South African National Essential Medicine List
Primary Healthcare Medication Review Process
Component: HIV & AIDs

MEDICINE MOTIVATION:

1. **Executive Summary**

Date: 27 July 2021 (second update of initial review of 26 January 2017) – see addendum
Medicine (INN): Dolutegravir
Medicine (ATC): J05AX12
Indication (ICD10 code): B24
Patient population: HIV-infected patients commencing first-line antiretroviral therapy (ART)
Prevalence of HIV infection: South African general population: 13.1%; women in their reproductive ages (15–49 years): 20%; youth aged 15–24:5.5% *(Statistics South Africa, Mid-year population estimates 2018).*
Level of Care: Primary
Prescriber Level: Nursing practitioner or medical doctor
Current standard of care: Efavirenz (EFV) in combination with two nucleoside/nucleotide reverse transcriptase inhibitors (tenofovir + lamivudine/emtricitabine)
Efficacy estimates: (preferably NNT) Viral suppression to <50 copies/mL at 96 weeks, RR 1.12 (95% confidence interval 1.04 to 1.21, I2=0%) of DTG-based vs EFV-based regimens i.e. 376/465 vs 338/469 events of undetectable viral load; ARR 8.79%, NNT 12.
(Rutheford et al, 2016)
Motivator/reviewer name(s): Michelle Moorhouse; Karen Cohen
PTC affiliation: N/A

2. **Name of author(s)/motivator(s)**

Michelle Moorhouse *
Karen Cohen**

3. **Author affiliation and conflict of interest details**

* Wits Reproductive Health and HIV Institute.

Dr Moorhouse has received speaker fees and honoraria from Gilead Sciences, ViiV Healthcare, AbbVie, Cipla and HIV Virology, and has previously received conference sponsorship from Gilead, Merck, Dr Reddy, Cipla and Mylan. Wits RHI is part of optimisation collaborations – grants to improve testing, new drug regimens, linkage to care and has received drug donations for studies. This includes the ADVANCE study (RCT comparing three regimens in patients eligible for first-line ART: DTG/TAF/FTC versus DTG/TDF/FTC versus EFV/TDF/FTC)[i] in which DTG has been donated by ViiV Healthcare and TAF/FTC by Gilead Sciences.

Note: Dr Moorhouse was recused from the decision-making process regarding a recommendation.

** Division of Clinical Pharmacology, Department of Medicine; no conflicts of interest declared.

4. Introduction/ Background

The PHC ERC prepared a technical review of dolutegravir (DTG) in 2017. At that time NEMLC decided not to add DTG to the EML as an option for first line ART, pending availability of further evidence, particularly in pregnant women and patients on concomitant rifampicin. Further evidence is now available, and the NDoH HIV directorate is considering adding DTG to national ART guidelines. The DTG technical review has now been updated to inform NEMLC comment on the proposed ART guidelines and to inform NEMLC decision regarding including DTG on the EML.

Since the START and TEMPRANO studies, which demonstrated that ART should be started irrespective of CD4 count[ii iii], the WHO recommended that everyone infected with HIV should start ART[iv], doubling those eligible for ART, with significant programmatic and financial implications. In September 2016, this recommendation was implemented in South Africa.

While there is evidence of benefit of ART, even at high baseline CD4 counts, for those with earlier stage disease, benefits are modest, and need to be weighed up against the potential harms, including side effects result in poor adherence and resistance, with wider public health consequences[v]. Current first-line ART in SA is a fixed dose combination (FDC) of efavirenz (EFV) with two nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs), usually tenofovir (TDF) with lamivudine (3TC) or emtricitabine (FTC). For those patients in whom EFV is contra-indicated or poorly tolerated, nevirapine (NVP) or boosted lopinavir (LPV/r) are alternatives, depending on the CD4 count of the patient when initiating ART.

Current first-line treatment in South Africa has several challenges:

- **Tolerability:** Current first-line ART has side effects, resulting in non-adherence or discontinuation. Improved safety profiles would keep patients on first-line longer
- **Cost**: The cost of ARVs consumes a significant portion of the programme budget. Current cost is unlikely to decrease significantly[i]
- **Robustness/Resistance:** NNRTI-based regimens are vulnerable to resistance. Data on the number of first-line failures in South Africa are still elusive but a study looking at several programmes suggested just over 2% of patients migrate across to second-line annually (a larger percentage are lost to follow-up)[vi]. Finding a first-line regimen that is more robust and durable will limit transition to expensive and less well tolerated second- and third-line regimens
- **Pill size:** The currently used fixed dose combinations are large pills which some patients find difficult to swallow. The size of the pill has other effects as well, such as packaging and storage space requirements[i].

