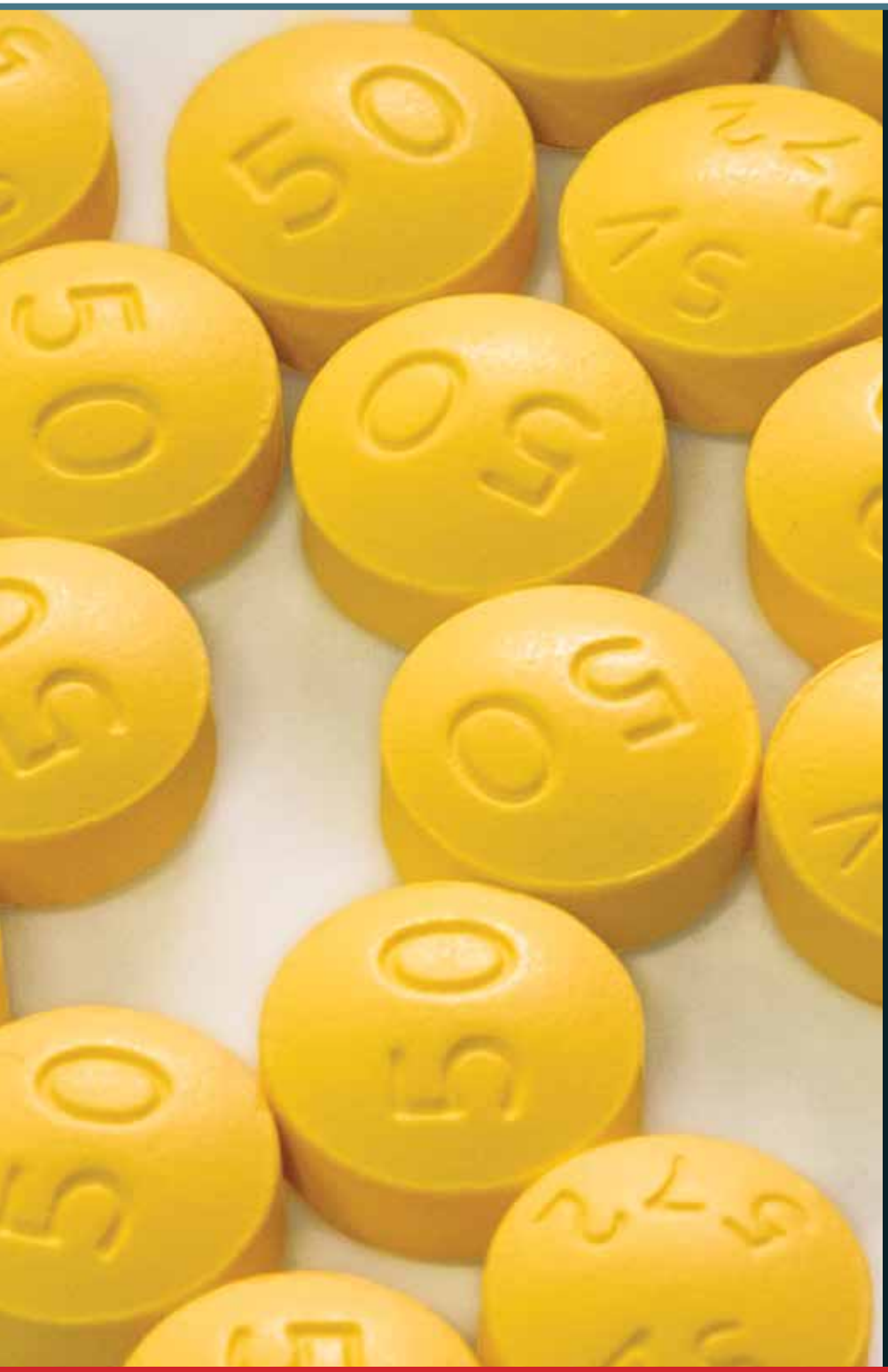
HIV NURSING MATTERS

A publication of the Southern African HIV Clinicians Society



Focus on dolutegravir

Dolutegravir: Superhero or mere mortal?

Resistance profile, side-effects and common drug interactions of dolutegravir

Dolutegravir safety in pregnancy and breastfeeding

Dolutegravir: An opportunity to strengthen integrated HIV and sexual reproductive health services

CELEBRATING 20 YEARS

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STOP STOCKOUTS

WHAT IS THE STOP STOCK OUTS PROJECT?

The Stop Stock Outs Project (SSP) is an organisation that monitors availability of essential medicines in government clinics and hospitals across South Africa. The SSP aims to assist healthcare workers in resolving stock outs and shortages of essential medicines at their facilities, enabling them to provide patients with the treatment they need.

How do you report a stock out to the SSP?

Our hotline number is 084 855 7867

- **Send us a Please Call Me**
- **Send us an SMS**
- **Phone us or missed call us**

We will then phone you back to get some more information.

You can also email us at report@stockouts.org

What information do you need to report to the SSP?

The name of the medicine that is out of stock

The name of the clinic or hospital where you work

Reporting is an anonymous process and your name, if provided, will not be disclosed to anyone outside of the SSP.

MEDECINS SANS FRONTIERES · SOUTHERN AFRICAN HIV CLINICIANS SOCIETY · +SECTION27 catalysts for social justice · RUDASA · TAC TREATMENT ACTION CAMPAIGN · Rural Health Advocacy Project

inside

HIV Nursing Matters focuses on dolutegravir

Guest editorial

Maria Sibanyoni

Programme Manager: Southern African HIV Clinicians Society

It is a pleasure to write about innovations that epitomise hope for our country in terms of treatment optimisation in HIV management. Thinking back to the beginning of HIV treatment and the challenges regarding adherence, our country has made giant strides by launching the new drug dolutegravir (DTG). The drug has a high genetic barrier, is robust in terms of managing HIV, demonstrates rapid viral load suppression and is well tolerated. DTG also makes it easier for patients to adhere to treatment.

It is important to recognise milestones achieved through research, progressive policy and implementation that make it easier for people living with HIV to access life-saving antiretroviral (ARV) drugs, particularly DTG. Accordingly, this edition of *HIV Nursing Matters* presents a range of articles focused on DTG.

The article on page 4 explains what DTG is, including TLD (tenofovir/lamivudine/dolutegravir), and why DTG is considered better than many other available ARVs.

An important piece on the use of DTG in pregnancy (page 14) presents the signals from the Botswana Tsepamo study regarding the risk of neural tube defects. This has muddied the waters around DTG rollout, particularly for women of child-bearing age, although there are benefits of including DTG-based antiretroviral therapy (ART) in pregnancy. The World Health Organization has opted to recommend that DTG should be used for all populations including women of child-bearing potential. The South African prevention of mother-to-child transmission of HIV (PMTCT) guidelines are more cautious, however, recommending thorough exploration of a woman's fertility intention prior to prescribing DTG, and proposing that women who wish to conceive, or are in the early first trimester (<8 weeks), initiate efavirenz instead of DTG, and switch to DTG later in the pregnancy.

The new ART regimen: An opportunity to strengthen integrated HIV and sexual reproductive health (SRH) services article (page 18) reflects on the use of TLD in the national ART programme as an opportunity for the public health service to re-double its efforts to provide comprehensive and integrated SRH services for all women. It also discusses strategies to be used for women/adolescents of child-bearing potential. In addition, it emphasises the importance of effectively counselling and providing patients with appropriate family-planning and contraception services, and that the required commodities and equipment must be available consistently within health facilities.

Three further articles address DTG resistance (page 6), side-effects (page 9) and drug-drug interactions (page 12), and discuss strategies used to manage patients accordingly.

Lastly, the Stop Stockouts Project article (page 22) presents the impact of stockouts in the management of patients. It is encouraging that Dr Zweli Mkhize has put stockouts on top of the agenda.

Despise these advances, there is still a considerable amount that needs to be done!

We trust you will enjoy this edition.

HIV NURSING MATTERS

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Message from the president

Prof. Yunus Moosa
President: Southern African HIV Clinicians Society

This edition of *HIV Nursing Matters* introduces one of the most exciting and highly anticipated antiretroviral (ARV) drugs to enter the HIV treatment space. Dolutegravir (DTG) – a drug with low cost, convenient dosing schedule, high potency, rapid virucidal activity, low toxicity, high genetic barrier to resistance, limited drug-drug interactions, and availability in single-tablet regimen – appears to tick virtually all the boxes of an ideal ARV. However, concerns about teratogenicity emerged just prior to its anticipated entry into the South African formulary in 2018. This delayed its introduction into the South African public healthcare system because of the layer of complexity this imposed on mass rollout of this new 'wonder drug'. Finally, this drug is poised to make an entry into the SA public health sector, come 2020.

This edition of *HIV Nursing Matters* provides an in-depth overview of all relevant characteristics of DTG by experts in the field. The issue covers the mechanism of action, advantages of its use, role in treatment-naïve and -experienced subjects, risks associated with its use in situations where supporting drugs in the regimen are ineffective (functional monotherapy), side-effects of the drug, common drug interactions, impact on liver and renal function, use in the face of renal and liver dysfunction, and its use in women of child-bearing age and pregnancy. The issue ends with a most pertinent piece on the impact of drug stock-outs, a challenging reality of our fragile healthcare system.

Congratulations to the editors for putting together this concise, comprehensive encyclopedia on DTG. This edition is a must-read for all healthcare workers involved in the treatment of HIV.

Stay educated.

DTG, TLD and other TLAs...

(Dolutegravir, tenofovir/lamivudine/dolutegravir and other three-letter acronyms)

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What is DTG?

DTG is the abbreviation for dolutegravir – a new antiretroviral (ARV) medication used to treat HIV. It belongs to a class of ARVs called integrase strand transfer inhibitors (InSTIs). Other InSTIs include raltegravir, cabotegravir and bictegravir, however raltegravir and DTG are the only InSTIs available in South Africa.

How do InSTIs work?

To understand how InSTIs work, we need to remember how HIV multiplies within human cells:

Integrase enzyme is responsible for integrating the HIV DNA into the host cell DNA in the nucleus. The group of ARVs called integrase strand transfer inhibitors (InSTIs) block the integrase enzyme and therefore prevent the HIV DNA from integrating into the host cell DNA. This prevents HIV from multiplying. DTG is one of the InSTI ARVs.

