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REVIEW

Simplified antiretroviral treatment regimens: the dolutegravir revolution

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Introduction

The complexity of antiretroviral treatment (ART) over the last three decades has evolved significantly as new drugs, regimens, and strategies have been introduced and implemented to improve the outcomes and quality of life of people living with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS).

The main factors that have influenced the complexity of ART over time include:

- The cost and availability of antiretroviral drugs (ARVs): in the 1990s, the cost of ARVs was prohibitively high and the South African government was reluctant to provide ART to the public sector, citing concerns about the safety, efficacy, and feasibility of sustainable treatment.[1] Passing legislation to allow procurement of cheaper generic ARVs from neighbouring countries attracted legal battles with the pharmaceutical industry. However, following a campaign by civil society activists, the price of ARVs dropped significantly, making them more affordable for developing countries, including the South African government, which subsequently provided free ARVs to the public sector.[1] Access has since expanded through voluntary licensing agreements with generic manufacturers.[2]
- The efficacy and safety of ARVs: the first generation of ARVs had limited potency and high toxicity, requiring the frequent intake of many tablets, hampered adherence, and increased the risk of resistance.[2] Later classes of ARVs with novel mechanisms of action, such as protease and integrase inhibitors, were discovered and developed, which have relatively higher potency and lower toxicity.[2] Moreover, the introduction of once-daily single-tablet regimens (STRs) with three medications combined into one fixed-dose combination (FDC) tablet has simplified dosing and improved adherence with comparable or superior efficacy and safety to multiple tablet regimens.[2]
- The guidelines and strategies for ART: the World Health Organization (WHO) and the South African government have revised their ART guidelines and strategies over time based on the latest scientific evidence and best practices. For example, in 2010, the South African government revised its ART guidelines to start treatment earlier and use more effective and less toxic regimens. In 2015, the South African government adopted the WHO's "test and treat" strategy, which offered ART to all people diagnosed with HIV, regardless of their CD4 count or clinical stage. The government also expanded the provision of pre-exposure prophylaxis (PrEP), a daily tablet that can prevent HIV infection, to high-risk groups such as sex workers and men who have sex with men. These changes have increased the number of people eligible for and receiving ART, and have reduced the incidence and mortality of HIV/AIDS.[3]

Discussion

Despite the progress made in improving the complexity of ART regimens, there are still many challenges and opportunities for further innovation and optimisation. There still is a need for new agents and long-acting formulations that can be dosed less frequently to further facilitate treatment adherence.[2] Research and development towards curative strategies that can eliminate the latent HIV reservoir remains challenging.[2]

Dolutegravir (DTG), a second-generation integrase strand transfer inhibitor (INSTI), inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration, which is essential for the HIV replication cycle. DTG also dissociates slowly from the active site of the wild type of integrase-DNA complex (half-life $t_{½}$ 71 hours), an attribute that explains DTG's many advantages/benefits, including:[4]

- High potency and efficacy: DTG can suppress viral loads to undetectable levels in most patients, even those who have failed previous treatments or have drug-resistant strains of HIV.[5]
- Low toxicity and side effects: DTG has a favourable safety profile with fewer adverse events than other ARVs. The most common side effects are headache, nausea, insomnia, and weight gain.[5]
- High genetic barrier to resistance: DTG is less likely to lose its effectiveness due to mutations in HIV. Resistance to DTG is rare and usually requires multiple mutations.[5]
- Low cost and pill burden: DTG is available as a single tablet taken once a day, with or without food. It is also affordable,

especially in low- to middle-income countries where it is part of the FDC of tenofovir, lamivudine and dolutegravir (TLD).[6]

Because of these benefits, DTG has been recommended by the WHO as the preferred first-line and second-line treatment for HIV in all populations, including children, pregnant women, and those of childbearing potential.[6] Many countries, including South Africa, have updated their national HIV guidelines to include DTG as the preferred drug for patients initiating or switching ART.[7]

It is important to note that it is not common for new medicines to offer a combination of better safety, efficacy and cost compared to established comparator medicines. DTG is non-inferior to raltegravir (RAL) in terms of efficacy (Spring-2) and superior to darunavir (DRV) (Flamingo) and efavirenz (EFV) (Single). Interestingly, when RAL (a first-generation INSTI) was registered in South Africa, it was reserved as a third-line treatment for patients who had failed protease inhibitor (PI)-based lines of ART.

