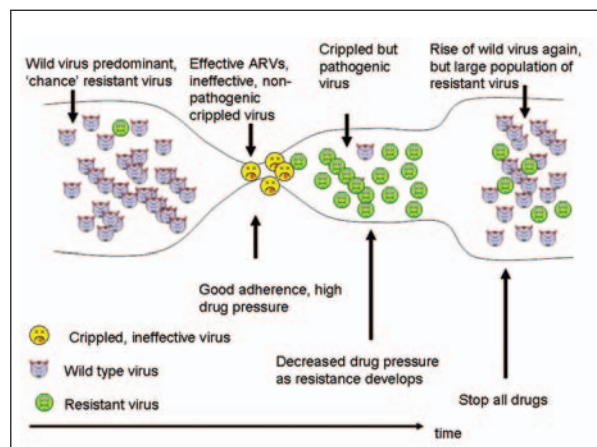
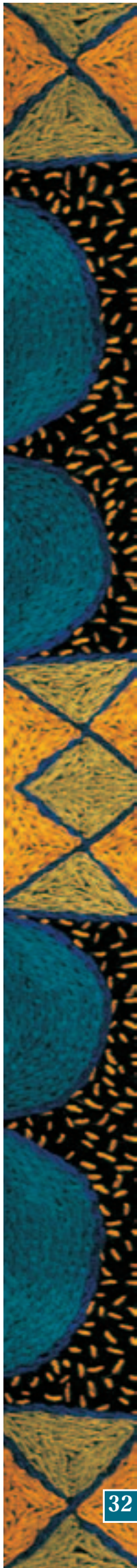


Fig. 2. The evolution of HIV resistance.

### IS DRUG RESISTANCE LIKELY TO BE A MASS PROBLEM IN AFRICA?

Probably, but mathematical modelling suggests not for at least a decade, and that the impact may be limited.<sup>5,6</sup> The spectre of some sort of a multidrug-resistant, super-infectious, super-virulent super-virus is the stuff of newspaper headlines, but has never been reliably identified. In Europe and America, as treatment evolved during the late 1980s and early 1990s, ARVs were initially used as monotherapy, then as dual therapy, resulting in a high background prevalence of NRTI resistance in treatment-experienced patients. More recently, even some triple combinations (e.g. AZT/3TC/ABC, Trizivir) have been shown to be associated with a high likelihood of treatment failure and development of resistance. Along with this, patients on ARVs in developed countries have a high rate of non-adherence, making the general community resistance to everyday commonly used ARVs a big problem. Interestingly, it seems that community resistance to ARVs in developed countries may be on the wane – possibly because the use of more potent cocktails decreases the transmissibility of drug-resistant virus.<sup>7,8</sup> However, on deeper analysis of the patterns of transmitted resistance it appears that non-nucleoside reverse transcriptase inhibitor (NRTI) community resistance is steadily increasing, while other class mutations are decreasing.



However, individual patients with drug-resistant virus are already cropping up in South Africa, and several case and anecdotal reports have emerged of people with mutations associated with severe drug resistance.<sup>9,10</sup> These patients are difficult and expensive to manage. It is every clinician's responsibility to reduce the community prevalence of resistance by looking after their patients responsibly and carefully, checking adherence at every visit, avoiding drugs that interfere with ARV metabolism, and checking the viral load regularly. This is the same model as for TB treatment – multidrug-resistant (MDR) TB is a product of poor adherence and poor patient follow-up by the health services. HIV evolves resistance much faster than TB, so poor management is likely to have rapid consequences.

In future, as is the case in developed countries, we may begin recommending routine resistance testing of infected people. At present, this is probably unnecessary in the vast majority of patients.

### KNOWING THE ENEMY: SIGNATURE MUTATIONS

HIV specialists, like other medical professionals, are addicted to deep and impenetrable jargon. There are over 200 known resistance mutations, and new ones are being described all the time. However, there is little point in remembering the mutations. It is necessary to understand the drugs you use, and then how to spot and deal with resistance.

We believe that the average clinician needs to know how quickly resistance develops to the ARVs they use regularly, and the clinical implications of that resistance. For the sake of completeness, we will cover the more common resistance mutations, and explain how the nomenclature evolved.