Dolutegravir (DTG), an integrase inhibitor, has been shown to be efficacious when used in both salvage and first-line ART. We reviewed the evidence forthe efficacy and safety of DTG compared with EFV, the current standard of care. We also summarised the evidence for its use in pregnancy, and with concomitant TB treatment.

5. Purpose/Objective i.e. PICO question[comparison to current standard of care for a specific indication]:

-P *(patient/population):* Adult patients commencing first-line ART
-I *(intervention):* Dolutegravir plus two nucleoside/nucleotide reverse transcriptase inhibitors (N (t) RTIs)
-C *(comparator):* Efavirenz plus two N (t) RTIs
-O *(outcome):*1. Efficacy (virological suppression) 2. Adverse effects 3. Neuropsychiatric adverse effects

Question: Amongst adult patients on first-line combination ART, is the integrase inhibitor dolutegravir more efficacious and/or better tolerated than the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz?

6. **Methods:**
   a. **Data** sources: PubMed

   b. **Search strategy**
   ("dolutegravir"[MeSH Terms] OR "dolutegravir"[All Fields]) AND ("efavirenz"[MeSH Terms] OR "efavirenz"[All Fields]).

We ran the search on 20 January 2017 using the search terms above. We identified 63 abstracts, from which we selected 12 for further review(Hill, Mitchell et al. 2018).

These 12 abstracts describe the following:

- Systematic reviews (6 publications)[vii] [viii] [ix] [x] [xi] [xii]
- RCT (6 publications) [xiii] [xiv] [xv] [xvi] [xvii] [xviii]

In addition, we ran two searches for information on use in two patient groups: patients requiring concomitant TB treatment, and DTG in pregnant women.

- We ran a search for information regarding use of DTG with rifampicin-containing tuberculosis (TB) treatment. (In our setting concomitant TB treatment and ART are frequently required):
  - Search terms “dolutegravir” AND “(rifampicin OR rifampin.). This search identified six abstracts, of which one was relevant to our question: we identified one phase 1 healthy volunteer pharmacokinetic study, regarding the interaction between DTG and rifampicin (and rifabutin) [xix].
- We ran a search on DTG in pregnancy:
  - We conducted a search in Pubmed using the terms “dolutegravir” AND “pregnancy”. We retrieved 12 abstracts, none of which included data on safety of dolutegravir in pregnancy.
  - We also reviewed information in the antiretroviral pregnancy registry to date [xx].

<u>Update February 2019</u>

We ran the same searches above in Pubmed on 2 Feb 2019 and reviewed the abstracts with a 6 month overlap (i.e. June 2016 to 2 Feb 2019).

- For the main search identified 99 abstracts. We selected two abstracts not previously retrieved for review (Fettiplace, Stainsby et al. 2017[xxi], Hill, Mitchell et al. 2018[xxii])

<u>Pregnancy:</u>

- We used the same search terms as the previous search. We identified 42 abstracts. We retrieved seven for further review (Mounce, Pontiggia et al. 2017[xxiii], Bornhede, Soeria-Atmadja et al. 2018[xxiv], Grayhack, Sheth et al. 2018[xxv], Hill, Clayden et al. 2018[xxvi], Mulligan, Best et al. 2018[xxvii], Zash, Jacobson et al.

2018[xxviii], Zash, Makhema et al. 2018[xxix]). In addition, we reviewed the most recent version of the antiretroviral pregnancy registry (Committee 2018[xxx])

Tuberculosis

- We used the same search terms as the previous search. We identified 12 abstracts. We retrieved 2 for further review (Cevik and McGann 2018[xxxi], Pena, Chueca et al. 2019[xxxii]). In addition, we reviewed a CROI conference presentation(Dooley, Kaplan et al. 2018[xxxiii])

7. Summary of included and excluded studies

a. Excluded studies:

