ARV OPTIONS IN DRUG RESISTANCE

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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 confer significant resistance. This is in contrast to other antiretroviral drugs, such as zidovudine (AZT) and most of the ritonavir-boosted protease inhibitors (PIs) (such as lopinavir (LPV), atazanavir (ATV) and darunavir (DRV)), which have high barriers to resistance necessitating the accumulation of multiple mutations. These drugs are generally not used in first-line treatment because of cost, complicated dosing schedules and adverse effect profiles.

Treatment failure (i.e. 2 HIV plasma viral load levels of >1000 copies/ml at least eight weeks apart despite adequate adherence to ART) can occur with or without drug resistance. While the absence of resistance mutations usually signals adherence problems requiring an adherence intervention, the presence of drug resistance necessitates a change in regimen in which at least two of the three drugs are substituted. A patient failing TDF, 3TC/FTC, EFV 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 (NNRTI) 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.

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 most of the nucleoside reverse transcriptase inhibitor (NRTI) class, together with the M184V and NNRTI mutations. The nucleotide reverse transcriptase inhibitor (NtRTI), TDF, can also be compromised once three TAMs inclusive of either M41L or L210W have developed. In addition, patients failing on d4T for a long time can develop the K65R mutation, which will make TDF ineffective.

Rilpivirine (RPV) is a second-generation NNRTI, which can be dosed once daily and does not have the neuropsychiatric side effects of EFV. It is an attractive option for first-line therapy and even though it is not yet available as FDC, a co-formulation with TDF/FTC should be available soon. It should not be used in patients with HIV plasma viral loads in excess of 100 000copies/ml or co-prescribed with drugs that induce or inhibit cytochrome P450 or increase gastric pH. The development of drug resistance to RPV may compromise other NNRTIs, and DRT is recommended when treatment failure occurs.

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 NRTIs 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 rifamycin, 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. MC

References available on request.