The enzyme reverse transcriptase transcribes viral RNA to DNA. The reverse transcriptase gene is 560 amino acids long. A common resistance mutation to the drug 3TC is at the 184 location, where valine replaces methionine. This is called M184V (methionine is the 'normal' nucleic acid replaced at position 184 with valine). Similarly, K103N is a mutation to NNRTIs in adults, with lysine (K) replaced at position 103 with asparagine (N). The first letter is sometimes left off, as shorthand – i.e. 184V, 103N.

Proteases assemble the virus in the cytoplasm. The protease gene is only 99 amino acids long, and a D30N (where aspartic acid (D) is replaced with asparagine (N) at position 30) is a common mutation associated with the protease inhibitor nelfinavir.

The term 'drug resistance' as a blanket term is fuzzy – it may be total or partial, depending on the drug, and resistance to one drug may even confer increased susceptibility to another. The nomenclature is further confused by terms such as 'major' and 'minor' mutations, or 'primary' and 'secondary' mutations, muddled even further by the fact that the field is evolving so fast that new insights often make these terms archaic before they enter common use. To make life even more difficult,

different clades seem to have different patterns in the development of resistance. Luckily, the resistance patterns tend to consign themselves to a distinct class, although some subtle overlaps are starting to emerge. These are not yet of clinical significance.

Three classes of drugs are currently available in southern Africa.

### 1. THE NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Nevirapine and efavirenz are widely used in southern Africa and throughout the world. The drug binds directly to the reverse transcriptase enzyme, rendering it ineffective. The commonest mutation in the reverse transcriptase gene stabilises the site that binds the enzyme, making it less able to bind effectively. New NNRTI drugs in development are able to bind despite this mutation.

Resistance to this class is the easiest to understand – resistance occurs rapidly (often after a single dose if used alone). There is complete class resistance, so complete resistance to efavirenz means that nevirapine is useless, and vice versa.

There are several NNRTI resistance mutations, almost all contributing profound resistance throughout the class – the commonest is K103H, and another is Y181C. A distinct mutation has been described to clade C virus (V106M) which is the predominant clade in SA, and this resistance mutation has been described in this the country.<sup>11,12</sup> Only one point mutation is necessary to cause complete resistance to both efavirenz and nevirapine. The resistance mutations unfortunately do not seem to alter the virus's replicative ability, and transmission of resistance from one person to another is of major concern – the mutation does not affect fitness.

The use of nevirapine for the prevention of mother-to-child transmission deserves special mention in southern Africa. Large numbers of women are being exposed to this treatment, which involves a single dose of nevirapine to the mother during labour, and a postpartum dose to the neonate. It is remarkably effective and safe in preventing transmission to unborn children, but high rates of nevirapine resistance mutations have been described months after administration.<sup>13,14</sup> This makes sense, as only a single mutation confers resistance, and the drug has a very long half-life, meaning that the virus is exposed to it for a prolonged period (resulting in several days of nevirapine monotherapy), increasing the period of selection pressure. A trial done in Thailand suggests that women with mutation may be at high risk of failing a subsequent NNRTI-based regimen.<sup>15</sup> However, the evidence is not completely clear-cut, and the World Health Organization and local experts are currently reviewing the guidelines and evidence as it emerges. Until clear guidelines are available, it is probably acceptable to treat women treated with single-dose nevirapine and subsequently with regimen 1a as if they had not been exposed.

**In summary:** NNRTI resistance is of major clinical significance – it is easy to mess it up; mess it up, and you confine this very useful class to the dustbin of options.

## 2. NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS – THESE DRUGS MIMIC DNA'S BUILDING BLOCKS

d4T and 3TC are part of the South African Department of Health (DoH) first-line regimen, AZT and ddI are part of the DoH's second-line regimen (see Fig. 1). Other drugs used in SA include abacavir. Tenofovir (TDF), a new variation in the NtRTI class with a unique resistance profile, is eagerly anticipated as a once-daily and safe alternative to d4T. TDF (a nucleotide RTI) shares resistance mutations with ddI and ABC (K65R), and is rendered ineffective by NRTI-class resistance mutations.

Resistance to NRTIs is far more complex. There is cross-resistance between some drugs in this class, and none for others. Resistance mutations occur on the reverse transcriptase enzyme. These are often far from the area coding for the active site, but induce conformational changes that have indirect changes at the active site making it more 'discerning' towards NRTIs, or facilitate the removal of the drug from the binding site.