Author, date	***Type of study***	***Reason for exclusion***
You J, 2016 [viii]	Systematic review and meta-analysis of RCTs, non-RCT clinical trials, case-control studies, cohort studies, case reports (n > 10)	Compares various integrase inhibitors (InSTIs)(EFV is an NNRTI)
Jiang J, 2016 [xii]	Meta-analysis of RCTs	Compares various InSTIs (EFV is a NNRTI)
Raffi F, 2015 [viii]	Cross comparison of key subpopulations across different DTG studies in ARV-naïve subjects	Third drug used differs in each study – the studies included use EFV (SINGLE), raltegravir (SPRING-2) or darunavir (FLAMINGO). RAL and DRV not relevant to this medicine review and PICO

b. Included studies

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Kanters S, 2016 [vii]	Systematic review and network meta-analysis of RCTs	31 404 patients	ART-naive adults and adolescents (aged 12 years or older)	154 treatment groups, pertaining to 16 'third drugs' incl EFV and DTG	Viral suppression, mortality, AIDS-defining illnesses, discontinuations, discontinuations due to adverse events, and serious adverse events	Effect [OR (95% CI)] of DTG relative to EFV is 1·87(1·34–2·64)for viral suppression at 48 weeks and 1·90(1·40–2·59)at 96 weeks; 0·26(0·14–0·47) for treatment discontinuations; 0·84(0·49–1·43) for treatment emergent SAEs (NSS)	DTG was significantly better than EFV at 48 weeks and at96 weeks. InSTIs tended to be protective of discontinuations due to adverse events relative to standard-dose EFV. The most protective effect relative to EFV was that of DTG, followed by low-dose EFV.
Rutherford GW, 2016 [ix]	Systematic review and meta-analysis of RCTs	465 patients on DTG and 469 on EFV	ART-naïve adults	DTG-based regimens compared to EFV-based regimens (first-line)	Viral suppression to < 50 copies/mL at 48, 96 and 144 weeks	RR = 1.10(95% CI 1.04–1.16) at 48 weeks; RR = 1.12(95% CI1.04–1.21)at 96 weeks and RR = 1.13(95% CI 1.02–1.24) at 144 weeks	DTG-containing regimens were superior to EFV-containing regimens. No difference in risk of death between the two regimens (RR = 0.26, 95% CI 0.01–4.20). One study reported discontinuation of initial ART regimen due to AEs or death at 96 and 144 weeks. At both time points, the DTG regimens were superior to the EFV regimens (RR = 0.27, 95%CI 0.15–0.50 at 96 weeks and RR = 0.28, 95% CI 0.16–0.48 at 144 weeks). Risk of SAEs was similar in each regimen at 96 weeks (RR = 1.15, 95% CI 0.80–1.63) and 144 weeks (RR = 0.93, 95% CI 0.68–1.29).
Ford N, 2015 [x]	Systematic review of RCTs and quasi	8466 patients on EFV and	ARV-naïve HIV-infected adults	EFV-based ART versus non-EFV	Drug discontinuation as a result of an	RR of discontinuation was greater for	No statistically significant difference in risk of SAEs. Absolute risk of severe lab AEs was higher comparing EFV with

	randomised trials	9631 on comparator drug	(children included in theory but no paed studies met inclusion criteria)	based ART (NVP in 9; ritonavir-boosted lopinavir in 7, rilpivirine in 4, DTG in 2)	adverse event (AE)	EFV compared to DTG(RR: 4.3, 95% CI: 2.2-8.3) but absolute risks were not significantly different	DTG (2.8, 95% CI: 0.2 to 5.3), but relative differences were not significant. Severe neuropsychiatric AEs were more common for EFV compared to DTG (RR: 16.7, 95% CI: 2.0 to 137.8; RD: 3.0,95% CI: 1.4 to 4.6)
Patel DA, 2014 [xi]	Systematic review and network meta-analysis of phase 3/4 RCTs	17 000	ART-naive patients with HIV-1infection; aged ≥ 13 years	DTG, EFV, ATV/r, DRV/r, EVG/c, LPV/r, RAL, or RPV	Not clearly stated. Virologic suppression <50 copies/mL	Mean odds of virologic suppression were significantly higher for DTG than EFV. OR = 1.85 (1.34, 2.50)	Virologic suppression = HIV RNA<50 copies/mL. DTG had significantly lower associated TC, HDL, and LDL increases than EFV. Odds of experiencing an AE were significantly lower for DTG Compared to EFV:0.57 (0.38, 0.81). Odds of discontinuation due to AEs were lower for DTG relative to EFV: 0.26 (0.14, 0.43).
SPRING-1 Van Lunzen J, 2012 [xiii]; Stellbrink H, 2013 [xvii]	RCT (phase 2b)	205	ARV-naïve HIV-infected adults	DTG 10/25/50 mg versus EFV 600 mg (in combination with TDF/FTC orABC/3TC)	Proportion with VL < 50 copies/mL at week 16	Week 16 response rates were 93% (144/155) for all doses of DTG (with little difference between dose groups) and 60% (30/50) for EFV(no CI/p-values provided)	Week 48 response rates were 90% (139/155) for all doses of DTG and 82% (41/50) for EFV (no CI/p-values provided).At week 96, the proportion with VL < 50 copies/mL was 79, 78, and 88% for DTG 10, 25, and 50 mg, respectively, compared with 72% for EFV. 6 participants withdrew due to AEs: two on DTG (grade 2 dyspepsia in the 25 mg group and grade 4 Burkitt's lymphoma in the 50 mg group) and 4on EFV(one each of drug intolerance, drug hypersensitivity, abnormal dreams, and suicide attempt).At 96 weeks, fewer of DTG group withdrew due to AEs (3%) compared with EFV group (10%). No SAEs due to DTG. More in EFV group had drug-related AEs of moderate or higher severity (10 [20%]