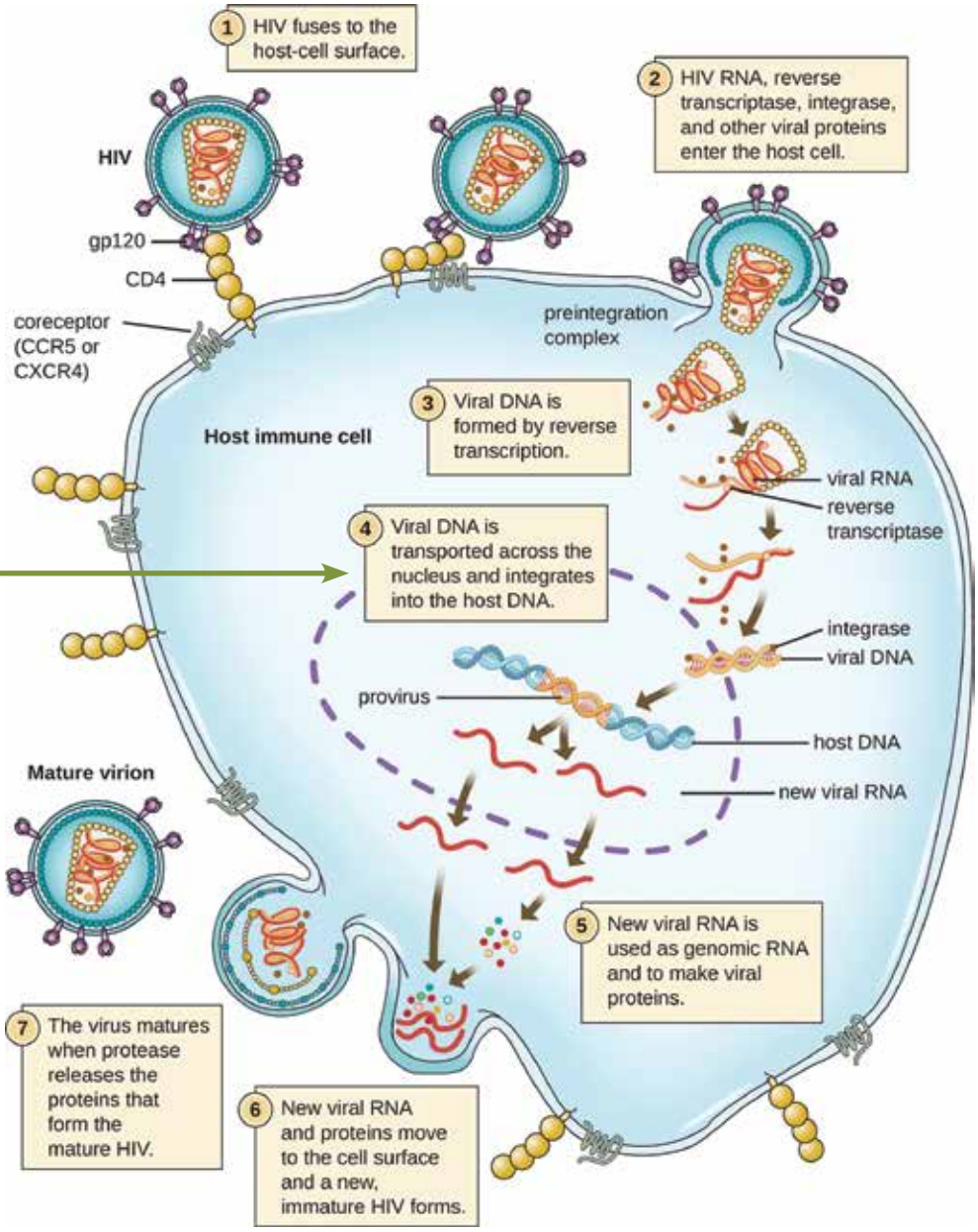
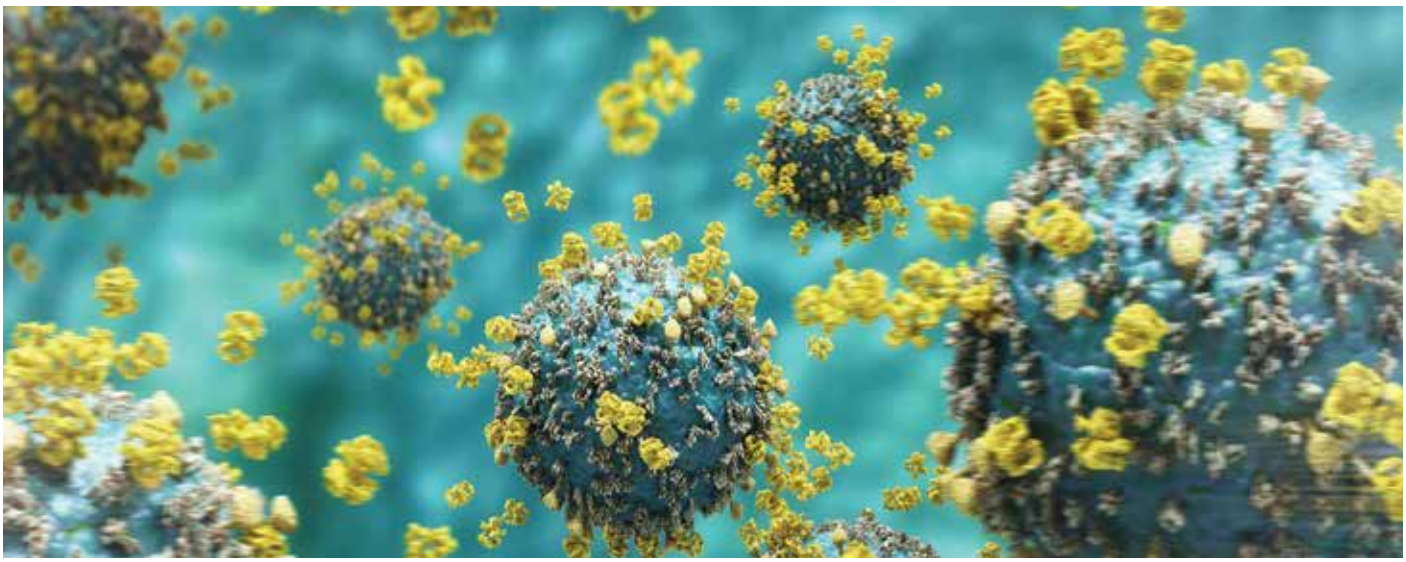


Figure 1: HIV life cycle[1]



Why is DTG better than many other ARVs?

DTG is better than most other ARVs because:

1. When used correctly with at least one other active ARV, HIV does not develop resistance to DTG (discussed in the article on page 6)
2. It has few side-effects (discussed in the article on page 9)
3. It has few drug interactions (discussed in the article on page 12)
4. It comes in a fixed-dose combination tablet called TLD
5. It is going to be provided to the South African National Department of Health quite cost effectively.
6. It can be used as first-line ART, and in certain situations as second- or third-line ART (discussed in the article on page 6)
7. The 50 mg tablet can be used in children from 20 kg in weight right up to adulthood.

What are the concerns about DTG?

1. There was a concern that DTG may cause neural tube defects when used in early pregnancy (discussed in the article on page 14)
2. The 50 mg dose cannot be used for children weighing <20 kg and we do not yet know what dose is required for children under 20 kg
3. There have been reports of some weight gain in patients receiving DTG
4. Because DTG is relatively new, there may be side-effects and drug interactions that are still unknown; therefore, we need to report all possible side-effects on adverse drug reaction forms
5. We do not have evidence on whether DTG will develop resistance if it is taken with two other inactive drugs; therefore, we need to have a recent viral load result for the patient and follow the guidelines carefully before changing to a DTG-containing regimen (discussed in more detail on page 6).

What is TLD?

TLD is the name given to a fixed-dose combination (FDC) tablet which contains:

Tenofovir
Lamivudine
Dolutegravir

Why is TLD a great tablet for many South Africans who have HIV?

1. Patients only need to take one tablet per day
2. It is a small tablet which is easy to swallow
3. It can be given to children aged ≥10 years and weighing ≥35 kg (provided their kidney function is normal)
4. There are few major side-effects to TLD
5. It is affordable for rollout across South Africa
6. The regimen has a high genetic barrier to resistance.

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We are very excited to have DTG and TLD available in South Africa for our patients! **However,** there can be a few challenges with DTG and TLD, so it is very important for you to read the rest of this issue of *HIV Nursing Matters* to learn all about when and how DTG and TLD can be prescribed safely to patients.

Dolutegravir: Superhero or mere mortal?

Dolutegravir and resistance

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There has been significant hype about the new antiretroviral (ARV) drug dolutegravir (DTG). Since it is basically going to be used for first-, second- and third-line regimens, it is easy to presume that every patient will respond to DTG. However, that may not necessarily be the case. What is so fantastic about DTG from a resistance point of view?

To put DTG into perspective, let's look at our current first- and second-line regimens. Our first-line antiretroviral therapy (ART) regimen tenofovir/emtricitabine/efavirenz (TEE) fixed-dose combination (FDC) is a wonderful, well-tolerated, one-tablet-a-day regimen. However, if the patient is not adherent, then resistance develops rapidly, within 2 - 4 weeks.[1] We call this a low genetic barrier to resistance.

On the other hand, our current second-line regimen of zidovudine (AZT)/lamivudine (3TC)/lopinavir/ritonavir (LPV/r) is a poorly tolerated, twice-daily regimen consisting of six tablets a day, but takes 1 - 2 years to develop resistance.[2] We call this a high genetic barrier to resistance.

What we really need is a well-tolerated, one-tablet-a-day, first-line regimen that takes a long time to become resistant, i.e. with a high genetic barrier to resistance. That is where DTG comes in: the FDC tenofovir/lamivudine/dolutegravir (TLD) is a one-tablet-a-day regimen and is well tolerated with a very high barrier to resistance.[3]

Use of DTG in first-, second- and third-line regimens

You may be excused for thinking that we could use DTG in every patient requiring ART without any consideration for their prior ART history. Let's see if that is true ... In two situations – first- and third-line ART – it is relatively straightforward, so let's look at those situations first.

First-line ART

Patients who have never been on ART (ARV-naïve) and patients who are virally suppressed on a first-line regimen

This is the simplest scenario. Patients who have never been on ARVs before do very well on DTG plus two nucleoside reverse

transcriptase inhibitors (NRTIs), and it is virtually unheard of for a patient to develop DTG resistance in this situation.[4] In the Botswana rollout of DTG-containing regimens in ARV-naïve patients, 98.6% were virologically suppressed (viral load (VL) <400 copies/ml) at 12 months.[5] This is phenomenal and unheard of with other regimens. If the patient is virally suppressed on a first-line regimen consisting of a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two NRTIS, then there is no reason why that patient cannot receive DTG plus the same two NRTIs. It may be possible to use other NRTIs, but it is best to discuss this with an expert. In the new National Department of Health (NDoH) guidelines, TLD will be used as first-line regimen in ART-naïve adult patients and in patients who are virologically suppressed on TEE. We predict that almost none of these patients will develop resistance on TLD.