The easiest to understand is resistance to 3TC. A single mutation, the famous M184V mutation, confers complete resistance to 3TC, similar to the way a single mutation confers complete resistance to the NNRTIs. The 184 mutation can also occur in the presence of emtricitabine (FTC, a new NRTI, not yet available in SA but very similar to 3TC), abacavir, and occasionally ddI. Its impact on ddI and abacavir is far less profound than on 3TC. Also similar to NNRTIs, resistance occurs rapidly, although it tends to occur at a slightly slower pace, usually within weeks of exposure to 3TC in the presence of a detectable viral load.

There is one potentially important difference to the NNRTIs: the M184V mutation seems to deeply affect the pathogenicity and possibly the transmission potential of the virus. There is interest in keeping people on 3TC even if they are resistant to it, in salvage therapy, usually after failure of two regimens. The M184V virus that one sees in the blood of patients on failing 3TC-containing regimens is less 'fit', and more easily controlled by the immune system and subsequent drug treatments. While the M184V mutation makes the drug slightly less effective than abacavir and ddI, it seems to 'sensitise' HIV to AZT, ddT and tenofovir. Increasingly, experienced clinicians are using it as a viral 'crippler', adding a triple cocktail on top of the 3TC therapy. Evidence for this is sparse at present, but 3TC is regarded as a safe drug, and adding it on seems to make sense. However, until clearer guidelines are available it should only be done in consultation with an expert.

The situation with the 'thymidine analogues' AZT and d4T is more complex. Both drugs have cross-resistance, and both need several mutations before clinically important resistance

occurs. This often takes several months of unopposed non-suppressive treatment, and resistance therefore accumulates serially. Resistance mutations to these are known snappily as TAMs (or, less snappily, as thymidine analogue mutations). Examples include the bewildering array of 41L, 67N, 70R, 210W, 215 Y/F and 219Q/E. 'TAM' is probably a misnomer, as these mutations affect more than d4T and AZT, and may decrease the efficacy of other nucleosides including didanosine, tenofovir and abacavir, although other NRTI mutations are necessary. The development of mutations at area 69 (most commonly T69S) confers variable low-level drug resistance against almost all nucleosides, but this seems to increase the impact of subsequent mutations. Interestingly, TAMs seem to have no effect on the efficacy of 3TC, and the combination of AZT, 3TC and a potent third drug like Kaletra appears to be very effective even when several TAMs are present.

So called 'non-thymidine' mutations include K65R, which is selected by tenofovir and reduces susceptibility to all NRTIs except AZT, where it improves sensitivity; and Q151M and L74V, which decrease the efficacy of a range of NRTIs.

Didanosine (ddI) has a high resistance barrier, requiring serial mutations before it loses efficacy, and tends to select mainly for L74V. Abacavir is a 'dirty' drug, as the resistance mutations to it are very difficult to predict clinically. Multiple TAMs and the K65R mutation, however, are likely to decrease the effectiveness of abacavir.

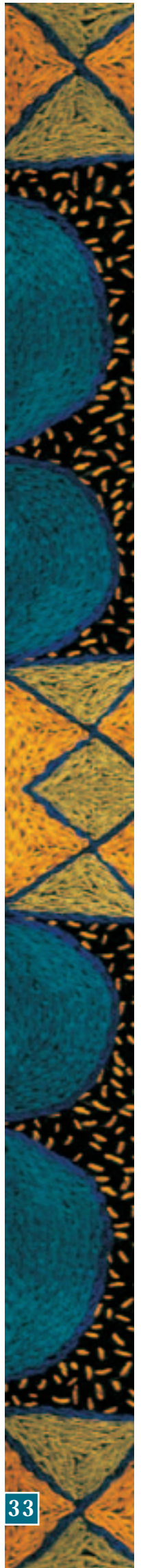
**In summary:** Unlike the NNRTIs, resistance is not generally catastrophic. However, it is much more complex, and approaches to resistance are steadily becoming more sophisticated, dealing with issues of cross-resistance, partial 'revertants' and hypersusceptibility.

## 3. PROTEASE INHIBITORS (PIs)

Generally the PIs require multiple mutations to acquire resistance. They are the 'tough guys' of the ARV revolution, but some are tougher than others.