							/50) than those in the combined DTG groups (13 [8%] /155). Across all DTG doses, but not EFV, small non-progressive mean increases in creatinine concentrations from baseline at week 1 remained constant to about week 16 (0.10 mg/dL [SD 0.108] DTG overall vs 0.01 [0.079] EFV; p<0.0001 with *post-hoc* t test); values gradually returned to baseline over 48 weeks. The increases happened across both NRTI backbones. 4 participants who received DTG 25 mg had treatment-emergent grade 1 increases in creatinine concentration, and one had a grade 2 increase; no other graded creatinine abnormalities. More participants in the DTG groups (21 participants; 14%) than in the EFV group (1; 2%) had treatment-emergent increases in dipstick urine protein (≥1), which were neither time nor dose dependent.
SINGLE study Walmsley S, 2013 [xiv]; Walmsley S, 2015 [xv]	RCT phase 3 Double blind, double dummy	833	ARV-naïve HIV-infected adults	DTG 50 mg with ABC/3TC versus EFV/TDF/FTC	Proportion with VL < 50 copies/mL at week 48	At week 48, the proportion with VL < 50 copies/mL significantly higher in DTG arm than in EFV arm: 88% vs. 81%, P = 0.003.This met criterion for superiority	At 144 weeks, 71% on DTG and 63% on EFV maintained VL < 50 copies/mL. DTG arm had shorter median time to viral suppression than the EFV arm (28 vs. 84 days, P<0.001). Discontinuations due to AEs on DTG less than EFV 3% vs. 11% at 144 weeks. Rash and neuropsychiatric events (including abnormal dreams, anxiety, dizziness, and somnolence) significantly more common with EFV, whereas insomnia reported more frequently with DTG.

							No participants on DTG developed integrase or nucleoside resistance through 144 weeks.
Sub analysis of SINGLE [xvi]	RCT phase 3	833	ARV-naïve HIV-infected adults	DTG 50 mg with ABC/3TC versus EFV/TDF/FTC	Sub analysis assessed long-term bone turnover biomarker effects over144 weeks	Relative to baseline, CTx, osteocalcin, BSAP, and P1NP increased; vitamin D decreased in both groups at weeks48, 96, and 144. Changes from baseline typically peaked at weeks 48 or 96 and for the four analytes, excl vitamin D, with the EFV/FTC/TDF group having significantly greater changes from baseline at all time points.	The sub analysis evaluated vitamin D serum levels and bone turnover markers (BTMs), including type 1 collagen cross-linked C-telopeptide(CTx), osteocalcin, bone-specific alkaline phosphatase (BSAP), and procollagentype 1 N-terminal propeptide (P1NP), at baseline and weeks 48, 96, and 144. Changes described are likely attributable to the different NRTI backbones used in the two arms of the study, and unlikely to be related to the third drugs used in either arm, namely DTG or EFV.
Risk of CVS or CNS AEs and IRIS: Meta-analysis of randomised trials(Hill, Mitchell et al. 2018 [xxii])	Systematic review of RCTs both non-switch and switching	8 published trials + 1 trial presented at IAS 20187	Patients on DTG containing ART dose 50mg	Control arm on other ARV	Number of "key adverse events and SAES. cardiac disorders, suicide-related disorders, insomnia, IRIS	<u>Serious cardiac events</u> :(SINGLE to 144 week) DTG 4/414 vs EFV 2/419 <u>Suicidality SAES</u> (SINGLE and SPRING-1) DTG 5/465 (1.1%) vs EFV 6/469(1.3%) DTG vs any other ARV RR1.21 (0.59 to 2.47) <u>Insomnia all grades</u> DTG 165/2716	No break down grades of insomnia RCTS excluded CDC stage C patients who are at more risk of IRIS Limitation-quality of AE data in published papers

