Dolutegravir and the management of HIV/AIDS in the South African adult population

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Abstract

The safety and efficacy of medicines are important considerations in antiretroviral treatment programmes. Previous first-line regimens that showed initial success have subsequently demonstrated several resistance pathways. Newer medicines such as dolutegravir have the potential to provide a safer and more effective management option for HIV/AIDS patients. This paper aims to provide an overview of dolutegravir and its role in the management of HIV/AIDS in the adult population, addressing the limitations and challenges faced by previous treatment regimens within the South African context. Information in this review was obtained from peer-reviewed articles and organisations' reports related to dolutegravir. We established as the main finding that dolutegravir has a higher genetic barrier to resistance, superior efficacy, tolerability, and durability. However, initial clinical trials, funded by the manufacturer, were done in well-resourced countries. With the high levels of non-nucleoside reverse transcriptase inhibitor resistance and the need for countries to incorporate dolutegravir into national treatment guidelines, poorly resourced countries need to collect further data on its safety and efficacy. Dolutegravir holds great promise and is currently a key medicine in the treatment of HIV/AIDS in the South African population. Findings from this review highlight the importance of dolutegravir being incorporated into national treatment guidelines and the need for ongoing safety data.

Keywords: dolutegravir, integrase strand transfer inhibitors, antiretrovirals, HIV, AIDS

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Introduction

In 2021, an estimated 38.4 million people were living with human immunodeficiency virus (HIV) worldwide.[1] In developing countries such as South Africa (SA), there were approximately 7.5 million people infected with HIV, 210 000 new infections, 51 000 acquired immunodeficiency syndrome (AIDS) related deaths, and roughly 5.5 million people accessing antiretroviral therapy (ART).[2] In addition, the highest prevalence rates (27.0%) were from the KwaZulu-Natal province.[3] Between 2010 and 2020, the number of new HIV infections and AIDS-related deaths in SA had almost halved.[4] Key factors contributing to the reduction in new infections and AIDS-related deaths include the ability to sustain the provision of ART to all people living with HIV/AIDS, and to treat all newly diagnosed patients with ART irrespective of CD4 cell counts.[5]

Traditional first-line ART regimens generally consisted of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI). While these regimens have been successful in treating millions of people over the past several years, many of these drugs have been shown to have a low barrier to resistance and significant adverse effects.[6]

ART is currently recommended for all HIV-positive individuals and the advantages of early initiation of ART include decreased HIV/AIDS-associated infections, Kaposi sarcoma, tuberculosis, hospitalisations, sexual transmission of HIV,[7] and AIDS-related deaths.[5] Since the introduction of the test and treat policy in 2016, the SA National Department of Health has been faced with the challenge of increasing the eligibility for ART coverage whilst reducing the cost of the treatment.[6] Hence, in 2018, the World Health Organization (WHO) interim guidelines recommended the use of dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI) as first-line as well as second-line treatment regimens.[8]

In September 2017, the SA Government had already negotiated a pricing agreement with international collaborators undertaking to make generic DTG available to low- to middle-income countries (LMICs).[9] As early as November 2017, about 60 LMICs had already undertaken to revise their national treatment guidelines to include DTG. By 2018, some LMICs including Brazil, Botswana, Kenya and Uganda had already started rolling out DTG in public sector health facilities. A fixed-dose combination containing DTG in combination with tenofovir (TDF) and lamivudine (3TC) was proposed to cost $75 per patient per year compared with about $110 for previously available first-line regimens. For SA, this would have translated into an annual cost saving of at least $100 million.[10] Therefore, the SA National Treatment Guidelines were revised in 2019 to include DTG together with TDF and 3TC as a first-line regimen in public sector healthcare facilities.[11]

This paper aims to provide an overview of DTG and its role in addressing the limitations and challenges faced by previous ART regimens within the SA context.

Review findings

Historical background of development, classification, and approval of ART

In 1987, zidovudine was the first antiretroviral (ARV) to receive approval from the United States Food and Drug Administration

(FDA).[12] To date, there are several ARV classes, and more than 20 ARVs that have been approved for the treatment of HIV with each medicine class named as per its mechanism of action.