'Boosting' is the term used to describe increasing the level of PIs by adding ritonavir to the mix. This dramatically increases the blood concentrations, and makes development of resistance much more difficult. The ritonavir role is pharmacological only – it has minimal ARV activity at this very low dose. Boosting seems to protect against the development of multiple PI mutations. Interestingly, this strategy also seems to protect other classes of drugs, especially the nucleosides, from developing resistance. Nelfinavir is the only PI not 'boostable' – the addition of ritonavir only marginally increases the blood levels.

New mutations to PIs are being described, and clinicians have begun classing mutations into 'major' and 'minor' – based on how much the mutation actually stops the action of the drug. As mentioned above, this nomenclature is challenged by the new information on these mutations. It is often possible to



change one PI for another, much like the nucleoside analogues, although resistance testing makes this less like guesswork. Kaletra (lopinavir/ritonavir), used in the South African rollout, appears to need more than 6 mutations to acquire resistance, while nelfinavir usually requires only 1 to reduce its efficacy 5-fold, and 2 to reduce it 50-fold. Some PIs need specific mutations, but the common mutations occur at positions 82, 84 and 90.

A new PI, atazanavir, appears to induce a mutation (150L) that actually *increases* susceptibility to other PIs. This has also been described with saquinavir and amprenavir. Whether this is clinically useful is still up for debate.

So what to do? There is lots of clinical debate about which PI is best to start with, and which to use next. It appears that we may have third- and fourth-line choices now, and the old 'one strike and you're out' has evolved into a place where it seems that certain PIs may even be recycled, despite archiving, a theory considered heresy a few short years ago. New PIs are on the horizon, with new resistance profiles. If these drugs were less toxic, the future would seem rosy.

**Bottom line:** In South Africa the national guidelines use Kaletra, the ARV equivalent of the Great Wall of China. Failing this drug is very difficult, but is possible (the first patient to fail it was described from SA!<sup>9</sup>). Other PIs can then be used in its place, although these do not form part of the national guidelines. Generally, the world is moving away from indinavir and saquinavir, because of toxicity and because the resistance profile is 'dirty', influencing the choice of future regimens.

Once the first PI regimen has failed, it is not recommended that nelfinavir, unboosted atazanavir or unboosted amprenavir is used, as cross-mutations to these make them less likely to succeed. However, 'sequential' PIs can be used. Atazanavir and amprenavir will probably soon become available in SA. Experts are increasingly using 'double-boosted' PIs, sneakily adding two PIs to a single dose of ritonavir – but it is not clear which two PIs to add to the ritonavir, although lopinavir and saquinavir are popular.

**In summary:** We feel NNRTIs are more appropriate than PIs initially, for reasons of ease of use, toxicity and cost. We advocate lopinavir/ritonavir as the first PI you use, and then suggest you consult expert help for the next choice. Let's hope that by then we'll have sorted out the bewildering array of options available.

### ROLE OF DRUG INTERACTIONS AND DRUG RESISTANCE

Drug interactions may decrease the effective dose of certain ARVs, leading to resistance. TB drug co-administration is common, as patients enter the programme from TB programmes, or get placed on rifampicin-containing regimens after developing immune reconstitution syndromes. Rifampicin, NNRTIs and PIs all affect CYP 3A4 and therefore can decrease the plasma levels. Rifampicin administration

increases efavirenz and nevirapine metabolism and theoretically could drop levels leading to potential dual therapy. Some authorities recommend increasing the dose of efavirenz in the presence of rifampicin, but evidence suggests that this is unnecessary. The current South African guidelines suggest no dose adjustment of efavirenz, and our anecdotal experience is that this is correct. Similar concerns with Kaletra exist, and here the SA guidelines suggest adding a whopping 300 mg ritonavir bd to the standard Kaletra dose, to counter the accelerated metabolism.<sup>2,3,16-19</sup>

### IS DRUG RESISTANCE TESTING AN OPTION?

The answer to this is a highly qualified yes. Genotypic resistance testing is available through a large number of laboratories in SA, but not in the DoH rollout, as the benefit is not felt to justify the cost.