Third-line ART

In these rather complicated patients, the use of DTG is relatively straightforward. Why? Because these patients all qualify for HIV-resistance testing. Experts can use the results of resistance testing to put together a third-line regimen (frequently using DTG) to give excellent virological suppression, although often with high pill burden regimens.[6] The NDoH Third Line Committees use relatively straightforward algorithms to design these regimens.[7] In a recently published review of suppression in adult patients managed using this algorithm (albeit in the days before DTG was available), 83% suppressed their VLs to <1 000 copies/ml.[8] We can expect that this suppression will be even further improved now that we are using DTG.

We see that the use of DTG is rather straightforward in first- and third-line regimen patients, but what about in second-line regimens? Here's the catch ...

Second-line ART

The concern here is that the NRTIs might have become resistant during the first-line regimen, with cross-resistance developing to the second-line NRTIs. In other words, there may not be two fully active NRTIs together with DTG in the second-line regimen. Would that make a difference?

We know from the EARNEST study[9] that in scenarios where an active protease inhibitor (PI) such as lopinavir/ritonavir (LPV/r) is used together with two fully resistant NRTIs, it is as effective as a regimen with two fully active drugs. But does the same apply to DTG? The answer is: we don't know.

What we do know is that monotherapy with DTG is not a good idea. Not only does the regimen stop working, but the development of resistance to DTG also arises.[10,11] So, although DTG is a powerful ARV with a very high genetic barrier to resistance, if used on its own (monotherapy), then resistance to DTG develops.

Another study called the DAWNING study[12] showed, in patients who had failed a first-line NNRTI regimen, that DTG plus at least one active NRTI demonstrated phenomenal results – even better than results of the LPV/r regimen to which it was compared. Patients were only allowed to participate in the trial if resistance testing showed that they had at least one active NRTI. About 30% of patients were not allowed to participate in the trial because they did not have an active NRTI. So, clearly, we must ensure that second-line patients have at least one active NRTI before switching them to DTG plus two NRTIs.

Does that mean we have to perform resistance testing on every patient failing two NRTIs plus EFV? Our country would not be able to afford such testing. Luckily, it is not necessary because in certain situations it is possible to predict whether or not there is an active NRTI. For example, in a patient failing TDF/FTC/EFV, AZT will be fully active (even a bit overactive) and so that patient can receive AZT/3TC/DTG. This applies to a patient failing ABC/3TC/EFV as well, where a regimen of AZT/3TC/DTG will be expected to work. So, in patients failing a first-line NNRTI regimen, we can safely use DTG plus two NRTIs, provided we can be certain that there is at least one active NRTI.

Summary

Let's summarise the use of DTG in first-, second- and third-line regimens:

- First-line regimens
  - ART-naïve patients can safely use DTG plus two NRTIS
  - Virally suppressed patients on a first-line NNRTI plus two NRTI regimen can safely use DTG plus the same two NRTIs
- Second-line regimens
  - Patients can safely use DTG plus two NRTIS provided there is certainty that there is at least one active NRTI (discuss with an expert if in doubt)
- Third-line regimens
  - The third-line committee will decide on a regimen based on the HIV-resistance testing, and frequently include DTG.

DTG drug interactions

(especially DTG and rifampicin-containing TB treatment)

This is discussed elsewhere in this issue of *HIV Nursing Matters* (see page 12). If a patient is receiving DTG and needs to receive rifampicin for tuberculosis (TB) treatment, then the DTG dose must be increased to 50 mg twice daily.[13-15] If, for example, the patient is taking one TLD FDC tablet at night, then they should take a further single 50 mg DTG tablet in the morning while receiving rifampicin. There is already one documented case in South Africa where a patient receiving rifampicin only took 50 mg DTG once daily and as a result, developed DTG resistance.[16] Thus, it is very important to explain to patients receiving DTG who are about to receive rifampicin that they need to take a second dose of DTG 12 hours later. The consequences of not doing so could be disastrous. This could also apply to all other cases of drug interactions with DTG where the level of DTG in the body is decreased (see article on page 12).

Previous use of raltegravir

DTG is an ARV from a class of drugs called integrase strand transfer inhibitors (InSTIs). The other drug from this class of drugs in use in South Africa is raltegravir (RAL). RAL is a first-generation InSTI, whereas DTG is a second-generation InSTI. Unlike DTG, RAL has a low genetic barrier to resistance, meaning it develops resistance very quickly (one to two mutations).[3] If a patient develops RAL resistance and they continue to use RAL, then they may accumulate more InSTI resistance until DTG stops working as well.[17] For this reason, it is probably best to avoid using RAL where possible, because it may compromise our ability to use DTG at a later stage in that patient. In certain situations, DTG dosed at 50 mg 12-hourly may be able to overcome the resistance,[18] but it is best to avoid RAL in the first instance where possible.

Conclusion

DTG is a wonderful ARV with a very high barrier to resistance. However, when used as monotherapy, resistance does develop. The DAWNING study[12] has shown that as long as there is at least one active NRTI together with DTG, the regimen will be effective. This must be taken into account when designing a second- or third-line regimen with DTG. Consulting the advice of an expert in this regard is essential. Clinicians must beware of drug interactions with DTG which could lead to DTG resistance, especially with rifampicin-containing TB treatment. It is absolutely essential to ensure that DTG is dosed at 50 mg 12-hourly when used together with rifampicin. If possible, the use of RAL should be avoided, as it may lead to DTG resistance.

So, to come back to our title: is DTG a superhero or a mere mortal? I think DTG is a superhero with flaws – like all of us!

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Side-effects of dolutegravir

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In 2018, the World Health Organization (WHO) recommended that the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV) be replaced by the second-generation integrase strand transfer inhibitor (InSTI) dolutegravir (DTG) as the preferred drug in first-line antiretroviral therapy (ART) regimens because of its better tolerability and higher genetic barrier for resistance.[1] The motivation for this change is a consequence of the high prevalence of pre-treatment resistance to NNRTIs in many parts of the world, including South Africa, estimated to be at 10%.[2]

The implications are that many people living with HIV infection who are currently receiving EFV-based therapy will be switched to DTG, and all people initiating ART will be preferentially started on DTG-based therapy. At present, this is the case in some countries on the African continent, such as Botswana, Kenya, Malawi, Nigeria, Tanzania and Uganda, and South Africa is launching the fixed-dose combination (FDC) in December 2019.[2,3]

Pharmacology

DTG is a second-generation InSTI. Its mechanism of action is to impair the function of the HIV integrase-DNA complex to which it binds, preventing the integration of the viral genome into the host cell DNA. Its metabolism is primarily through hepatic glucuronidation by UDP-glucuronosyltransferase 1A1, with minimal urinary excretion.[4,5] Renal failure does not in any way significantly affect the metabolism of DTG, therefore no dose adjustment is necessary.[4] DTG pharmacokinetic properties are such that it retains plasma concentrations well above the protein-adjusted 90% inhibitory concentration (IC90) for HIV.[6] It is rapidly absorbed following oral administration and reaches peak plasma concentrations within 2.5 hours after oral intake. Food intake does not dramatically affect serum concentrations, thus DTG can be taken with or without food.[7,8]

DTG has good penetration to many body compartments including crossing the blood-brain barrier. This is achieved by having a high affinity for plasma proteins. A study designed to assess the extent of DTG entry into the cerebrospinal fluid (CSF) found that CSF concentrations of DTG were similar to unbound DTG concentrations in plasma. These levels were such that they exceeded the *in vitro* 50% inhibitory concentration for wild-type HIV virus by ≥66-fold, indicating that DTG achieves therapeutic concentrations in CSF.[9]

DTG has minimal drug-drug interactions, as it has little ability to alter drug-metabolising enzymes. A small study has reported an interaction with valproate, which may result in a substantial reduction of DTG trough concentrations.[10] Until such time that the mechanism of this interaction is better understood and this report is confirmed in other studies, the co-administration with valproate should be avoided. If this is not possible, then double-dose DTG should be considered.

The main interactions to be concerned about are co-administration of DTG with rifampicin and metformin. DTG can be taken with or without food in the absence of mineral supplements.[4]

Adverse reactions

DTG is well tolerated in the many clinical trials with <2% of patients experiencing severe adverse reactions.[4] However, reports outside of clinical trials suggest that this could be as high as 14%.[11,12] Commonly reported side-effects include headache, nausea and diarrhoea.[13-15] The most frequently reported adverse reactions in clinical trials are headache and insomnia.[6] Hypersensitivity reactions are uncommon and have been reported in <1% of patients.[4,6]

A number of reports outside of clinical trials include neuropsychiatric adverse reactions related to DTG with rates of 5.6 - 9.9%,[12] most commonly insomnia and sleep disturbance.[16] Other neuropsychiatric adverse reactions that occur to a lesser extent include: dizziness, nervousness, restlessness, depression, poor concentration, slow thinking and paraesthaesia.[11,16] A German study reports that female patients and patients aged >60 years are more likely to experience neuropsychiatric toxicity with DTG.[11] At this stage a pathophysiological explanation for DTG-related neuropsychiatric adverse effects is lacking; however, some preliminary data suggest that increased DTG trough levels may provide an explanation.[17]

Recent publications have reported an unexpected weight gain in patients receiving DTG,[18] ranging between 4 kg and 12 kg,[19] with females seeming to be at higher risk. The clinical implications are not quite clear at this time and more studies are needed to confirm this observation. A recent meta-analysis reported that DTG had no significant effect on the risk of cardiac, immune reconstitution inflammatory syndrome (IRIS) or suicide-related serious adverse events compared to other antiretrovirals (ARVs).[20]

Table 1: Common side-effects of dolutegravir

Adverse reactions	Recommendation
Insomnia (common)	Recommend morning dosing of DTG
Headache (very common)	Usually mild to moderate; monitor – if it persists, then refer to specialist
Depression (common)	Stop DTG and switch to alternative drug
Dizziness (common)	Usually mild to moderate; monitor
Diarrhoea (common)	Usually mild to moderate; often resolves

Abbreviations: DTG – dolutegravir.

