ISSUES IN MEDICINE

Dolutegravir as first-line antiretroviral therapy in South Africa: Beware the one-size-fits-all approach

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Dolutegravir (DTG) is a pivotal antiretroviral medicine that has become the backbone of several HIV programmes, especially in sub-Saharan African countries. It has recently replaced efavirenz as the preferred third drug for people initiating antiretroviral therapy in South Africa (SA). Its tolerability, cost-effectiveness and favourable resistance profile have had a global influence on HIV management, including the recent revision of the World Health Organization antiretroviral guidelines. As with any medicine, however, informed decisions are important. Despite the several advantages DTG offers, additional data informing risks over benefits have emerged that warrant clinical attention before DTG is prescribed. This article aims to give the primary care provider an overview of the benefits and risks associated with the roll-out of DTG in SA.

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In July 2019, the World Health Organization (WHO) recommended the use of the integrase inhibitor dolutegravir (DTG) as the preferred first-line and second-line treatment for HIV for all populations, including pregnant women and those of childbearing potential.[1] Since then, many low- and middle-income countries (LMICs) have updated their guidelines and transitioned to DTG-based HIV treatment regimens from the efavirenz (EFV)-based initial first-line antiretroviral therapy (ART). South Africa (SA) updated its national HIV guideline in 2020 to include DTG as the preferred drug for patients newly initiating ART, those experiencing side-effects on EFV and those who prefer to use DTG.[2] It is anticipated that a new drug in the ART arsenal will offer benefits such as lower cost, reduced pill burden, suppressed viral load, fewer side-effects and a higher genetic barrier to resistance. While DTG does offer many of these benefits as a first-line option, there are a few considerations when initiating a patient on a DTG-based regimen.

The rationale for DTG as an anchor drug in first-line ART regimens

DTG falls into a relatively new class of ART drugs known as integrase strand transfer inhibitors (INSTIs). The mechanism of action involves preventing HIV nucleic acid integration into the host T-lymphocyte genome, which terminates the life cycle of the virus. In SA, raltegravir (RAL) was the first INSTI registered with the South African Health Products Regulatory Authority (SAHPRA) and was largely reserved for third-line regimens and salvage therapy in patients failing protease inhibitor-based second-line regimens. Since then, DTG has been approved for first-line therapy and will largely replace EFV as the third drug co-administered with two nucleoside/nucleotide reverse transcriptase inhibitors. Compared with EFV, DTG is linked to superior viral suppression, lower risks of drug-drug interactions and lower risk of emergence of drug resistance mutations.[3-5]

In terms of its posology, DTG is rapidly absorbed, may be taken with or without food, and only requires once-daily dosing without the need for pharmacological boosting.[6,7] Impaired renal function does not significantly alter the pharmacokinetics of DTG, as the drug has low urinary excretion.[8] DTG is available as a 50 mg tablet or a fixed-dose combination together with tenofovir disoproxil fumarate (TDF) 300 mg and lamivudine (3TC) 300 mg and can be prescribed for persons weighing >35 kg and those >10 years of age. The efficacy and superior safety profile of DTG is well established in numerous clinical trials in both ART-naive and pretreated patients.[9-14]

Rapid viral suppression

In a recent systematic review and meta-analysis, DTG was found to be the most effective treatment for patients with HIV, even in difficult-to-treat individuals.[15] Moreover, in patients with a high viral load (>100 000 copies/mL), DTG was associated with a higher proportion of patients achieving viral suppression at 96 weeks compared with those on other ART regimens.[15] Rapid viral suppression is a critical public health goal to reduce HIV transmission. Compared with EFV, DTG appears to be superior in attaining viral suppression and immunological recovery.[16] This potency means that fewer patients will need to switch to costly second-line regimens – an important factor to consider, as Joint United Nations Programme on HIV and AIDS (UNAIDS) 2019 data showed that only 54% of people living with HIV (PLWHIV) in SA are virally suppressed.[17]

Improved tolerability

Another attractive feature of DTG is its improved side-effect profile compared with EFV, which includes fewer central nervous system side-effects such as depression and anxiety. Patients on DTG are therefore more likely to remain adherent to treatment owing to improved tolerability and retention in care.[18] Moreover, DTG does not require pharmacological enhancement and can be prescribed as

a fixed-dose combination tablet together with TDF and 3TC. The small dose of DTG required means that it can easily be combined with other antiretrovirals as a fixed-dose combination pill or as a single-ingredient pill.