Genotype testing involves the extraction and amplification of the predominant viral genome in the blood, and seeing if known genetic mutations to ARVs are present. The weakness of the testing is that it does not detect archived virus, may miss small populations of resistant virus in the blood, only detects known resistance mutations, takes time and is expensive. The test should ideally be done while still on the 'failing' regimen, otherwise 'wild' non-resistant virus may obscure the smaller population of resistant virus. There must be enough virus to do the test (at least 1 000 copies/ml). Results have to be interpreted against an accurate history of ARV use, and must be interpreted by an expert in the field. Resistance testing is useful on a population basis, for the surveillance of prevalent drug resistance, but our experience is that most of these tests, when ordered by non-experts, are a waste of money and time. In the hands of experts, they may add to the chance of success of a subsequent 'best guess' ARV regimen.

**The rule is:** Do not order a resistance test *unless* you have spoken to an expert.

Phenotypic resistance testing is more analogous to a conventional microscopy, culture and sensitivity (MC&S) most clinicians are very familiar with, with the virus grown against different types and concentrations of antiretrovirals. Unfortunately, it is expensive and currently only available in research laboratories in developed countries. 'Virtual phenotyping' uses genotyping and match genotypes to known phenotypes and ARV history to predict overall resistance patterns, and may hold promise for improved use of genotype testing in the future.

### DOES STOPPING ARVs SUDDENLY CAUSE RESISTANCE?

This is a thorny issue. The commonest reason for stopping treatment is possible toxicity, or running out of funding for treatment.

Consider a patient on d4T, 3TC and efavirenz (Fig. 3): If you suddenly stop treatment, the level of d4T drops very soon, as it has a short half-life, leaving the patient effectively on 3TC and efavirenz (dual therapy). Then the levels of 3TC drop, and the only effective drug left is efavirenz. Efavirenz has a half-life that lasts days and occasionally weeks, and has a very low resistance barrier, so it makes sense that resistance will develop quickly. Preliminary studies have demonstrated resistance, but it is unclear whether this is clinically important.

Many clinicians now 'cover the tail' – they continue the drugs with high resistance barriers to cover the vulnerable NNRTIs (see Fig. 4). No one is sure how long we should continue these (although many of us use a week), or even if it is effective. If the drug level of efavirenz dropped suddenly, and you're left with just d4T and 3TC for a few days, significant resistance is unlikely. The difficulty with this is that if you are stopping due to NRTI toxicity, e.g. pancreatitis, you would need to stop the NRTIs at the same time.

In many situations it is not practical to cover the tail, especially if there is severe illness where it is unclear whether it is a drug reaction or immune reconstitution. In these cases, rather stop all the drugs, and pick up the resistance pieces once the crisis is over.

### CAN I DELIBERATELY CRIPPLE THE VIRUS?

The 3TC mutation appears to decrease viral fitness, and may even make other drugs more potent, especially AZT, d4T and tenofovir. If there is existing 3TC resistance, some clinicians (including ourselves) continue 3TC, adding it to the next regimen as a way of decreasing fitness. Do *not* add 3TC as a viralcripler if there is no resistance to it – use it as a normal ARV!

### HOW LONG DOES RESISTANCE PERSIST FOR?

Resistance mutations acquired sexually from someone else (i.e. passed directly on) seem to persist for much longer than those found when selected by the virus. Resistance usually 'disappears' slowly from the bloodstream, as wild or fitter virus comes back in the absence of ARVs. Some mutations disappear before others – the 3TC mutation M184V disappears within a few weeks, while others can persist for years.

### WHAT ABOUT DOING DRUG LEVELS?

Therapeutic drug monitoring (TDM) is not yet generally available to southern African clinicians. It seems likely that it will be very useful in the future, especially in dealing with complex drug interactions, side-effects, or difficult physiological conditions (such as pregnancy), and where genetic or other factors impact on plasma levels. In the case of PIs in particular, this may make life significantly easier. Testing is not available for the NRTIs. Watch this space for future recommendations regarding TDM.

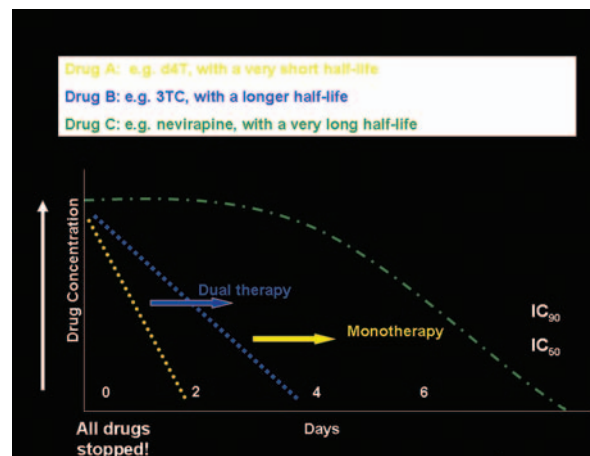


Fig. 3. Different half-lives mean that triple therapy can evolve into dual and monotherapy ...