Pregnancy and breastfeeding

The use of DTG in pregnancy is safe, with no increased risk for stillbirth, preterm birth, small for gestational age (SGA) or congenital anomalies.[21] There has been concern regarding the use of DTG in women who conceive while receiving DTG and preliminary data from Botswana seem to suggest a potential risk of neural tube defects.[2] This led the WHO to make a recommendation that women of child-bearing age should receive alternative ART regimens with better evidence to support safe use in pregnancy.[2] In July 2019, the WHO updated their recommendation based on further data from Botswana, indicating that DTG should be offered to women of child-bearing age as risk-benefit models suggest the benefits outweigh the risks.[22]

Since the 2018 report, further data indicate that the risk of neural tube defects associated with DTG at conception has declined, though the risk remains statistically significantly higher than other ARV drug exposure groups.[22] At this stage, further data are required to either confirm or refute this potential safety signal, with several studies underway to address this. Further to the WHO recommendation, women of child-bearing age should have the option to use DTG, but must be informed of this potential safety signal and advised to use effective contraception throughout treatment. This advice will be modified once further results become available.

Conclusion

The rollout of DTG as the anchor drug in first-line ART is an important step in the evolution of HIV treatment programmes in Africa. As an effective ARV agent, its strength is mainly driven by effective virological suppression, good tolerability, once-daily administration and infrequent drug-drug interactions. Further to this, is its high barrier to resistance, making its introduction into HIV treatment programmes an important public health intervention, the benefits of which would be a reduction in the development and subsequent transmission of resistance mutations.

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Common drug interactions with dolutegravir

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Dolutegravir: An integrase strand transfer inhibitor

The integrase strand transfer inhibitors (InSTIs) are a class of antiretroviral therapy (ART) drugs with potent anti-HIV activity. Their mechanism of action is based on the inhibition of an enzyme responsible for the integration of viral DNA into the host cell genome.[1] Dolutegravir (DTG) is classified as a second-generation InSTI and has a high barrier to resistance.[2] A DTG-based first-line ART regimen has been shown to be superior to an efavirenz (EFV)-based first-line ART regimen.[3] In South Africa, DTG will soon be replacing EFV for ART-naïve HIV-positive patients. National guidelines recommend using the fixed-drug combination (FDC) of tenofovir (TDF), lamivudine (3TC) and DTG as preferred first-line regimen.[4]

Because of the foreseeable increase in prescribing and dispensing of DTG nationally, a clear understanding of the pharmacokinetics of the drug is necessary, as this will inform its rational and safe use. DTG has a rapid absorption with a median time to maximum blood concentration of 0.5 - 2 hours.[5] It has an elimination half-life of 12 hours and metabolism predominantly occurs via uridine diphosphate (UDP) glucuronosyltransferase (UGT) 1A1 enzymes, and to a lesser extent, cytochrome P450 (CYP) 3A4 enzymes.[1] DTG is not known to significantly induce or inhibit any metabolising enzymes at clinically relevant concentrations. DTG is a substrate for the membrane transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), however it does not induce or inhibit either of these.[1] Collectively, the pharmacokinetic profile of DTG allows for a low drug-drug interaction risk.[6] However, there are several important drug-drug interactions with commonly used drugs, of which prescribers and dispensers should be aware. The most important of these will be discussed.

Chelation with cations

The mechanism of action of InSTIs involves the binding of magnesium to the active site of the integrase enzyme. Subsequently, InSTIs are subject to potential chelation (binding of ions and molecules to metal ions) drug-drug interactions.[7] DTG co-administered with an aluminium- or magnesium-containing antacid in fasting, healthy volunteers, significantly reduced the DTG mean area under the plasma concentration time curve (AUC – a plot of the drug's concentration in blood versus time) by 74%.[8] Similarly, a drug-drug interaction study that assessed the co-administration of calcium with DTG in fasting, healthy volunteers, found that the DTG AUC was reduced by 39%.[9] This was also true for co-administration with iron supplementation. For this reason, the current recommendation is to take magnesium- or aluminium-containing antacids either 2 hours after or 6 hours before the ingestion of DTG. Calcium or iron supplements can be taken at the same time as DTG if ingested with food; however, calcium and iron supplements should be taken at least 4 hours apart (Table 1).[4]

Metformin drug-drug interaction

Metformin is largely excreted unchanged in the urine. Its renal elimination is subject to both glomerular filtration and active secretion.[10] Secretion is subject to organic cation transporter 2 (OCT2)-mediated uptake of metformin into renal tubular cells. DTG is a known inhibitor of OCT2, thereby causing a drug-drug interaction with metformin. A healthy volunteer study that assessed the effect of DTG on metformin serum concentrations, found a 79% increase in the AUC of metformin.[10] A retrospective assessment of HIV-positive patients with type 2 diabetes using metformin that were switched to a DTG-based ART regimen, did not reveal any clinically significant changes in mean fasting blood glucose concentrations or HbA1c, and there were no new episodes of hypoglycaemia reported.[11] However, current guidelines err on the side of caution, and it is advocated that the daily metformin dose should not exceed 1 000 mg (i.e. 500 mg 12-hourly) when prescribed with DTG (Table 1).[4] Furthermore, patients should be counselled regarding potential metformin adverse effects and receive frequent blood glucose monitoring when initiating co-administration.

Induction drug-drug interactions

A number of drugs have the ability to induce membrane transport proteins and metabolising enzymes within the human body. The induction of membrane transport proteins and metabolising enzymes has the potential to significantly lower the plasma drug concentration of so-called 'victim drugs'. DTG is an example of a victim drug.

Most first-line anticonvulsants are potent inducers. Particularly CYP 3A4, UGT 1A1, and P-gp are affected by carbamazepine, and for this reason, co-administration of carbamazepine and DTG has shown a 49% reduction in the AUC of DTG among healthy volunteers.[12] A similar reduction in pharmacokinetic parameters was observed with co-administration of DTG and phenobarbital.[13] It is recommended to avoid using DTG with either carbamazepine, phenobarbital or phenytoin. Anticonvulsants that do not interact with DTG include valproate,

Table 1: Important drug-drug interactions with DTG and corresponding recommendations

Interacting drug	Effect of co-administration	Recommendation
Polyvalent cation (Mg^{2+}, Fe^{2+}, Ca^{2+}, Al^{3+}, or Zn^{2+})-containing drugs: aluminium or magnesium-containing antacids; sucralfate; multivitamins; iron and calcium supplements	↓ DTG	Take magnesium-/aluminium-containing antacids either 2 hours after or 6 hours before ingesting DTG. Calcium or iron supplements can be taken at the same time as DTG if ingested with food; however, calcium and iron supplements should be taken at least 4 hours apart.
Metformin	↑ Metformin	Daily metformin dose should not exceed 500 mg 12-hourly. Patients should be counselled regarding potential metformin adverse effects.
Anticonvulsants: carbamazepine; phenobarbital; phenytoin	↓ DTG	Avoid co-administration if possible (valproate, lamotrigine, levetiracetam and topiramate can be used) or double the DTG dose to 50 mg 12-hourly with carbamazepine if an alternative anticonvulsant cannot be used.
EFV	↓ DTG	Avoid co-administration if possible (RPV can be used) or double DTG dose to 50 mg 12-hourly.
NVP	↓ DTG	Avoid co-administration if possible (RPV can be used) or double DTG dose to 50 mg 12-hourly.
Rifampicin	↓ DTG	Double the DTG dose to 50 mg 12-hourly.

DTG – dolutegravir; EFV – efavirenz ; RPV – rilpivirine.

lamotrigine, levetiracetam and topiramate; should one of these not be available, doubling the dose of DTG (i.e. 50 mg 12-hourly) with carbamazepine can be considered (Table 1).[4]

The non-nucleoside reverse transcriptase inhibitors (NNRTIs), EFV and nevirapine (NVP), are also inducers of CYP 3A4, and can potentially lower the plasma drug concentration of DTG secondary to this effect.[14,15] Although it is unlikely that DTG and either one of these NNRTIs will be prescribed simultaneously, prescribers should be cognisant of the lingering induction effect (up to 4 weeks after stopping) of EFV and NVP when switching to a DTG-based regimen. However, current national ART guidelines do not recommend doubling the dose of DTG when switching virologically suppressed patients from EFV or NVP to DTG in order to compensate for the induction effect.[4] Co-administration of EFV or NVP and DTG should be avoided (rilpivirine (RPV) can be used as substitute, and if not possible, doubling the dose of DTG (i.e. 50 mg 12-hourly) is advised) (Table 1).[4]

Rifampicin is a key component of first-line anti-tuberculosis therapy. Rifampicin is a potent inducer of membrane transporter proteins (P-gp and BCRP) and metabolising enzymes (UGT 1A1 and CYP 3A4), thereby subjecting DTG to a significant blood-concentration-lowering drug-drug interaction.[16] A drug-drug interaction study among healthy volunteers that assessed the pharmacokinetics of DTG when co-administered with rifampicin found a 54% reduction in the AUC of DTG.[17] Current guidelines recommend administering double the dose of DTG (i.e. 50 mg 12-hourly) with rifampicin (Table 1).[4]

Conclusion

DTG is set to improve the management of HIV-positive patients in low- to middle-income countries. It has a favourable adverse drug reaction profile and high barrier to resistance, can be utilised in first- and second-line therapy with greater efficacy and tolerability than the current standard of care, and it comes in a convenient once-daily dosing regimen at reasonable cost. It does have a few potential drug-drug interactions, all of which can easily be prevented or addressed by altering the dose or timing interval. Currently, the benefit of using DTG outweighs the risk, and its implementation nationwide should be celebrated.

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Dolutegravir in pregnancy

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Prevention of vertical/ mother-to-child infection

Over the past two decades, globally, in sub-Saharan Africa (SSA) and South Africa, tremendous progress has been made regarding access for pregnant women to antiretroviral therapy (ART) for their own health, but also for the prevention of vertical transmission to infants. Worldwide in 2015, 77% of women living with HIV had access to ART.[1] Overall, in 2014, vertical transmission rates were 14%,[2] but 13 out of 21 priority countries – most in SSA – reported 6-week HIV transmission rates of ≤5%.[2]

South Africa boasts >95% coverage of ART for pregnant women who are living with HIV, and in 2016/2017, only 1.3% of HIV-exposed infants were infected with HIV at the 10-week HIV polymerase chain reaction (PCR) test.[3] The previous option B+ (ART for life for all pregnant and breastfeeding women) and the current treat-all approach adopted in 2016 – with ART initiation for all people living with HIV – includes triple therapy with an efavirenz (EFV)/emtricitabine (FTC)/tenofovir (TDF) fixed-dose combination (FDC) as first-line therapy.[4] Protease inhibitor (PI)-based second-line therapy is used, and for third-line therapy usually an integrase strand transfer inhibitor (InSTI), a PI and other drugs are used, depending on the known or anticipated resistance profile.[4]

Pregnancy is a time where adherence and viral load (VL) suppression in the pregnant woman is essential to prevent vertical transfer of HIV; thus, optimal treatment regimens are required. Despite this, because of concerns regarding birth defects, safety concerns related to the pregnancy, regarding the mother and the infant, and the efficacy of antiretrovirals (ARVs) during pregnancy due to changes in absorption, metabolism, distribution and elimination, there is a lack of available data in pregnancy for newer and some older drugs.[5]

Dolutegravir: What is known in pregnancy?