						(6.1%) vs any other ARV 124/2727 (4.5%) RR 1.30 (1.03 to 1.63) IRIS: few events and no difference SINGLE DTG 1/414 vs EFV 2/419 (studies excluded CDC grade C)	
Fettiplace et al. (Fettiplace, Stainsby et al. 2017 [xxi])	Review of psychiatric symptoms reported in 5 phase 3 clinical trials, the OPERA observational cohort, and spontaneous reports. Industry funded (ViiV). (Only RCT data is presented in this table)	5 phase 3 RCTs, of which one DTG vs EFV	ARV-naïve HIV-infected adults	Control arm on other ARV	RCTS:"Psychiatric symptoms" (PS): Insomnia, anxiety, depression and suicidality ("Company safety physician"grouped related MedDRA terms)	More EFV treated patients with withdrawal due to PS than other drugs EFV 15/419 (4%) vs DTB 4/1672 (0.2%) SINGLE study- more insomnia with DTG than EFv: 71/414 vs 52/419; 3 vs 0 Gr3/4, 1 vs 4 withdraw as a result	

8. Evidence synthesis

Efficacy

The SINGLE trial compared DTG/abacavir (ABC)/3TC to EFV/TDF/FTC in ART-naïve adults [xiv]. At week 48, the DTG arm was superior to the EFV arm: 88% of participants in the DTG arm had HIV viral load <50 copies/mL versus 81% in the EFV arm. The difference was driven by the superior tolerability of the DTG arm, with 2% on DTG vs 10% on EFV discontinuing study drug due to an adverse event [xiv]. A systematic review of RCTs showed that DTG was superior to EFV in terms of viral suppression to <50 copies/mL:RR = 1.10(95% CI 1.04–1.16) at 48 weeks; RR = 1.12(95% CI1.04–1.21) at 96 weeks and RR = 1.13 (95% CI 1.02–1.24) at 144 weeks [ix].

Tolerability

A systematic review including 42 randomised control trials showed that the relative risk for discontinuations due to adverse effects was higher for EFV compared with most other first-line options, including DTG [x]. The systematic review demonstrated that neuropsychiatric adverse events were common with EFV, affecting close to 30% of patients (29.6%; 95% CI: 21.9% to 37.3%), of which 6.1% (95% CI: 4.3% to 7.9%) were severe. Dizziness and abnormal dreams were the most commonly reported neuropsychiatric adverse events experienced by patients treated with EFV [x]. Notably, most of the studies included were conducted among predominantly white populations and therefore would not account for differences in metabolism of EFV in African populations, which may result in more frequent neuropsychiatric adverse effects. There is a high prevalence of EFV slow metaboliser genotypes in South Africa (17% versus 3% in Caucasian groups)[xxxiv].

A systematic review compared reported cardiovascular and central nervous adverse events, as well as incidence of the immune reconstitution inflammatory syndrome (IRIS), in patients initiating DTG-containing ART and patients switching to DTG-containing ART (Hill, Mitchell et al. 2018 [xxii]).

There was significantly more insomnia in patients treated with DTG vs efavirenz. There was no significant difference in cardiovascular events (rare events, therefore underpowered to show difference). No difference in suicidality when compared with efavirenz; 1% of participants in both arms. There was no difference in incidence of IRIS, but exclusion of patients with more advanced HIV disease (CDC stage C) from the phase 3 studies is a limitation, as this is the group at highest risk of IRIS (see table of included studies).

A manufacturer funded review of psychiatric symptoms in patients receiving DTG versus non-DTG containing regimens found that more patients on efavirenz withdrew from phase 3 studies because of psychiatric symptoms than those on regimens with DTG or other drug as backbone (Fettiplace, Stainsby et al. 2017 [xxi]).