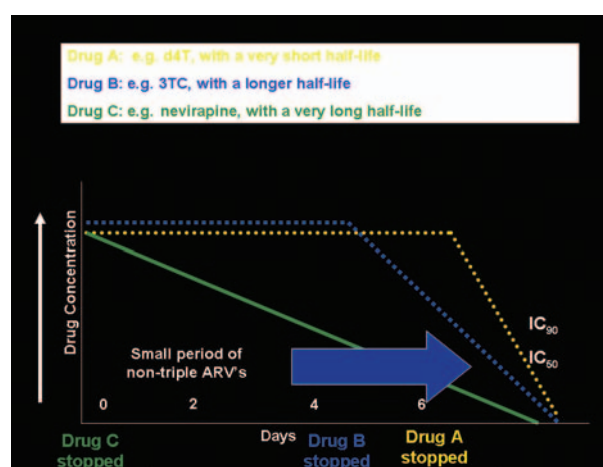


Fig. 4. Cover the tail! How to stop drugs with different half lives ...

### A PRACTICAL APPROACH TO A PATIENT FAILING THEIR FIRST REGIMEN

Questions to ask when faced with a patient on ARVs and possible drug resistance ...

#### 1. HOW DO YOU KNOW THAT THE PERSON IS RESISTANT?

A viral load persistently detectable on *stable* treatment generally equates to resistance. Remember that it takes 3 - 4 months for the viral load to 'decay' (although an effective regimen should cause a 1.5 log<sub>10</sub> drop in viral load after 4 weeks).

It is generally wise to confirm the elevated viral load, by repeating the test. Many people have viral 'blips' or sudden increases for some reason, and occasionally the test can yield a falsely elevated level. Confirm the increase before substituting the regimen.

If someone has a detectable viral load, and you know or suspect that the patient has interrupted therapy, or is not completely adherent, or has a drug interaction, or is inadequately dosed, intensify adherence support, sort out the problem and measure the viral load a few weeks later. If it

becomes undetectable, you have probably avoided an unnecessary drug substitution.

However, a persistently raised viral load usually means drug resistance and you need to consider a change. In the SA programme, a persistently raised viral load above 5 000 copies (preferably measured on two occasions 4 weeks apart) should signal the need for a change.

## 2. WHAT CLASSES OF DRUGS IS THE PERSON ON?

Resistance is fairly predictable (see Fig. 3). NNRTIs are very vulnerable, and a single mutation confers complete resistance. This is usually the first class to show resistance.

Next is usually 3TC, which is also vulnerable to a single mutation.

The other drugs (nucleosides and PIs) generally follow, albeit slowly. It usually takes months to develop resistance to these. Resistance testing is useful to show whether there is actually resistance to NNRTIs and 3TC, and how much resistance there is to the other nucleosides and PIs, if any.

## 3. HOW LONG HAS THE PATIENT BEEN ON THIS REGIMEN?

If only a few months, it is unlikely that significant resistance will have accumulated to anything other than the NNRTI and 3TC. However, if a patient has been left on a failing regimen for many months, the other drugs in the regimen are increasingly likely to have resistance mutations develop against them.

## 4. WHAT ARE YOUR OPTIONS NEXT?

If you have resistance testing results and it has been done properly, consult with an expert.

If resistance testing is not an option:

- Consider using a boosted PI. The resistance barrier in this class is significant.
- Consider adding 3TC as a 'crippler' – but only if you are sure you have pre-existing viral resistance.
- Consider new drugs – consult with an expert, as a host of new drugs are eagerly awaited in the next few years. Or ask around if a clinical trial is being conducted.
- Consider a treatment interruption. In some cases, interrupting therapy seems to allow for some resistance to wane, and for future options to be more effective. Again, get expert help – consider the indication for the original decision to start ARVs; the risk of illness and decline in CD4 must be weighed carefully against the benefit.
- Finally, consider just leaving them on the regimen – if there are no other options. It is clear that patients with resistant virus left on their failing regimens live longer and better.<sup>20,21</sup>

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