Favourable drug resistance profile

DTG has a high resistance barrier explained by the long half-life of 71 hours due to its slow dissociation rate.[19] In clinical trials evaluating DTG in ART-naive patients on a DTG regimen, no cases of drug resistance have been reported. However, there are emerging anecdotal reports in the literature of drug resistance in treatment-experienced patients, particularly those who were previously taking a first-generation INSTI such as RAL.[20]

Cost

The smaller DTG dose needed by patients means that a lower quantity of the active pharmaceutical ingredient is required for manufacturing, thereby contributing to a lower manufacturing price. Global advocacy efforts and the introduction of generic competitors have also influenced a decrease in the price of DTG. In September 2017, a deal was announced that capped the public sector price of a fixed-dose combination of TDF plus 3TC plus DTG (TLD) in 92 LMICs at USD75 per person per year. At the time of writing, the lowest private sector price for DTG listed on the Medicine Price Registry was ZAR352.20 (USD20.72). Furthermore, the large-scale programmatic roll-out of DTG-based regimens requires increased ART harmonisation, and simplified drug procurement.

Considerations when prescribing DTG

Drug-drug interactions

Before initiating a patient on an appropriate ART regimen, it is imperative to take a medication-related history to identify any potential drug-drug interactions. Drug interactions can result in suboptimal drug levels, leading to an increased viral load and the emergence of drug resistance. While current research shows that DTG has fewer drug interactions than EFV, more evidence is still needed, given the relative novelty of DTG in comparison with EFV.

Tuberculosis co-infection

The interaction between rifampicin and DTG is critical in the SA context, given the high rates of HIV and tuberculosis co-infection. Rifampicin lowers the concentration of DTG, which requires increasing the frequency of dosing to 50 mg twice a day or substituting with rifabutin, as no adjustments are required.[21] If a patient is on a fixed-dose combination of TLD, an additional dose of 50 mg DTG must be supplied separately and should be taken 12 hours later. Patients need to be counselled about the additional dose, as this may affect adherence.

Polyvalent cations

Polyvalent cations (multivitamins, supplements and antacids) can affect plasma levels of DTG. They may bind to DTG, resulting in complex formation in the gastrointestinal tract and consequent poor absorption. A randomised trial examining the pharmacokinetics of DTG when administered with calcium or iron suggests that calcium or iron and DTG can be co-administered if taken with a meal, but should be separated if under fasting conditions for improved absorption.[22] Antacids may also attenuate the efficacy of DTG, which should be taken 2 hours before or 6 hours after ingestion of an antacid.[23]

Epilepsy

Co-administration of anticonvulsants such as carbamazepine, phenobarbital and phenytoin should be avoided, as this has been observed to result in a clinically significant decrease in DTG absorption.[24] Alternative anti-epileptic agents that are safe for use with DTG include valproate, lamotrigine, levetiracetam and topiramate.

Diabetes and insulin resistance

HIV-infected diabetic or prediabetic patients on metformin should be aware of the alteration in the pharmacokinetics of metformin when co-administered with DTG, resulting in an increase in metformin levels. Dose adjustments of metformin should be considered to maintain optimal glycaemic control when patients are starting or stopping DTG while taking metformin. The maximum recommended metformin dose while on DTG is 500 mg 12-hourly. This is an important consideration, as metformin remains a good treatment option for type 2 diabetes mellitus and has been used for other metabolic comorbidities that are associated with HIV.[25]

DTG and weight gain

Data suggest that patients receiving DTG-based ART are at higher risk of becoming overweight than HIV patients on other regimens. Two clinical trials in sub-Saharan Africa demonstrated that women on DTG gained more weight than men.[26] Clinically significant weight gain may increase the risk of adverse birth outcomes, diabetes, cardiovascular disease, cancer, and other serious non-AIDS events. Moreover, body fat changes can be deleterious to self-perception and ART adherence.[27]