DTG in pregnancy

There was very little data on use of DTG at the time when this medicine review was first compiled. Since then, data from a prospective cohort study have been published which suggest increased risk of neural tube defects in infants born to women taking DTG at the time of conception, relative to other antiretrovirals. This has led WHO to recommend that DTG be avoided in women of child-bearing potential who are not on reliable contraception.

Preclinical toxicity studies for DTG in pregnancy did not reveal any significant concerns, and DTG was classified as FDA pregnancy category B, prior to the removal of this classification from use.

The Botswana cohort study prospectively captured birth outcomes at 8 hospitals from 2014. Botswana moved to first-line use of DTG in 2016. The risk period for neural tube defects is the first 28 days post-conception. The Botswana group analysed outcomes in women commencing DTG or non-DTG containing-ART prior to conception, and found a higher prevalence of neural tube defects in those exposed to DTG: 4/426 (0.94%) versus 14/11300 (0.12%). Defects in the DTG group were anencephaly, encephalocele, myelomeningocele with undescended testes, and iniencephaly with a major limb defect. None of the 4 on DTG were epileptic or diabetic, none received folate supplementation. At the time of the first analysis, there were no neural tube defects in 2812 women who started DTG during pregnancy. There were neural tube defects in 61 of 66057 (0.09%) infants born to HIV negative women (Zash, Makhema et al. 2018 [xxix]). This is a safety signal of concern.

The investigators presented an updated analysis at the AIDS conference 2018, at which time there had been 2 further neural tube defects: one myelomeningocele in an infant exposed to DTG starting in the 7th week of pregnancy, and one in infant with an HIV negative mother. Updated prevalence in the group with DTG exposure at the time of conception is 4/596 (0.67%, 95%CI 0.26% to 1.7%)(Zash, Holmes et al. 2018[xxxv]). The next planned analysis is March 2019.

In another analysis in the same cohort the Botswana group compared birth outcomes between 1729 women who initiated DTG during pregnancy and 4593 who initiated efavirenz based ART; median gestational age at ART initiation 19 weeks (IQR 14 to 25) and 21 (IQR 16 to 27) respectively. Risk of adverse outcome (stillbirth, preterm <37wk, small for gestational age <10th percentile, neonatal death) and severe adverse outcome (stillbirth, neonatal death, very preterm <32 wk.) were similar: DTG versus efavirenz 33.2% vs 35.5%, aRR 0.95 (95% CI 0.88 to 1.03) and 10.7% vs 11.3% aRR 0.94 (95% CI 0.81 to 1.11) respectively. There were no differences in those individual outcomes. This study is limited in that data on congenital anomalies is based on surface examination at birth, with results for 675 first trimester exposures only (280 exposures to DTG and 395 to efavirenz); they reported one major congenital anomaly (skeletal dysplasia in an efavirenz-exposed infant) and six cases of postaxial polydactyly type B (Zash, Jacobson et al. 2018 [xxviii]).

In registration trials and Compassionate Use programmes, among 38 pregnancies, 1 congenital anomaly, 18 live births without any anomalies, 9 elective terminations without any anomalies, 13 spontaneous

abortions without any anomalies, and 3 ectopic pregnancies were described. In post marketing surveillance, 74 pregnancies were reported as of 16 January 2016, with 18 live births without any anomalies, 2 live births with congenital anomalies, 4 spontaneous abortions without anomaly, 1 spontaneous abortion with anomaly, 1 stillbirth without anomaly and 39 pregnancies ongoing or lost to follow-up[xxxvi]. In the 2018 Antiretroviral pregnancy registry update, no neural tube defects had been observed in 688 periconception integrase stand transferase inhibitor (InSTI) exposures reported to the registry; this includes 201 DTG exposures (Committee 2018 [xxx]). To date there have been 401 DTG exposures reported and 12 defects: in 6 of 201 patients with exposure at conception, 2 of 61 with first trimester exposure, and 4 of 139 with 2nd/3rd trimester exposure. The current estimate of prevalence of birth defects with first trimester DTG exposure is 3.5% (95% CI 1.5 to 6.8) (Committee 2018 [xxx]).