Dolutegravir (DTG) is an InSTI which is well tolerated and has an improved VL suppression compared to EFV.[6] DTG has been introduced into guidelines since 2015, although it was noted that there were insufficient data regarding

pregnancy and breastfeeding.[7] There have been studies which have evaluated DTG in pregnant women, either opportunistically when pregnant women are receiving DTG, or where pregnant women are purposefully included in studies. Opportunistic studies have shown that DTG levels are lower in pregnancy compared with the postpartum period,[8] but this decrease does not seem to result in VL elevation or vertical HIV transmission.

The DolPHIN (DTG in Pregnant HIV mothers and their Neonates) study was conducted in South Africa and Uganda, in HIV-positive women initiating ART in the third trimester, who were randomised to receive either EFV- or DTG-based ART combined with two nucleoside reverse transcriptase inhibitors (NRTIs). The study showed that in the women receiving DTG, the time to achieve VL suppression (<50 copies/ml) was more rapid, and that more women in the DTG arm had achieved suppression at 2 weeks post-partum than those receiving EFV.[9]

Rapid VL suppression in pregnant women, especially those presenting in the third trimester, is of tremendous benefit, given that infants of HIV-positive women who present late to antenatal care, or become HIV-infected late in pregnancy, are at two to three times higher risk of being HIV-infected.[10] DTG has a high genetic barrier to resistance, and unless there has been previous use of integrase inhibitors, pre-treatment resistance is very unlikely.[11] This is in contrast to EFV, where high numbers of women may have pre-treatment transmitted resistance,[12] or may have developed resistance as a result of previous exposure to nevirapine (NVP) or EFV for prevention of mother-to-child transmission of HIV (PMTCT).[13]

Botswana and the Tsepamo study

Although there are benefits of including DTG-based ART in pregnancy, particularly in late pregnancy, recent evidence has muddied the waters around DTG rollout, particularly for women of child-bearing potential. From August 2014, the Botswana Tsepamo surveillance study has prospectively collected data on birth outcomes. The study has included HIV-negative and HIV-positive women, on various ART regimens, spanning about 90 000 births (45%) in Botswana.

In 2016, the National Programme changed to DTG-based ART for all and this allowed the study to collect outcomes related to DTG.[14] In 2018, Tsepamo investigators were asked to do an early analysis, specifically evaluating DTG exposure in women who had conceived on DTG, and in their infants. Unexpectedly, they found that a higher number of infants exposed to DTG from conception developed neural tube defects (just < 1%), compared with those exposed to other ART regimens and with infants of HIV-negative women (0.1%).[15] When more data were available, an updated analysis showed that the risk was a bit lower (0.7%), but still much higher than in women conceiving on other ART regimens or in HIV-negative women.[16] The most recent analysis from July 2019, shows a further reduction to 0.3%, still slightly higher than in other pregnant women.[17] These results are reassuring, but still suggest a slight increased risk in women who conceive on DTG.

However, since these findings are only reported in one population, in relatively few infants, they are difficult to interpret in isolation.[14,15,18] Neural tube defects occur within the first 8 weeks post conception, therefore the greatest risk for exposure is peri-conception and in the first 8 weeks post conception. DTG appears safe after 8 weeks. The same study found no differences between DTG and other ART regimens in terms of pregnancy outcomes and adverse pregnancy outcomes such as premature or very premature births, stillbirths, neonatal deaths or being small for gestational age.[19]

These results came at a time when international World Health Organization (WHO) and local guidelines were planning to start introducing DTG as first-, second- and third-line regimens with different combinations of other ARVs depending on current regimen and previous exposure. However, these plans were put on hold and a more cautious approach was adopted, varying between countries and regulatory bodies. Some countries went to the extreme of recommending no DTG use at all for women of child-bearing potential, which resulted in an outcry

from HIV-positive women activists who felt that they had not adequately been consulted.

The most recent findings have been incorporated into WHO and local South African guidelines. The WHO has opted for recommending that DTG should be used for all populations including women of child-bearing potential.[20] The South African PMTCT guidelines are more cautious, recommending thorough exploration of a woman's fertility intention prior to prescribing DTG, and recommending that women who wish to conceive, or are in the early first trimester (<8 weeks), initiate EFV instead of DTG and switch to DTG later in the pregnancy. adequately.[21] This requires a focus on family planning and contraceptive access, which will hopefully be strengthened through the implementation of these guidelines.[21]

Conclusion

Substantial progress has been made with the prevention of vertical HIV infection to infants, largely through improved implementation of ART to all HIV-positive women for their own health and for PMTCT. Optimisation of ART regimens regarding tolerability, efficacy and improved resistance profile is particularly important in pregnant women. Additional benefit is seen in women who present late to care or become infected later in pregnancy, requiring rapid VL suppression.

DTG, an InSTI, is to be included in ART regimens in the next months; however, a signal for neural tube defects has been detected in a Botswana surveillance study. Cautious rollout of DTG is likely in future months until more data are available, and women of child-bearing age should be counselled regarding their fertility intentions, encouraged to use hormonal or other long-acting contraception if no fertility intent, or switch to EFV if they wish to conceive. Increased, improved surveillance is essential to evaluate this signal and to detect other potential signals in pregnant women, where new or under-studied drugs are being used.

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What to do with dolutegravir in patients with abnormal kidney and liver function tests

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Fortunately, dolutegravir (DTG) does not appear to cause true kidney dysfunction. It is also not metabolised in the kidneys, and therefore no dose adjustments are required for DTG in patients who have renal dysfunction.

However, it is important to note that DTG causes a rise in serum creatinine in most patients, due to it interfering with renal creatinine handling. DTG inhibits a transporter protein called organic cation transporter 2 (OCT2), which is usually involved in secreting creatinine from the kidney's proximal tubules into the urine.[1] By inhibiting this process, it causes the serum creatinine to rise. This creatinine elevation is benign and does not represent a decline in the patient's actual glomerular filtration rate (GFR). However, since commonly-used estimators of GFR use creatinine in their calculations (such as the Cockcroft-Gault or Modification of Diet in Renal Disease (MDRD) formulas), it may appear as if the GFR has fallen after starting DTG when in fact it has not. When the GFR is measured experimentally using non-creatinine methods, no decrease is seen.[2]

Two factors may prove helpful in distinguishing benign DTG-induced creatinine rises from more serious creatinine elevations due to other causes. Firstly, the rise in creatinine is typically modest, as is the corresponding fall in estimated GFR therefore. In one study, there was a mean decrease in calculated GFR of 9 ml/min/1.73m^2 for those taking DTG 50 mg daily, and 14 ml/min/1.73m^2 for those taking DTG 50 mg 12-hourly.[3] Similarly, most patients will see a rise in their creatinine of <15%, though the change may be more marked in a minority of cases. Secondly, the timing of the rise in creatinine is very typical: it occurs within the first few weeks after starting DTG and is stable thereafter for as long as the patient takes DTG. Thus, a fall in GFR within the first month that is greater than would be expected, or any substantial decline at all in GFR after the first month, should prompt a workup for other causes of renal dysfunction.

In formulations where DTG is co-formulated with tenofovir (TDF), TDF does not need to be discontinued if the estimated GFR falls <50 ml/min/1.73m^2, provided that this decline is thought to be due to DTG alone.

In general, integrase inhibitors like DTG remain the safest antiretroviral option to give to patients with pre-existing liver dysfunction. No dose adjustment is necessary for such patients, though in patients with severe hepatic impairment, caution should be used since the drug is hepatically metabolised.[4] DTG can cause a hepatitis, although this occurrence is rarer than is seen with either efavirenz or the protease inhibitors. In clinical trials, the incidence of alanine aminotransferase (ALT) elevations >5x the normal range was just 2%.[4] Patients with underlying hepatitis B or C may be at increased risk for a DTG-induced hepatitis. In many cases, it may be difficult to tease out whether an adverse change in liver function tests that occurs after starting a DTG-containing regimen represents a drug-induced liver injury or an immune reconstitution inflammatory syndrome (IRIS) reaction, though a predominant elevation in cholestatic enzymes, as opposed to hepatic enzymes, is more typical of the latter for most IRIS subtypes.

Take-home messages

- DTG does not cause kidney dysfunction
- DTG can cause an elevated serum creatinine level, usually by <15% in the first few weeks, but this alone does not signify kidney dysfunction and therefore DTG and TDF can be continued
- No DTG dose adjustment is necessary in patients with renal dysfunction
- DTG can rarely cause drug-induced hepatitis.

When should we worry?

- If serum creatinine rises by >15% in the first month, or if serum creatinine rises after the first month on DTG
- If ALT rises to >3x the upper limit of normal with symptoms of hepatitis (nausea, vomiting, abdominal pain, jaundice), or if ALT rises to >5x the upper limit of normal even in the absence of symptoms.

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The new antiretroviral treatment regimen:

An opportunity to strengthen integrated HIV and sexual reproductive health services

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South Africa will soon launch a new first-line antiretroviral therapy (ART), the fixed-dose combination (FDC) tenofovir (TDF)/lamivudine (3TC)/dolutegravir (DTG) (known as TLD) on 1 December 2019. In the new regimen, DTG, an integrase inhibitor, is replacing efavirenz (EFV). The switch to TLD has been highly anticipated by South African clinicians, policy makers and advocates due to DTG's profile as a highly effective therapy with few side-effects and high genetic barrier to resistance. It is hoped that, given DTGs tolerability and efficacy, the integration of TLD into the national ART programme will improve retention in care and maximise population-level viral suppression.

