Antiretroviral treatment (ART) has dramatically changed the course of (HIV) infection, allowing for control of the virus in the peripheral circulation, significant reconstitution of the immune system and achievement of near-normal life expectancy. Similar to other antimicrobial agents, the efficacy of ART is, however, curtailed by the development of drug resistance. Resistance can either be transmitted from an infected partner/mother or acquired through inadequate drug pressure, usually caused by suboptimal adherence, treatment interruptions, improper treatment regimens, impaired drug absorption or drug interactions. Of these, adherence problems are by far the most common cause and remain a significant obstacle to achieving lifelong virological control.

FIRST-LINE ANTIRETROVIRAL THERAPY
The current first-line regimen used in SA and throughout most of the world consists of tenofovir (TDF), lamivudine (3TC)/emtricitabine (FTC) and efavirenz (EFV), usually given as a once-daily fixed-dose combination (FDC). This regimen has the advantage of ease of administration and limited toxicity, but is troubled by a very low barrier to resistance of all three components, especially in subtype C infection. In the case of all three agents, only a single mutation is necessary to avert full resistance to all three drugs. Such patients can usually be changed to a regimen consisting of AZT, 3TC, LPV/r without drug resistance testing (DRT), since we know that the presence of the K65R and M184V mutations renders the virus hyper susceptible to AZT and that the PIs should still be fully active. DRT is, however, useful in ruling out non-adherence and informing future regimens.

Patients who have failed multiple regimens and those failing on stavudine (d4T) or AZT for a long time should always have DRT, since the pattern of drug resistance cannot be predicted with certainty. One caveat is that DRT can only detect resistance to the drugs the patient is currently taking and can therefore better inform regarding the drugs that are ineffective as opposed to those that are effective. DRT results should always be discussed with someone experienced in their interpretation. Patients failing on some of the older regimens, such as a combination of d4T or AZT with 3TC and EFV or nevirapine (NVP) usually develop thymidine analogue mutations (TAMs), which result in resistance to TDF, EFV and NVP and the presence of TAMs inclusive of either M41L or K65R (giving intermediate/high-level resistance to TDF, ddI, ABC and d4T; M184V (giving high-level resistance to 3TC/FTC) and one or more of the common non-nucleoside reverse transcriptase inhibitors (NNRTIs) mutations, amongst others K103N, V106M, Y181C and G190A (giving high-level resistance to EFV and NVP). Such patients failing on d4T for a long time will most likely have the following mutations: K65R (giving intermediate/high-level resistance to TDF, ddI, ABC and d4T); M184V (giving high-level resistance to 3TC/FTC) and one or more of the common non-nucleoside reverse transcriptase inhibitors (NNRTIs) mutations, amongst others K103N, V106M, Y181C and G190A (giving high-level resistance to EFV and NVP). Such patients can usually be changed to a regimen consisting of AZT, 3TC, LPV/r without drug resistance testing (DRT), since we know that the presence of the K65R and M184V mutations renders the virus hyper susceptible to AZT and that the PIs should still be fully active. DRT is, however, useful in ruling out non-adherence and informing future regimens.

SECOND-LINE ARV THERAPY
The EARNEST trial demonstrated that patients with significant resistance after first-line therapy may achieve virological suppression on a regimen consisting of 2 NRTIs and LPV/r without the addition of new drug classes, such as integrase strand transfer inhibitors (INSTIs). It is, however, crucial to note that patients in this trial achieved adherence of more than 95%, a crucial factor in ensuring treatment success. Nevertheless, the EARNEST trial taught us that ‘high-level resistance’ does not equal ‘no effect’ and that the NNRTIs positively impact on treatment outcomes even in the face of significant resistance.

LPV/r remains the PI of choice in second-line treatment but requires twice-daily dosing and is often complicated by adverse effects, such as diarrhoea and dyslipidaemia. In such cases, switching to ATV/r is a good option. The Southern African HIV Clinicians Society now recommends ATV/r as the preferred PI and this is supported by evidence of efficacy and good outcomes in developed countries. Given the once-daily dosing and limited side effects on ATV/r (the most common being jaundice without hepatic impairment), it is an attractive option, but ATV/r cannot be used together with rifampicin-based tuberculosis treatment, which affects a large proportion of the HIV-infected population. Concerns also remain about patients who have suboptimal adherence to treatment in which case the risk of resistance becomes significant and is most likely worse than that for LPV/r. Data from the public sector show that the vast majority of...
patients failing PI-based regimens have no evidence of drug resistance, suggesting that non-adherence may be playing an important role. Experience from the private sector, however, demonstrates that some patients do develop significant mutations to PIs over time, limiting treatment options considerably.

THIRD-LINE ARV THERAPY
It is advisable to undertake DRT in all patients who have been failing a PI for longer than one year. This will reveal if the patient has developed drug resistance to the PIs and whether some of the NRTIs may still be effective. It is optimal to perform DRT after both first- and second-line failure since this will allow for better assessment of susceptibility to the NRTIs and NNRTIs, but is often prohibitively expensive (around R5000 at the time of writing). In patients with major PI mutations, which compromise LPV/r and ATV/r, treatment should be changed to third-line and should consist of an NRTI that still has some activity, together with 3TC, the second-generation PI, DRV/r, and either the second-generation NNRTI, etravirine (ETR) or the INSTI, raltegravir (RAL). This is a complicated regimen with twice-daily dosing and adherence support is critical to ensure a successful treatment outcome.

ETR remains active against HIV, which has acquired the common NNRTI resistance mutations, K103N and Y181C, since it follows a slightly different mutational pathway and requires a combination of mutations to accumulate before resistance develops. Even though it is generally well tolerated, cases of hypersensitivity reactions, such as Stevens–Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and drug rash with Eosinophilia and Systemic Symptoms (DRESS) have been described. ETR is metabolised by the CYP family and restrictions therefore apply to co-prescription with rifampicin, certain anti-epileptics and St. John’s wort. It should also not be combined with ATV/r, PIs without ritonavir boosting and other NNRTIs. RPV is usually no longer active after previous NNRTI use and should not be used after a patient has failed such a regimen.

RAL should be fully active in a third-line regimen but it has a low genetic barrier to resistance and can easily be compromised if two other fully active drugs are not present in the regimen. RAL has a very good safety and side-effect profile but it should be noted that cases of severe hypersensitivity reactions, myopathy and rhabdomyolysis have been reported. Safety with TB co-treatment has not been established – although some recommend doubling the dose to 800mg b.d. - and it should not be used with aluminium and/or magnesium-containing antacids.

DRV is a very potent PI and generally retains activity in the presence of multiple PI mutations. Importantly, it contains a sulfonamide moiety and should therefore be avoided or used with the utmost caution in patients with a known sulfonamide allergy. Safety and optimal dosing when combined with TB treatment have also not been established. Co-formulation of DRV with ritonavir is not yet available and use of the latter is complicated by a requirement for refrigeration.

CONCLUSION
Current first-line ART is effective and easy to take, such that patients on this regimen should remain virologically suppressed for a long time. However, optimal adherence is critical if this goal is to be achieved. Although second and third-line options have a higher pill burden necessitating twice-daily dosing, they are effective when adherence is excellent. Fortunately, exciting new drug combinations are on the horizon and may well change the face of ART in the coming years.