Triple-medicine regimens of ARVs were introduced in 1998. These regimens known, as highly active antiretroviral therapy (HAART), consist of two classes of ARVs that target the virus at two different stages of their life-cycle and it is the standard of care for HIV/AIDS patients.[13] Highly active ART led to significant suppression of viral replication resulting in better treatment outcomes[14] and subsequently led to the transformation of HIV from a killer disease into a chronic, manageable condition that required a lifelong commitment to treatment adherence.

New ARV medicine classes have been developed to target other stages of the HIV life cycle. Figure 1 shows the HIV life cycle and points of interruption by the various classes of ARV medicines,[15] and Table I summarises the approved ARVs categorised in terms of their mechanism of action, the international non-proprietary name, and approval dates.

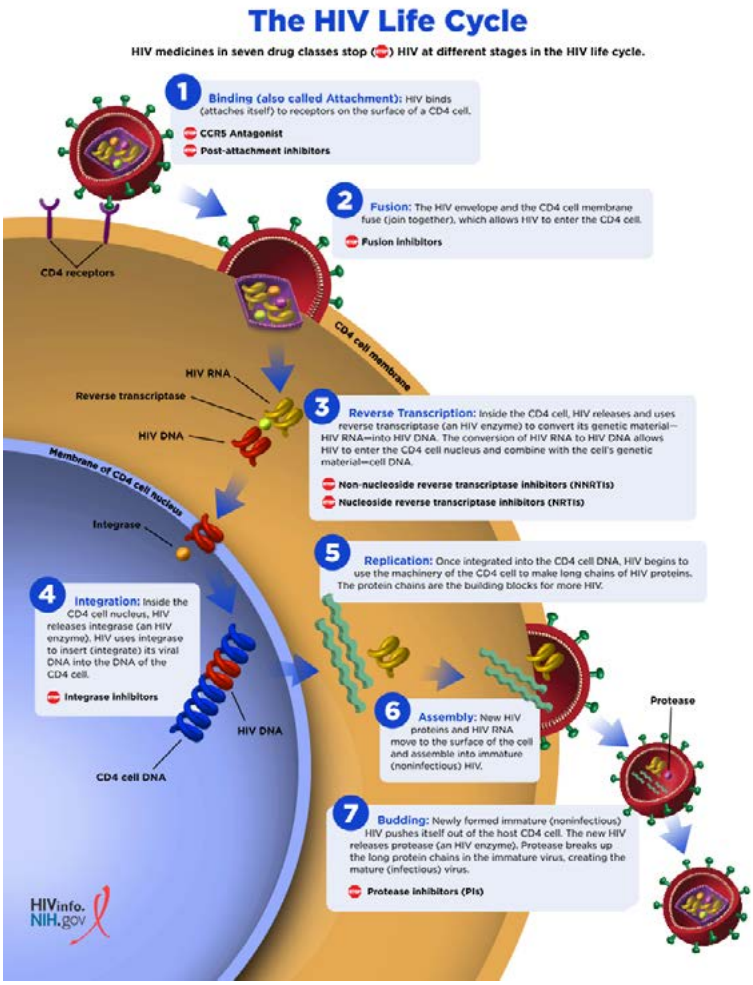

Figure 1: HIV life cycle showing points of interaction of the various ARV classes[15]

Integrase strand transfer inhibitors (INSTIs)

INSTIs are a comparatively newer class of ARVs used in the treatment of HIV-1 infection.[17] They display a unique mode of action against HIV-1 by inhibiting the integrase enzyme.[18] As shown in Table I, there are currently three INSTIs approved by the South African Health Products Regulatory Authority for the treatment of HIV, raltegravir, DTG and bictegravir. Cabotegravir, also an INSTI is registered by the South African Health Products Regulatory Authority for HIV prevention.[16]

Mechanism of action

INSTIs disrupt the HIV life cycle at the point of integration, described as step 4 in Figure 1. Integration is an essential step in the replication cycle of HIV, allowing the transference of virally encoded deoxyribonucleic acid (DNA) into the host chromosome. This step can be described in three stages: formation of a pre-integration viral DNA complex; 3′ processing; and strand transfer. INSTIs prevent the strand transfer stage by interacting with divalent cations of the catalytic core of the integrase enzyme. This inhibition allows INSTIs to maintain activity against strains that have acquired resistance to other classes of ARVs.[17-21]