The relatively smooth acceptance of DTG/TLD as the preferred first-line regimen for the country's ART programme hit a significant hurdle in May 2018 when a potential safety issue was identified in an ongoing observational study in Botswana.[1] Four cases of neural tube defects (NTDs) were found in infants born to 426 women (0.9%) who became pregnant while using TLD – in comparison to 0.1% in women taking other antiretroviral (ARV) regimens at the time of conception. NTDs occur early in pregnancy – the neural tube closes at 4 weeks of pregnancy – therefore, the recommendation was that DTG should be avoided peri-conception and in the first trimester of pregnancy until more data were available to better understand the potential risk of DTG use in women of child-bearing potential.

On the back of the Botswana data, country programmes had to weigh the potential risk of DTG use with its known benefits, and civil society groups jointly advocated against blanket exemptions for women and for equitable access to DTG.[2] Ultimately, South Africa chose to move forward with universal use of TLD as first-line therapy for anyone initiating ART, with no restrictions for women of child-bearing age.[3] Given that South Africa has the largest number of people on HIV treatment in the world – the majority of whom are women, coupled with a high rate of unplanned pregnancies, including among women living with HIV – the use of TLD in the national ART programme is an opportunity for the public health service to re-double its efforts to provide comprehensive and integrated sexual and reproductive health (SRH) services for all women. Family planning (FP) and HIV testing services (HTS) should always be provided together. At every FP visit, offer HTS. At every HTS visit, offer FP.

Women should be classified according to their current needs. Patients may fall into one of the following three categories:

A. Women currently wanting to conceive
B. Women who do not currently desire a child, but may do so in the future
C. Women who do not desire a child now or in the future.

What does this mean for healthcare providers?

Although the rationale for integrated HIV and SRH services is well known, in practice, comprehensive family planning services and HIV prevention and treatment are often not well integrated, particularly during antenatal, post-delivery and post-partum visits, when counselling about fertility intentions and contraception options should be routine.

Ideally, the healthcare provider should engage the women living with HIV and her current partner in a couples-based approach, as the health and co-operation of both partners is important for safe contraception or conception. To understand current fertility desires and healthcare needs, it becomes crucial to discuss regularly issues of child-bearing and contraception.

Under the new ART guidelines, healthcare providers must now inform their HIV-positive female patients about the potential risk of NTDs with the use of DTG/TLD and provide accurate information and choice to the full range of contraception options if desired. For women choosing to use DTG/TLD, providers are required to document that patients were fully informed about the potential risks of NTDs.[3]

Adult women and adolescent girls weighing ≥35kg* and ≥10 years of age:

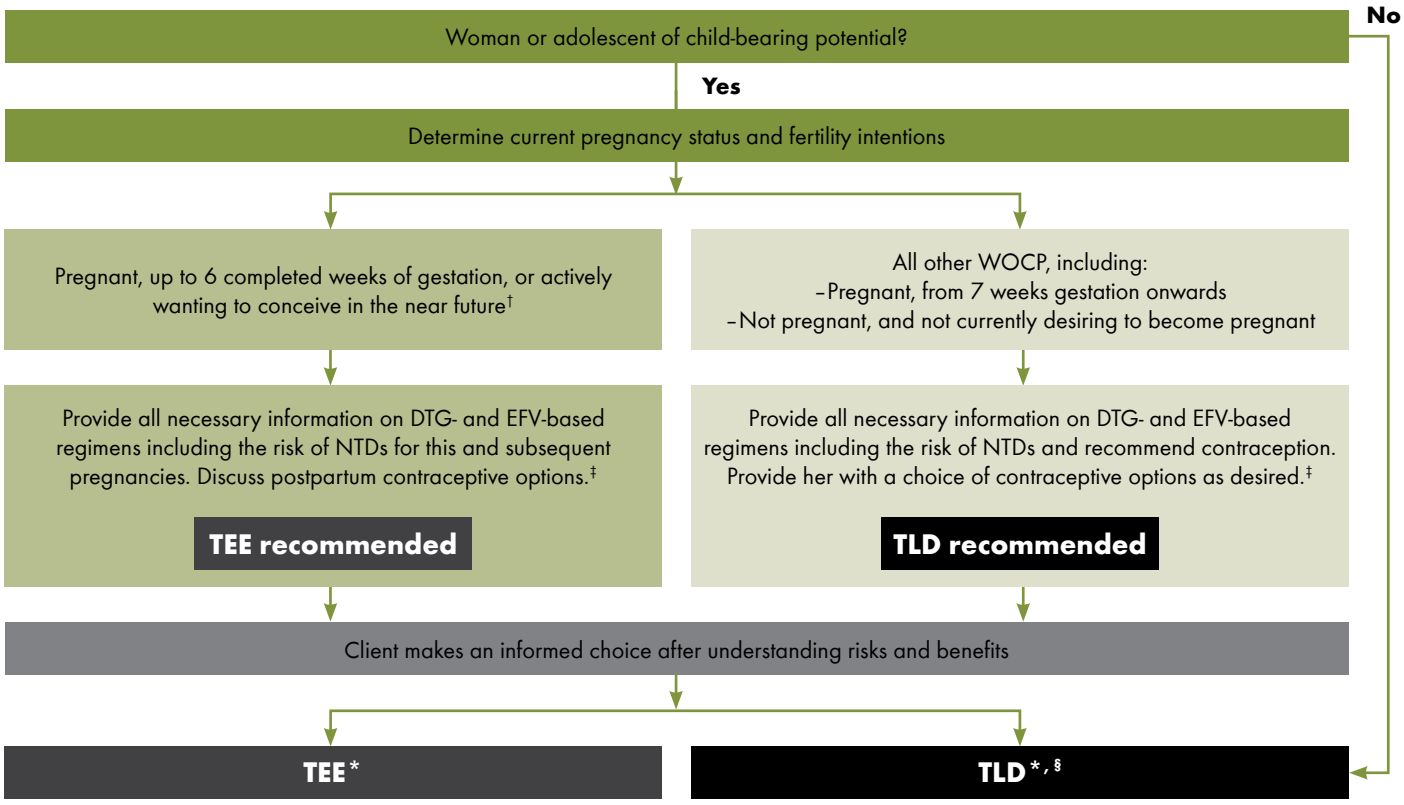


Figure 1: 2019 Guidelines from the South African National Department of Health for TEE versus TLD regimens for adult women and adolescent girls.[3]

Abbreviations: ABC – abacavir; EFV – efavirenz; DTG – dolutegravir; IUCD – intra-uterine contraceptive device; NTDs – neural tube defects; TEE – tenofovir + emtricitabine + efavirenz; TLD – tenofovir + emtricitabine + dolutegravir; PMTCT – prevention of mother-to-child transmission of HIV; WOCP – women of child-bearing potential.

* For adolescent girls who weigh <35kg, replace tenofovir (TDF) with abacavir (ABC).

† Women wanting to conceive should be started on folate and should be counselled to defer attempts to conceive until they are virally suppressed. See also 'Contraception and Safe Conception' on Page 9 of the PMTCT Guideline.

‡ Women should be provided a choice of contraceptive options (which includes condoms, oral contraceptives, implants, injectables, IUCD)

§ Documentation that the woman has been counselled and consents to receive DTG must be included in the patient's chart/file.

This new guideline requirement is an important prompt for healthcare providers to discuss fertility intentions and contraception options with their patients to assist them in making an informed, voluntary choice of a contraceptive method. Women should be counselled about the variety of contraceptive methods available and supported in choosing a method that best meets their needs. Family planning needs and preferences will vary from person to person, and may change over time as a person's needs, desires and life context changes. For this reason, it is important for providers to discuss fertility desires and contraception use/needs at every patient visit. In addition, women should be advised to use a reliable contraception if they choose to use TLD.

Healthcare providers should also be prepared to counsel and provide information on NTD risk to women on TLD/DTG who become pregnant, and to provide accurate information and access to ultrasound, if available, and in the unlikely event that an NTD is seen, the choice to terminate can be provided.

Potential risks of using DTG around the time of conception

Women should be counselled about the potential risk of NTDs when DTG is taken around the time of conception and should be allowed to make an informed choice.

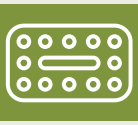
For women starting ART:

- It is not recommended that women wishing to conceive are started on DTG: women taking or starting DTG should be on effective contraception and folic acid supplements.

For women already on a DTG-containing regimen:

- Once the patient is taking DTG, fertility intentions should be discussed at every visit
- Should the patient desire a pregnancy, then it is recommended that DTG is switched to EFV.

Dual method is always recommended:



A hormonal method (including implants) or intra-uterine contraceptive device to prevent pregnancy

A barrier method (male/female condoms) to augment the hormonal method, and prevent STIs and HIV

Discuss the different contraceptive options available for use in the women living with HIV (See PC101, and the National Contraceptive Clinical Guideline, 2018). Available options include:

- Injectable progestins
- Combined oral contraceptive pills
- Intra-uterine contraceptive device
- Emergency contraception

Figure 2: Reversible contraception options available for women who do not currently desire to have a child, but in whom permanent contraceptive methods are not appropriate.[3]

Women who fall pregnant on DTG

If the patient chooses to start/remain on DTG, despite wanting to conceive and having received appropriate counselling, her choice should be documented in her clinical file. If she is currently in the first trimester, then discuss with a doctor. If her gestational age can be determined accurately, and the neural tube has already closed (6 weeks post conception), then she may be able to remain on her DTG-containing regimen. If the patient is over 6 weeks post conception, then continue DTG. Counsel the mother on the risks of NTDs for her subsequent pregnancies and discuss the need for contraception after delivery. Enter the patient into the antiretroviral pregnancy register: http://www.APRegistry.com/

Women who do not currently desire a child

Women who do not desire a child may fall into one of the remaining two categories:

B. Women who do not currently desire a child but may do so in the future:

- Provide counsel on options for contraception including long-acting reversible contraceptives (intra-uterine contraceptive device (IUCD) and implants) and barrier methods (Figure 2).

C. Women who do not desire a child now or in the future:

- Counsel about contraception options including **permanent methods** (male and female voluntary sterilisation), long-acting reversible contraceptives (IUCD and implants) and barrier methods.
- If permanent methods are not deemed appropriate, then proceed to an alternative dual method as outlined in the next section.

In order to effectively counsel, assist and provide patients with the appropriate FP and contraception services, providers must be competent clinically and proficient in methods of patient-centred counselling, and the required commodities and equipment must be available consistently within health facilities.