A study from IMPAACT 1026 of pharmacokinetics of DTG in pregnancy (presented at CROI in 2016, and now published) in 29 mother-infant pairs, reported seven infant abnormalities at birth: total anomalous pulmonary venous return (1 case, mother started DTG at 16 weeks, assessed as unrelated to drug exposure); renal anomalies in 2 infants which were both assessed as possibly related to drug exposure (1 isolated renal cyst and 1 multicystic dysplastic kidney); congenital chin tremor (1 case) which resolved; congenital filum terminale lipoma (1 case); 2 vessel umbilical cord (1 case); supernumerary digit (1 case) (Mulligan, Best et al. 2018 [xxvii]).

A systematic review of studies reporting birth outcomes and congenital anomalies in DTG-exposed pregnancies included 1200 pregnancies with DTG exposed pregnancies and compared these to controls from 5 historical studies. The largest contributor of DTG exposures to this systematic review was the Botswana cohort; the systematic review included data from a conference proceeding for this cohort. (Those data were later published (Zash, Jacobson et al. 2018 [xxviii])). There was no difference in pregnancy outcomes (stillbirth, preterm birth (<37 wk.), or small for gestation age between DTG exposed pregnancies and historical controls. Percentage with congenital anomalies ranged widely, between 0% in Botswana study (n=845) and the IMPAACT P1026 study- the systematic review reports a prevalence of 13.3% in this study based on the conference abstract; in the peer reviewed publication 7/29 (24%) has defects, of which 2 were thought to be possibly caused by DTG as described above (Mulligan, Best et al. 2018 [xxvii]).

A retrospective cohort analysis from 2 urban clinics in the USA reported outcomes in 66 DTG exposed pregnancies, of which 57 delivered. There were 2 birth defects (non-immune hydrops fetalis and a cardiac defect: endocardial fibroelastosis versus ventricular septal defect); 31.6 were born prematurely and 15.8% were small for gestational age (Grayhack, Sheth et al. 2018 [xxv]). A small retrospective cohort analysis of 36 DTG exposed pregnancies (14 commenced DTG before pregnancy and 22 during pregnancy) in Stockholm reported 4 early spontaneous abortions, 1 late termination and 1 loss to follow up. There was 1 preterm delivery for maternal indication, and no malformations (Bornhede, Soeria-Atmadja et al. 2018 [xxiv]). A very small retrospective cohort study compared 7 patients with InSTI exposure to 14 patients taking protease inhibitors and found similar outcomes; this study only included one patient exposed to DTG and outcomes are not disaggregated by drug (Mounce, Pontiggia et al. 2017 [xxiii]).

Background prevalence of birth defects in South Africa and risks of birth defects with efavirenz

Birth defect prevalence in South Africa was 20 per 1000 live births (2%) in the 2000 South African survey[xxxvii] and a recently established prospective pregnancy registry in KwaZulu Natal found a prevalence of 0.5% [xxxviii].

There were previously concerns about efavirenz exposure during pregnancy, in particular regarding neurodevelopmental defects but data on efavirenz exposure in pregnancy has not shown increased prevalence of birth defects with efavirenz exposure *in utero*. In a systematic review of observational cohort studies (16 studies; 1256 efavirenz-exposed live births) incidence of overall birth defects in infants with first trimester efavirenz exposure was 2.9% (95% confidence interval 2.1 to 4%). One neural tube defect was seen with first trimester efavirenz exposure, giving a prevalence of 0.08% (95% CI 0.002-0.44%). Relative risk of birth defect in efavirenz exposed women compared with those on other regimens was 0.87 (95% confidence interval 0.61 to 1.24)[xxxix].

Rifampicin-containing tuberculosis treatment

DTG metabolism (primarily by UGT1A1 with CYP3A as minor route) is induced by concomitant rifampicin. In a phase 1 pharmacokinetic drug interaction conducted in healthy volunteers (n=12) DTG concentrations were similar when dosed at 50mg daily without rifampicin and at 50 mg 12 hourly with rifampicin 600mg daily: geometric mean ratio (GMR) for the 24-hour area under the time-concentration curve (AUC_{0-24}) was 1.33 [90% confidence interval (CI): 1.14 to 1.53], and the GMR for the trough (C_{tau}) was 1.22 (90% CI: 1.01 to 1.48) [xix]. Based on this pharmacokinetic study, 12 hourly dosing of DTG is recommended with rifampicin-based TB treatment [xix].