INSTIs also maintain activity against HIV-1 strains that are resistant to NRTIs, NNRTIs, and protease inhibitors and block integrase enzymes that are virus-specific thereby leading to lower toxicity.[18] INSTIs have shown high virological efficacy, better safety and tolerability, lack of cross-resistance to other antiretroviral drugs, and low incidence of drug-drug interactions.[22]

Dolutegravir (DTG)

Clinical trials have demonstrated that DTG is effective in both the treatment-experienced and treatment-naïve populations.[17,23] Additionally, DTG has a good safety profile, the convenience of once-daily dosing, and a relatively low cost.[14] It was found that DTG was superior to efavirenz (EFV) in terms of viral load suppression.[24] When used as a first-line agent, resistance mutations to DTG by 2018 had not been observed.[8,19,20] Hence its inclusion in the WHO interim guidelines as first-line ARV treatment in adults.[8] However, recent reports have shown evidence of DTG-related resistance.[25-29] DTG does not require a pharmacokinetic booster and can be taken without regard to food. It has also demonstrated a higher genetic barrier to resistance than the first-generation INSTIs: raltegravir and elvitegravir.[13,17,20] There is also evidence that DTG is as effective against HIV-2 as it is against HIV-1.[30]

Pharmacokinetics

Absorption

DTG is well absorbed after oral administration with peak plasma concentrations occurring after two to three hours.[17,31] When co-administered with food, the extent of DTG absorption increases

Table I: Approved medicines for the treatment of HIV/AIDS[15,16]

Medicine class as per mechanism of action	International non-proprietary name	FDA approval date	South African Health Products Regulatory Authority approval date
Nucleoside reverse transcriptase inhibitors	Zidovudine Didanosine Zalcitabine Stavudine Lamivudine Abacavir sulphate Tenofovir disoproxil fumarate Emtricitabine	19 March 1987 09 October 1991 19 June 1992 27 June 1994 17 November 1995 17 December 1998 26 October 2001 2 July 2003	19 August 1995 9 May 2003 – 25 April 2003 13 June 1996 20 June 2001 13 April 2007 13 April 2007
Non-nucleoside reverse transcriptase inhibitors	Nevirapine Delaviridine Efavirenz Etravirine Rilpivirine Doravirine	21 June 1996 4 April 1997 17 September 1998 18 January 2008 20 May 2011 30 August 2018	5 July 2004 – 10 May 2007 – 11 September 2021 31 August 2021
Protease inhibitors	Indinavir Ritonavir Nelfinavir Amprenavir Atazanavir sulphate Fosamprenavir calcium Tipranavir Durunavir	1 March 1996 1 March 1996 14 March 1997 15 April 1999 20 June 2003 20 October 2003 22 June 2005 23 June 2006	30 November 2007 7 September 1997 8 May 2011 8 November 2006 25 November 2005 8 November 2006 – 19 June 2020
Fusion inhibitors	Enfuvirtide	13 March 2003	–
CCRF antagonists	Maraviroc	6 August 2007	3 January 2013
Integrase strand transfer inhibitors	Raltegravir potassium Elvitegravir Dolutegravir sodium Bictegravir	12 October 2007 27 August 2012 12 August 2013 07 February 2018	3 April 2011 – 21 April 2016 7 July 2020
Attachment inhibitors	Fostemsavir tromethamine	2 July 2020	23 August 2022
Post-attachment inhibitors	Ibalizumab-uiyk	6 March 2018	–

and its rate of absorption decreases.[17] These changes are clinically insignificant and DTG can be taken without regard to food.[17,31]

Metabolism and elimination

DTG has an elimination half-life of 12–15 hours. It is extensively bound to plasma proteins (98.9%) and is metabolised via two metabolic pathways. Whilst metabolism occurs predominantly in the liver by uridine diphosphate glucuronosyltransferases, UGT1A1, the second metabolic pathway (minor) occurs via cytochrome P450 (CYP3A).[17,32] Fifty-three per cent (53%) of the total dose is excreted unchanged in the faeces[17] and metabolites are eliminated in the urine. Co-administration of UGT1A1 inhibitors or inducers will impact DTG levels and dosage adjustment will be necessary in such instances.[31] DTG is metabolised extensively in the liver, however, dosage adjustment is not required in patients with mild to moderate hepatic impairment.[13, 17]