Drug-drug interactions with hormonal contraceptive methods

- Women should be counselled about the possibility of drug interactions between hormonal contraceptives and enzyme-inducing drugs such as **efavirenz, rifampicin** and certain epilepsy drugs.
- These interactions do not decrease the effectiveness of the HIV or tuberculosis (TB) medications but can potentially lead to **decreased effectiveness of some hormonal contraceptive methods**.
- Providers should always ask which specific HIV or TB medications a woman is taking in order to advise her appropriately on interactions.
- **Long-acting injectables (such as Depo Provera®) are not affected** by drug-drug interactions with HIV medications or rifampicin and therefore remain very effective at preventing pregnancy. There is no need to reduce the interval between injections.
- **All hormonal methods** including implants (e.g. Implanon NXT®), the combined oral contraceptive pills (COCPs), and the long-acting injectables (e.g. Depo Provera®) **are safe to use with DTG**.
- When used with EFV (NNRTI), the **the hormonal implant (e.g. Implanon NXT®) has reduced effectiveness**. Women who are already using a hormonal implant should consider an alternative non-hormonal method for contraception, e.g. the IUCD.
- When used with EFV and rifampicin, **COCPs have reduced effectiveness** – they remain unreliable and their use is best avoided.
- Regardless of the hormonal method used to prevent pregnancy, **all women should continue to use condoms correctly and consistently to prevent transmission of HIV and other STIs**.

Conclusion

The need for effective, user-friendly and convenient contraception options for women on DTG/TLD is an opportunity for the public health service to take stock of its existing SRH programme and determine where gaps remain, and opportunities exist to strengthen the integration of HIV and SRH services. The 2012 National Contraception and Fertility Planning Policy and Service Delivery Guidelines[6] provides the framework for how to increase access to and uptake of comprehensive FP and contraception services. Public health should now capitalise on and strengthen the existing blueprint to advance integrated HIV/SRH services for South African women.

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The impact of stockouts on antiretrovirals and other drugs

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Optimisation of current antiretroviral (ARV) medicine regimens is a critical component of supporting efforts to achieve the 90-90-90 treatment targets. As of 22 November 2019, South Africa is including dolutegravir (DTG)-containing regimens in their national protocols, as the preferred first-line option for antiretroviral therapy (ART), particularly the fixed-dose combination (FDC) tenofovir/lamivudine/dolutegravir (TLD). DTG is a much more robust and forgiving medicine, but women of child-bearing age should have options for safe contraceptives and a reliable supply of treatment.

The Stop Stockouts Project (SSP) is a consortium monitoring and reporting on shortages and stockouts of essential medicines, childhood vaccines and chronic medicines in South Africa. The project started in September 2013 with the aim of improving the right to health – including access to timely, acceptable and quality care (including essential medicines) – of citizens reliant on the public healthcare system in South Africa. The project has been monitoring stockouts across all nine provinces and currently the country continues to experience stockouts of second-line ART, contraceptives, isoniazid (INH) and vaccines across provinces. These stockouts have been unresolved since the second half of last year (2018). Therefore, with the TLD rollout, the SSP notes with deep concern the stockouts that may be experienced.

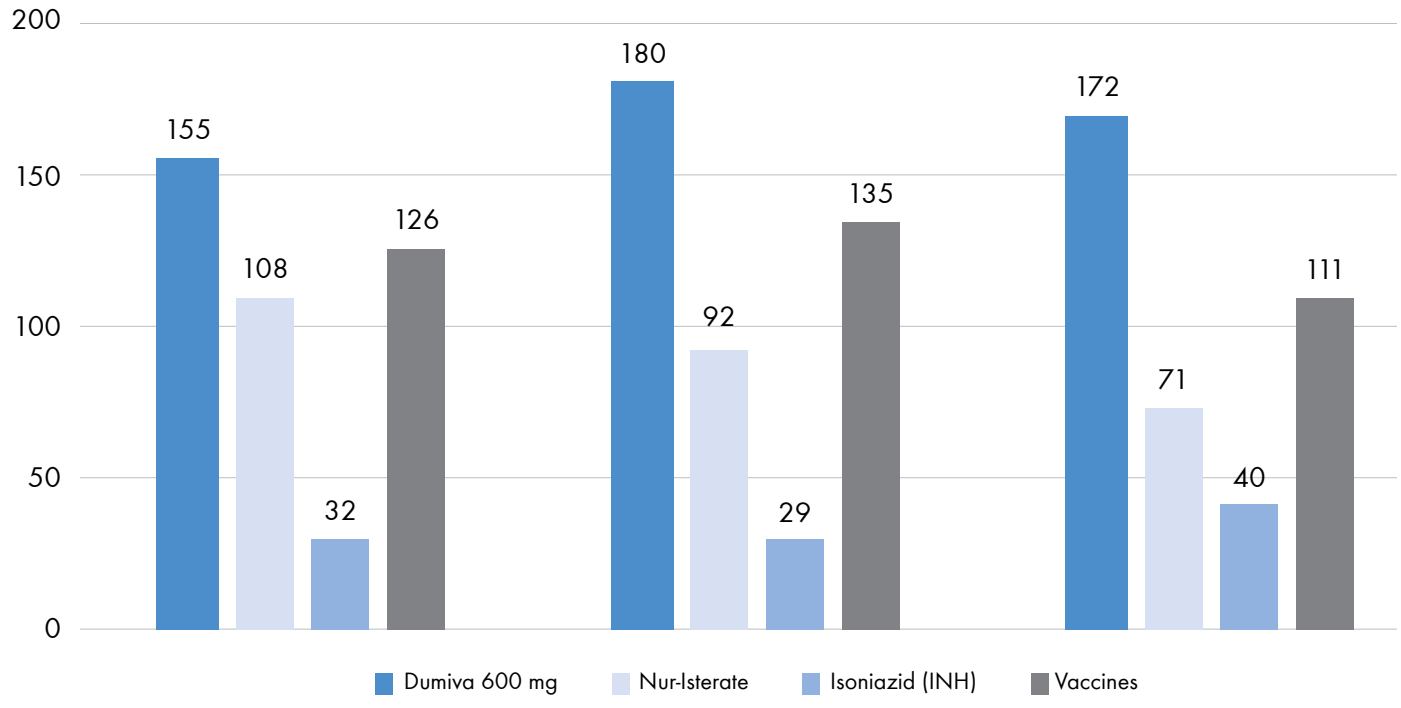

Figure 1: Number of facilities reporting stockouts (1 April 2018 - 28 June 2018)

Figure 1 shows the number of clinics that reported stockouts over the period 1 April to 28 June 2018 where no alternatives existed in other facilities. These clinics, distributed across the country in all nine provinces, had stockouts of Dumiva, Nur-Isterate, INH and vaccines.

Impact of stockouts

- Patients are at risk of defaulting on their treatment due to unavailability of ARVs
- Poor adherence impacts viral suppression, which results in treatment failure
- Patients with high unsuppressed viral loads have the potential to transmit HIV to their partners
- A shortage of ARVs undermines the critical component of supporting efforts to achieve the 90-90-90 treatment targets
- A shortage of contraceptives puts women at risk of unwanted pregnancy
- Children who are not vaccinated will be vulnerable to childhood diseases.

Conclusion

The failure of relevant stakeholders to act swiftly will put scores of patients' lives at risk. There appears to be a deficiency of suppliers of essential medicines, and this may contribute to shortages and possible stockouts. As the National Department of Health gears up to begin the transition from the efavirenz (EFV)-containing first-line ART regimen to a DTG-containing first-line regimen, swift action may minimise treatment failure which results from stockouts.

The SSP urges anyone who has been affected by medicine shortages or stockouts to call their hotline:

Phone, SMS, Whatsapp or send a Please Call Me
Email: report@stockouts.org

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Clinical tips

1. Identify and address possible barriers to linkage to care at the time of HIV diagnosis and explain the entire treatment plan and follow-up visit schedules
2. All patients receiving ART should be considered for IPT and screened for active TB – if any symptoms for active TB, then defer IPT and treat for TB
3. PrEP should be considered for HIV-negative people and those at significant risk of acquiring infection – currently targeting key population groups
4. VL monitoring is at 6 months after initiation, and 12-monthly (count from day of initiation) if undetectable
5. If the VL is 400 - 1 000 copies/ml, then this should prompt adherence counselling and repeat VL testing in 6 months
6. If the patient was previously on ART but has interrupted treatment with no transfer note, perform baseline bloods and reinitiate ART as soon as possible
7. Any threat to ART adherence must be taken seriously to prevent poor health outcomes – address reasons for non-adherence and increase support
8. All HIV-positive children, adolescents and adults, regardless of CD4 count, will be offered ART treatment as soon as the patient is ready
9. Viral blips are transient, low-level VL increases from previous viral suppression; they are never >1 000 copies/ml and follow-up VLs are suppressed again
10. Viral blips can represent laboratory error, laboratory processing artefacts, poor adherence, or transient bursts of HIV replication
11. If the VL is persistently <1 000 copies/ml, then this is low-level viraemia and not a viral blip; if the VL is 400 - 1 000 copies/ml, then further VLs should be performed
12. Patients on ART without VL monitoring are likely to develop treatment failure since the initial warning signs are not picked up early enough
13. Treatment failure is defined by a confirmed VL of >1 000 copies/ml on two measurements taken 2 - 3 months apart
14. Switch to a second-line regimen when two VL measurements have been >1 000 copies/ml taken 2 - 3 months apart with at least 4 weeks of intensified adherence
15. Multiple trials have shown that a sustainably undetectable VL essentially prevents HIV transmission to others
16. Patient readiness and inadequate adherence to the prescribed regimen remain the most common reasons for treatment failure
17. If a couple encounters difficulty in achieving pregnancy, then it is important to involve both and refer them for infertility interventions
18. Universal test and treat (UTT) and improved access to ART provide an important option in HIV-serodifferent couples; U=U (undetectable = untransmissible)
19. Although uncommon, ARV resistance is most likely to occur among those who initiate PrEP with undiagnosed acute HIV infection
20. Disclosure of HIV status should strongly be encouraged, since it has shown to be an important determinant of adherence and patient support
21. Going to a support group for people with HIV is a more reliable way of getting support and can be useful for people feeling vulnerable
22. Implementing support groups as intervention is expected to yield high impact on morbidity and retention in care and moderate impact on mortality
23. In a woman currently taking ART, check the VL on the day of pregnancy confirmation, regardless of when it was performed
24. Male involvement in antenatal and postnatal care has been shown to improve adherence and maternal and infant outcomes
25. Do not delay ART in favour of cotrimoxazole initiation; ideally initiate immediately at the first adherence visit if not done prior to ART.

Abbreviations: ART – antiretroviral therapy; ARV – antiretroviral; CD4 – cluster of differentiation 4; IPT – isoniazid preventive therapy; PrEP – pre-exposure prophylaxis; TB – tuberculosis; U=U – undetectable = untransmissible; UTT – universal test and treat; VL – viral load.