Weight gain in adolescents living with HIV is also of concern, particularly as this group represents a growing proportion of patients receiving ART in sub-Saharan Africa. In a cohort of 605 virally suppressed adolescents in Eswatini, switching to DTG was associated with weight gain.[28]

Factors associated with weight gain include HIV-positive patients naive to ART and those with lower CD4 counts when commencing DTG-based therapy.[29] Moreover, patients treated with DTG in combination with tenofovir alafenamide plus emtricitabine (FTC) or TDF plus FTC were more prone to experience weight increase.[30] Further research is needed on risk factors for becoming overweight or obese after starting DTG in PLWHIV.

Central nervous system side-effects

Insomnia and sleep disorders are the neuropsychiatric symptoms primarily reported by patients on DTG. Despite the fact that DTG has a better central nervous system (CNS) profile than EFV, practitioners should be alert to DTG's spectrum of neuropsychiatric symptoms. These include dizziness, anxiety, depression, headache, paraesthesiae, musculoskeletal pain, poor concentration and slow thinking.[31] These symptoms are a concern, as psychiatric morbidity in PLWHIV is generally higher than in the general population because HIV infection may increase the risk of acquiring psychiatric conditions and exacerbating current ones.[32] These side-effects may result in treatment discontinuation and poorer outcomes.[33] Notably, female patients and the elderly (>60 years) are more likely to experience neuropsychiatric toxicity with DTG.[34]

Neural tube defects

In 2018, the WHO among other regulatory bodies issued a drug safety warning that advised against prescribing DTG to pregnant women. This advice stemmed from a Tsepamo study in Botswana that demonstrated a 12 times higher risk of neural tube defects (NTDs) in infants born to mothers using DTG around the time of

conception compared with women receiving a non-DTG-containing regimen.[35] However, this association weakened as further data emerged demonstrating that the prevalence of NTDs in infants born to mothers who conceived while on DTG was no longer statistically significantly higher compared with infants whose mothers conceived while on alternative regimens.[36] In 2019, the WHO therefore amended its recommendation so that women could access DTG without requiring contraception – but only if counselled regarding the risks and benefits of the treatment.[37] An update in July 2021 aligned WHO guidance with the most recent data, which recommend DTG for first-line therapy for all people initiating ART, including women in their reproductive years.[38]

DTG and the paediatric population

The HIV-positive paediatric population is still disadvantaged owing to inequitable access to ART and lower viral load suppression rates compared with adults.[39] While treatment failure in children is multifactorial, the availability of and access to ART options are limited. For example, EFV, which has been used successfully in adult first-line regimens, is not recommended in children <3 years of age, and the current mainstay for paediatric ART, lopinavir-ritonavir, is unpalatable, resulting in poor tolerability.[40] Adolescents weighing ≥30 kg may use the adult formulation of DTG, as per the national guidelines.[2] Safety profiles and pharmacokinetic data from the ongoing ODYSSEY and IMPAACT P1093 trials[41,42] have informed SAHPRA approval for the use of paediatric DTG 50 mg dosing in children weighing 20 - 30 kg. The DTG 5 mg dispersible tablet, approved for use in children from 4 weeks of age or weighing at least 3 kg in the USA and European Union, was developed by the originator company. To improve access across regions for the paediatric population, a generically manufactured, scored 10 mg dispersible tablet is now available as a recommended first-line regimen for all children aged ≥4 weeks in the WHO guidelines. SAHPRA has yet to register this formulation, which will provide rapid viral load suppression, good tolerability, and alignment with national HIV programmes for adults.

Conclusion

While DTG is an attractive drug for first-line ART regimens, the primary care provider must be aware of the potential risks and considerations when prescribing the drug. These include drug-drug interactions and unwanted adverse effects that need to be weighed against the potential benefits of the treatment. Special populations such as pregnant women and children should also be considered for expedited access to DTG where it would be clinically advantageous. The roll-out of DTG is therefore not a one-size-fits-all model but rather a careful consideration based on a patient's history, comorbidities and preferences, coupled with an evidence-based approach.

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