Drug interactions

Rifampicin induces liver enzymes, increasing the metabolism of DTG with a consequent decrease in DTG concentrations. This interaction requires DTG to be dosed at 50 mg twice daily.[21,32,33] Antacids significantly decrease plasma DTG levels and DTG should therefore be administered two hours before or six hours after the administration of antacids.[32-34] DTG has modest interactions with other ARVs and no dosage adjustment is necessary except for etravirine.[32] Owing to organic cation transporter 2 (OCT2) inhibition, DTG results in a significant increase in plasma concentrations of metformin. Dosage adjustment is therefore suggested when DTG is co-administered with metformin.[35] DTG can form complexes with magnesium, aluminium, calcium, and multivitamins, and dosing with DTG should take place two hours before or six hours after their intake.[36] The following medicines: carbamazepine, phenytoin, oxcarbazepine, phenobarbital, dofetilide, and St Johns Wort, when taken in combination with DTG, result in decreased DTG concentrations hence such combination therapy should be avoided.[37]

Side effects

Common side effects noted included diarrhoea, nausea, insomnia and headache,[38] muscle and joint pain, general malaise, and respiratory tract complaints. Side effects are reversible and have been reported to subside upon DTG discontinuation.[39] Other side effects reported in phase II and phase III trials include nasopharyngitis, dizziness, abnormal dreams, pyrexia, depression, pharyngitis, bronchitis, anxiety, cough, rash, asthenia,[40] and weight gain.[41] DTG inhibits OCT2, resulting in a mild increase in

serum creatinine levels.[13,21,33]

Resistance

DTG has been shown to have a higher genetic barrier to resistance than raltegravir and elvitegravir. DTG also remains active against 155, 143, 66, and 92 mutations.[30] Furthermore, mutations at G118, R263, S153, N155, and Q148 can impact the *in vitro* activity of DTG, and cross-resistance to INSTIs can occur when multiple integrase mutations occur.[17] Studies have recommended a twice-daily dose of DTG in patients with known or suspected INSTI-associated resistance substitutions.[13,21] Pharmacokinetic studies have shown that people with undetectable HIV ribonucleic acid can be switched from EFV to DTG. Dolutegravir levels remain lower in the first two weeks of dosing, hence a potential problem for people with NRTI resistance.[10]

Use in pregnancy

Cohort studies in high-income countries reported no increased risk of birth defects in women who conceived while taking DTG.[42] This contrasts with an observational study in Botswana where there was an increase in neural tube defects in women who started DTG before conception, suggesting a potential safety issue.[43] There have been no studies which report increases in adverse birth outcomes if DTG is initiated during pregnancy.[44] The WHO interim guidelines, 2018, recommended that all women of childbearing age who prefer to take DTG must also be on reliable and consistent contraception.[8] However, further guidance in 2019 by the WHO adopted a more women-centred approach and recommended that women of childbearing potential should be advised of the potential risks and benefits and allowed to make a decision regarding the use of DTG.[45] The current SA ART guidelines