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EMGuidance digital platform

EMGuidance (or Essential Medical Guidance) is a mobile- and web-based medicines and treatment platform for medical professionals. We are pleased to announce that we have partnered with the National Department of Health to launch the 2019 guidelines for antiretroviral therapy (ART) and the prevention of mother-to-child transmission of communicable infections (PMTCT) on the EMGuidance platform.

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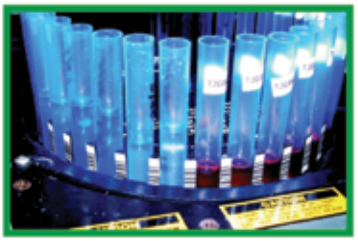

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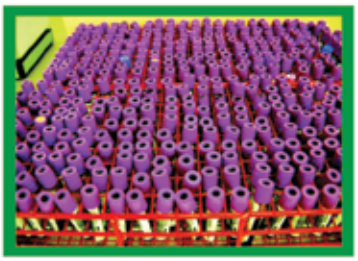
Once you are registered, you will be contacted with your unique number. This number is a security measure to ensure that the results are provided to an authorized user.



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Select option 2 to access laboratory results.

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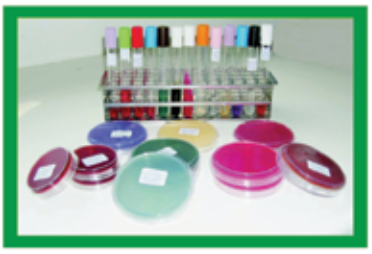
Should the results not be available when you call, you will be provided with a query reference number which must be used when you follow up at a later date to obtain the result.

Once you have a Reference number



Select option 3 to follow up on a reference number
Should the requested results not be available, a query reference number will be provided to you.
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- Post exposure prophylaxis (PEP)
- HIV testing
- Management of HIV in pregnancy & PMTCT
- Drug interactions
- Treatment/prophylaxis of opportunistic infections
- Drug availability
- Adherence support
- Management of tuberculosis
- Antiretroviral Therapy (ART)
  - ~ When to initiate
  - ~ Treatment selection
  - ~ Recommendations for laboratory and clinical monitoring
  - ~ How to interpret and respond to laboratory results
  - ~ Management of adverse events

Who answers the questions?

The centre is staffed by specially-trained pharmacists who share 50 years of drug information experience between them. They have direct access to the latest information databases, reference sources and a team of clinical consultants.

When is this free service available?

The hotline operates from Mondays to Fridays 8:30am - 4:40pm.

SA HIV/TB HOTLINE

DOWNLOAD OUR NEW FREE APP!

ANDROID APP ON Google play

ARV DRUG INFORMATION MONOGRAPHS
TB DRUG INFORMATION MONOGRAPHS
POSTER GUIDELINES
EDL-ANTIRETROVIRAL INTERACTIONS TABLE

MEDICINES INFORMATION CENTRE

Western Cape Government Health

BETTER TOGETHER.

Call us - we will gladly assist you! This service is free

2020 MEMBERSHIP APPLICATION FORM

PROFESSIONAL INFORMATION

Title: ☐ Prof ☐ Dr ☐ Mr ☐ Mrs ☐ Ms **Initials:** _____ **First Name(s):** _____

Surname: _____ **Institution/Organisation:** _____

Profession (check one):

☐ Doctor Generalist ☐ Doctor Specialist ☐ Pharmacist ☐ Professional Nurse ☐ Other: _____

If Doctor Specialist, select speciality:

☐ Cardiology ☐ Clinical Pharmacology ☐ Dermatology ☐ Family Physician ☐ Infectious Diseases ☐ OB GYN ☐ Paediatrics

☐ Physician / Internal Medicine ☐ Psychiatry ☐ Other: _____

Council number (e.g. HPCSA, SANC): _____ **Practice number** (if applicable): _____

Primary Employment affiliation (please chose one):

☐ Clinic ☐ Government (non-clinical) ☐ Hospital ☐ Industry ☐ Non-governmental Organisation (NGO) ☐ Private Practice

☐ Student ☐ University ☐ Other

Professional Activities (write '1' for primary and '2' for secondary):

☐ Administration ☐ Advocacy ☐ Patient care ☐ Programme Management ☐ Research ☐ Sales/Marketing

☐ Teaching/Education ☐ Other

Please enter the year you began treating HIV patients: _____

Please indicate if you have passed a postgraduate diploma on the clinical management of HIV from one of the following institutions:

☐ Colleges of Medicine of South Africa ☐ University of KwaZulu Natal ☐ Other: _____

Year completed: _____ Year completed: _____ Year completed: _____

Professional Associations: ☐ SAMA ☐ IAS ☐ FIDSSA ☐ Other: _____

CONTACT INFORMATION

Postal Address: _____

_____ **Suburb/Town:** _____ **Postal Code:** _____

Province: _____ **Country:** _____

Telephone: _____ **Mobile:** _____

Fax: _____ **Email:** _____

DEMOGRAPHIC INFORMATION

Race/ethnicity: ☐ Black ☐ Coloured ☐ Indian ☐ White ☐ Other: _____

Gender: ☐ Female ☐ Male ☐ Intersex/Transgender **Date of Birth:** ☐☐/☐☐/☐☐☐☐

MEMBERSHIP PREFERENCES

Would you like to receive a posted copy of the Society's magazine for nurses, *HIV Nursing Matters?* (Copies are available free on the Society's website: www.sahivsoc.org) ☐ Yes ☐ No

Would you like to participate in the Society's online membership directory? (Your contact information will be available only to other Society members through the members portal on the Society's website) ☐ Yes ☐ No

How would you like to receive communications from the Society (check all that apply): ☐ SMS ☐ Email

- **Doctors** **R400 per annum**
- **Nurses & Allied Health Professionals** **R300 per annum**
- **Pharma Package** **R14000 per annum**
  includes 10 pharma rep memberships, 2 mailers and 1 social media event / article
- **Organisation (NGO) Package** **R3500 per annum**
  for 10 staff memberships or R6000 per annum for 20 staff memberships

Signed: _____

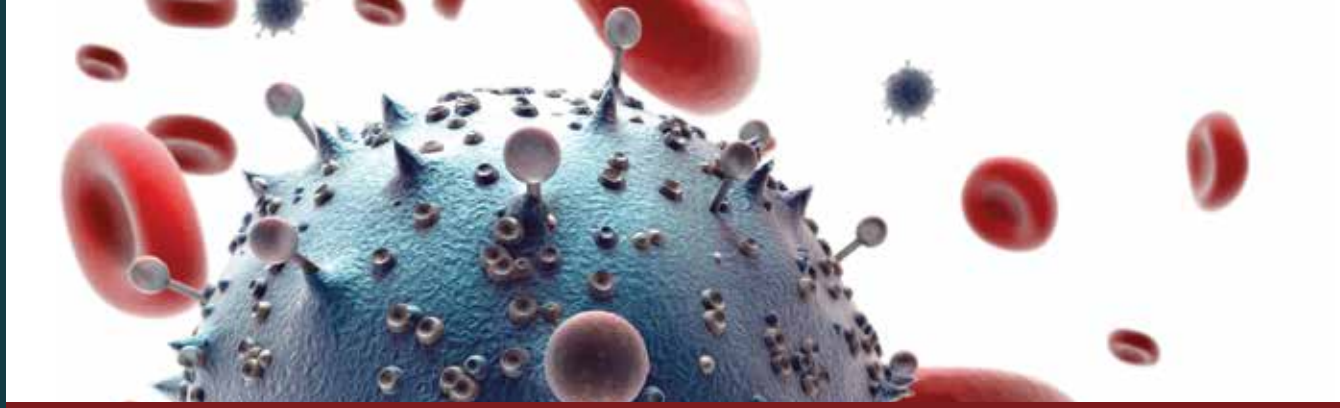
Date: _____

☐ I hereby agree to support the values and mission of the Society; and agree to the membership code of conduct

Method of payment: ☐ Electronic Transfer ☐ Direct Deposit ☐ Post/Cheque ☐ Cash Payment Date: ☐☐/☐☐/☐☐☐☐

Fees are now charged for a calendar year or pro rata according to the date of application. Payments may be made by cheque or electronic transfer payable to: Southern African HIV Clinicians Society, Nedbank Campus Square, Branch Code 158-105, Account No: 1581 048 033. For alternative online payment please go to **http://sahivsoc.org/about/membership-application** and click the "**Pay Now**" button. Please reference your surname and/or membership number on the payment. Please fax or email proof of payment to 011 728 1251 or sahivcs@sahivcs.org or post to: Suite 233, Post Net Killarney, Private Bag x2600, Houghton 2041.

HAVE QUESTIONS? Please contact us: 011 728 7365 / sahivcs@sahivcs.org / www.sahivsoc.org



UNITING NURSES IN HIV CLINICAL EXCELLENCE, BECOME A MEMBER.




Who are we?

We are a member-based Society that promotes quality, comprehensive, evidence-based HIV health care, by:

1. **LEADING • PIONEERING**
   We are a powerful, independent voice within Southern Africa with key representation from the most experienced and respected professionals working in the fight against HIV.

2. **CONNECTING • CONVENING • ENGAGING**
   Through our network of HIV practitioners, we provide a platform for engagement and facilitate learning, camaraderie and clinical consensus.

3. **ADVOCATING • INFLUENCING • SHAPING**
   With our wealth and depth of clinical expertise, we can help health care workers take their practice to a new level. We are constantly improving and expanding our knowledge, and advocating for clinical and scientific best practice.

Member Benefits

Join today and gain instant support from a credible organisation. The Society helps connect you with the best minds in HIV health care. Build your knowledge, advance your profession and make a difference by getting involved now!

- Free online subscription to the *Southern African Journal of HIV Medicine*
- Free quarterly subscription to the Society's e-newsletter, *Transcript*
- E-learning through CPD-accredited clinical case studies and online discussion group forums
- Free tri-annual subscription to *HIV Nursing Matters*
- Weekly SMS clinical tips for nurse members
- Free CPD-accredited continuing education sessions
- Listing in the Society's online HIV provider referral network

SOCIETY CONTACT DETAILS:

Tel: +27 11 728 7365 • **Fax:** +27 11 728 1251
Email: sahivcs@sahivcs.org

Post: Suite 233, Private Bag X2600, PostNet, Killarney, Houghton, 2041

www.sahivsoc.org