The high genetic barrier to resistance lends DTG to its utility in both first- and second-line ART regimens.[8] Consequently, DTG is used as part of first-line (TLD1) treatment for ART-naïve patients, as well as patients switching from their non-nucleoside reverse transcriptase inhibitor (NNRTI) or PI-based regimens. DTG remains useful in the second-line (TLD2) treatment in those who would have developed resistance to NNRTI/PI-based regimens, even in the face of compromised backbone nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs).

For instance, DTG coupled with tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) remains a robust regimen even when there are resistance mutations for both TDF and 3TC. The most common relevant mutations associated with these agents (K65R and M184V, respectively) tend to cripple the virus and limit its replication potential; a beneficial effect when the virus remains susceptible to DTG. This means that most patients on ART should be on DTG-based therapy, significantly simplifying a previously complex matter. The association between DTG and better viral suppression is even higher among people treated for tuberculosis, an important consideration for South African practitioners.[9]

Third-line regimen construction may also include DTG, depending on the resistance test results. Therefore, a resistance test is mandatory before considering third-line and salvage therapy. However, management with specialist input is strongly recommended.

INSTIs are relatively new among the following five major drug classes used in the treatment of HIV/AIDS:

1. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs)
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
3. Protease inhibitors (PIs)
4. Integrase strand transfer inhibitors (INSTIs)
5. Entry inhibitors (EIs)

Each drug class targets a specific stage of the virus's life cycle, inhibiting replication or entry into host cells. When used in combination therapy, these medications form a highly effective and powerful tool in the treatment of HIV infection. For detailed ART prescribing information, please refer to the latest national ART guidelines:[10] https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf. And/or SAHIVCS ART guidelines:[11] https://sahivsoc.org/Files/SAHCS%20Adult%20ART%202023%20Guidelines%20(1107).pdf.

In South Africa, DTG is currently only available as a 50 mg tablet, a 10 mg dispersible tablet, or a FDC together with TDF 300 mg and 3TC 300 mg (**TLD**) and with abacavir (ABC) 600 mg and 3TC 300 mg (**ALD**).

However, the DTG revolution has been associated with adverse effects. Some of these associations have been cleared as more data emerged over time:

- Weight gain: DTG has been associated with significant weight gain, which may increase cardiovascular risk.[12–16] Subsequent data suggests that this association is explained by the better tolerability of DTG. DTG (and tenofovir alafenamide TAF) are weight-neutral agents compared to weight-suppressive agents EFV (and TDF).[6] Therefore, a switch from a weight-suppressive agent to a weight-neutral agent may give an impression of the weight-neutral agent causing weight gain, especially in an obesogenic environment like South Africa.[17]
- Neural tube defects (NTDs): following its initial linkage to a higher risk of NTDs in infants born to women who were taking DTG at the time of conception or during the first trimester of pregnancy, subsequent data has dissociated this adverse effect from DTG treatment.[6]
- Drug interactions: DTG exhibits significant pharmacokinetic interactions with many medications, including cationic supplements and antacids, which reduce its absorption, as well as inducers of cytochrome P450 enzymes and transporters such anticonvulsants, antimicrobials such as rifampicin, antimalarials, and hormonal contraceptives.[5] The national HIV treatment guidelines give good, detailed approaches to managing these drug-drug interactions.[10,11]

Conclusion

The ongoing roll-out of DTG for first-line ART in South Africa, including among people treated for tuberculosis, is a significant advancement and simplification of ART. Clinicians are strongly encouraged to switch their patients to DTG-based ART in accordance with current treatment guidelines.

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