Table II: Key studies evaluating DTG in the adult population

Study description	Study location/s	Study outcome
A phase III randomised, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily to raltegravir 400 mg twice daily both administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects	USA, Canada, France, Germany, Italy, Spain, the UK, Russia & Australia	DTG demonstrated non-inferior efficacy and a similar safety profile to RAL[47]
A phase III randomised, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla® over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects	USA, Canada, Australia, the UK, Belgium, Denmark, France, Germany, Italy, Netherlands, Hungary, Romania & Spain	DTG plus abacavir-lamivudine demonstrated a better safety profile and was more effective compared with efavirenz/tenofovir/emtricitabine[48]
A phase IIIb, randomised, open-label study of the safety and efficacy of GSK1349572 50 mg once daily compared to darunavir/ritonavir 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral adult subjects	USA, Italy, France, Germany, Romania, Russia, Spain & Switzerland	Once-daily dolutegravir is associated with greater viral suppression than once-daily ritonavir-boosted darunavir. DTG compares favourably in efficacy and safety to a boosted darunavir regimen with a nucleoside reverse transcriptase inhibitor background[49]
A phase IIIb single-arm study of the safety, efficacy and central nervous system and plasma PK of GSK1349572 (dolutegravir, DTG) 50 mg once daily in combination with the abacavir/lamivudine fixed-dose combination tablet over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects	USA	DTG levels in CSF were similar to unbound plasma levels. The HIV-1 RNA reductions were similar in CSF and plasma[50]
A phase IIb study to select a once daily dose of GSK1349572 administered with either abacavir/lamivudine or tenofovir/emtricitabine in HIV-1 infected antiretroviral therapy naïve adult subjects	USA, France, Germany, Italy, Spain & Russia	DTG was effective when administered at a dose of 50 mg without the need for a pharmacokinetic booster[51]
A phase III randomised, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral-experienced adults	USA, Canada, Argentina, Brazil, Mexico, Chile, Australia, South Africa, the UK, Belgium, France, Greece, Poland, Hungary, Italy, Netherlands, Romania, Spain, Russia & Taiwan	Viral suppression was greater in the DTG arm. No treatment-emergent phenotypic resistance. A single daily dose of DTG in combination with two other ARVs were well tolerated and achieved greater viral suppression than twice-daily raltegravir[52]
A phase III study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1 infected adult subjects with treatment failure on an integrase inhibitor containing regimen.	USA, Belgium, Canada, France, Italy, Portugal & Spain	The twice-daily dosing of DTG 50 mg showed efficacy in treatment-experienced patients with INSTI resistance[53]
A phase III randomised, double-blind study to demonstrate the antiviral activity of dolutegravir (DTG) 50 mg twice daily versus placebo both co-administered with a failing antiretroviral regimen over seven days, followed by an open-label phase with all subjects receiving DTG 50 mg twice daily co-administered with an optimised background regimen (OBR) in HIV-1 infected, integrase inhibitor therapy-experienced, and resistant, adults	USA	Antiviral activity was observed at day 8 in INSTI-resistant patients due to DTG[54]
A pilot study to assess the antiviral activity of GSK1349572 containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance	USA, Canada, France, Italy & Spain	Twice daily DTG 50 mg provided greater VL suppression compared to once-daily dosing. Demonstrates activity of the integrase inhibitor in the presence of resistance to RAL[55]

Table III: Summary of key trials with DTG in the SA adult population[56]	
Study description	**Study outcome**
A phase IIb, randomised, partially blind, active-controlled, dose-range finding study of GSK3640254 compared to a reference arm of dolutegravir, each in combination with nucleoside reverse transcriptase inhibitors, in HIV-1 infected antiretroviral treatment-naïve adults	Stopped early/terminated
Standard versus double dose dolutegravir in patients with HIV-associated tuberculosis: a phase II non-comparative randomised controlled trial	Twice daily dolutegravir may not be necessary in people with HIV-associated tuberculosis
A phase IIIb, randomised, open-label study of the antiviral activity and safety of dolutegravir compared to lopinavir/ritonavir both administered with dual nucleoside reverse transcriptase inhibitor therapy in HIV-1 infected adult subjects with treatment failure on first-line therapy	Pending
A phase IIIb, randomised, open-label study of the safety and efficacy of dolutegravir or efavirenz each administered with two NRTIs in HIV-1-infected antiretroviral therapy-naïve adults starting treatment for rifampicin-sensitive tuberculosis	Pending
A phase IIb randomised, active-controlled, staged, open-label trial to investigate safety and efficacy of BMS-955176 in combination with dolutegravir and atazanavir (with or without ritonavir) in treatment-experienced HIV-1 infected adults	Pending
Safety and pharmacokinetics of dolutegravir in pregnant HIV mothers and their neonates: a pilot study	Pending
A phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults	Pending
A randomised clinical trial to evaluate solutions for the management of virological failure for individuals on TLD in sub-Saharan Africa (RESOLVE)	Pending
A cross-sectional, observational study to characterise the transition to dolutegravir-based regimens in South Africa in terms of the emergence of obesity, viral re-suppression and integration into routine programme care	Pending

recommends that due to an absence of increased birth defects, the integration of ART and family planning services should continue to be integrated especially in instances of unsuppressed viral loads.[46] The foetal transfer of DTG was shown to be significant, with infants displaying a terminal half-life of about 35 hours.[13,21]

DTG clinical studies

DTG, developed and licensed by ViiV Healthcare, has been subjected to several studies globally. Some key clinical trials that were conducted to establish the efficacy of DTG are summarised in Table II.

From the various studies described in Table II, only one phase III study included a SA cohort. Several key trials have since been conducted in SA as summarised in Table III. Furthermore, other studies are underway, including the use of DTG in tuberculosis, pregnancy, and switching between regimens.[56]

Currently, available data indicate that dosage adjustment is not required in the elderly population.[21] However, concentrations of DTG can also be higher in patients with low body weights.[57]

A multicentre, post-marketing observational study in the Netherlands found that although well-tolerated, the rate of discontinuation with DTG as part of combination ART was much higher than reported in clinical trials. Intolerability was cited as the reason for DTG discontinuation.[39] The NAMSAL trial in Cameroon did not demonstrate superior efficacy of DTG/TDF/3TC after 48 weeks compared with EFV (400 mg)/TDF/3TC once daily.[58]

While there is evidence from cohort studies in Europe that demonstrate an increased risk of immune reconstitution inflammatory syndrome,[59] other studies have shown that there is no association between the use of DTG and immune reconstitution inflammatory syndrome in LMICs.[43]

Implications of and recommendations for the use of DTG in SA

The increased resistance to NNRTIs once threatened the scale-up of ART. As more asymptomatic HIV and AIDS people are initiated on ART, there is an increasing need for a resilient first-line regimen comprising medicines that demonstrate minimal interactions, lower toxicity, higher barrier to resistance, lower pill burden, and lower costs.

Clinical trials are generally conducted in populations where screening tests for genotypic resistance are routinely done as per study design. Since DTG will be used as the first-line treatment regimen in the SA population, where there is already transmitted resistance to NNRTIs, further general data is needed. Furthermore, in randomised controlled trials, viral testing for resistance is done when there is a viral rebound. This may differ significantly from National ART programmes where patients may remain on a failing regimen for prolonged periods prior to resistance testing being done. Coupled with poor adherence, the development of new viral mutations may occur.[33]

Dolutegravir is increasingly being used in first-line regimens in poorly resourced settings. Data collected from clinical trials, cohort studies, and surveillance registers will be of paramount importance to establish the long-term benefits of DTG. The drug interaction between DTG and rifampicin, requires that DTG be dosed twice daily.[60] However, studies are being undertaken to

determine the efficacy of a single dose DTG in the presence of rifampicin in poor resource settings, where an increased dose of DTG may impact negatively on adherence.[56]

Integrase strand transfer inhibitors are a novel class of medicines that have revolutionised HIV treatment. A transition to the DTG-based regimen in SA is based on cost savings, the efficacy of DTG in the management of HIV-1 infection, the increased resistance to NNRTIs, and their high barrier to resistance. Data from clinical trials have demonstrated the safety and efficacy of DTG. While an increase in viral suppression is expected with the use of DTG as a first-line medicine, issues such as poor adherence and stockouts can lead to the emergence and transmission of drug-resistant HIV.[43]

Whilst DTG-based regimens remain the preferred choice of treatment, the low incidence of reported resistance may restrict the early detection of drug resistance and mutations. While an abundance of literature is available on the use of DTG in various treatment options in clinical studies, data is also needed in patients with advanced HIV, as this population is generally excluded from phase III clinical trials.[61]

There is therefore a definite need to conduct further studies and surveillance data is crucial to establish the long-term safety and efficacy of DTG in the management of HIV/AIDS patients in SA.

Conclusion

A review of the literature shows that DTG is safe and effective and can therefore play a pivotal role in the management of HIV/AIDS in the SA adult population. Being cost-effective is already a major advantage, especially in developing countries where the cost of health care and emergence of resistance, and treatment failures may lead to poor health outcomes in patients.

However, since there have been limited preregistration safety and efficacy trials done in the SA adult population, further clinical trials, cohort, and surveillance studies are required to conclusively assess the safety and efficacy of DTG in the SA adult population as well as to monitor for resistant mutations that may emerge.

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Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

Ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (reference number: BE442/19).

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