An interim analysis of a trial which randomised ARV naïve patients on rifampicin-containing TB treatment commencing ART to efavirenz (44 patients) or DTG 50mg 12 hourly (69 patients) found that 39/44 (89%) and 56/69 (81%) respectively had VL<50 copies/mL at 24 weeks (Dooley, Kaplan et al. 2018). DTG 50 mg 12 hourly was well tolerated. There were 2 discontinuations for adverse events, both on efavirenz. This RCT was presented at a conference (CROI 2018 [xxxiii]) and has not yet been published in a peer-reviewed journal. A case series of 10 patients treated with DTG 50 mg 12 hourly over 3 years in the UK reported virological suppression at 24 weeks of 9/10, and no severe side effects (Cevik and McGann 2018 [xxxi]). There was a case report of subtherapeutic DTG concentrations, virological failure, and emergence of virological resistance in a woman treated with rifampicin (for a staphylococcal infection) and commenced on DTG-containing ART, despite 12 hourly DTG dosing and directly observed medicine intake (Pena, Chueca et al. 2019 [xxxii]).

9. Other potential considerations

Barrier to resistance

DTG appears to have a high resistance barrier, with no cases of DTG resistance documented in ARV-naive patients in high-income countries where the drug has been used for over three years. Switching to DTG-based first-line ART might limit the number of patients transitioning to more expensive, less tolerable and less convenient second-line regimens, resulting in direct and indirect cost savings.

Renal function effects

DTG inhibits tubular creatinine excretion resulting in modest plasma creatinine elevations and corresponding reductions in creatinine clearance/eGFR. These changes typically manifest within 2–4 weeks and are non-progressive with no associated with haematuria, proteinuria or glycosuria. This change in eGFR does not reflect clinically significant kidney injury [xl]. However this might need to be taken into account in renal function monitoring guidelines especially if DTG is used in combination with tenofovir.

Potential cost savings

DTG requires a smaller dose than EFV (50 mg versus 600 mg). Low dose drugs require smaller amounts of Active Pharmaceutical Ingredients (API), which lowers manufacturers' costs. Moving from EFV-based first-line to DTG could result in significant cost savings once volumes are met [i].

Drug interactions

There are interactions between dolutegravir and other medicines. The interaction with rifampicin is dealt with in this medicine review, above. There are other clinically relevant drug interactions e.g. with anticonvulsants (phenytoin, phenobarbitone, carbamazepine, valproate), metformin, aluminium and magnesium containing antacids, calcium supplements, iron supplements.

For drug interactions and recommendations regarding implications for management, please refer to the following:

1. University of Liverpool drug interactions website: https://www.hiv-druginteractions.org/checker
2. The Medicines Information Center ARV/EML Drug interaction booklet.

10. Proposed DTG-containing antiretroviral regimens - refer to Annexure A.

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?
Confident [x] Not confident [ ] Uncertain [ ]</td><td>See evidence synthesis table</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?
Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td></td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [ ] No [x]

List the members of the group.

List specific exclusion from the group:</td><td>Rationale for therapeutic alternatives included:

References:

Rationale for exclusion from the group:

References:</td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [ ] Major [ ] Uncertain [x]

Is the option acceptable to key stakeholders?
Yes [x] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [X]</td><td>Price of medicines/ month:
<table><tr><th>Medicine</th><th>Price (R)</th></tr><tr><td>DTG (50mg)+ABC (600mg)+3TC (300mg), 30 tabs</td><td>R 507.04*</td></tr><tr><td>DTG (50mg), 30 tabs</td><td>R 423.46**</td></tr><tr><td>EFV (600mg), 28 tabs</td><td>R 49.36**</td></tr><tr><td>EFV (600mg)+FTC (200mg)+TDF (200 mg), 28 tabs</td><td>R 125.34**</td></tr><tr><td>DTG (50mg)+3TC (300mg)+TDF (200 mg), 28 tabs</td><td>R 85.03***</td></tr></table>*SEP Database 21 Dec 2018 - currently MCC registered products (average price)
Note: DTG is not currently listed on the MSH International Medical Products Price Guide. http://mshpriceguide.org/en/home/
**Contract circular HP13-2015ARV (weighted average price)
***Contract circular RT71-2019, wef 1 July2019 (weighted average price)

Additional resources:
Venter WDF, Kaiser B, Pillay Y, Conradie F, Gomez GB, Clayden P, Matsolo M, Amole C, Rutter L, Abdullah F, Abrams EJ, Casas CP, Barnhart M, Pillay A, Pozniak A, Hill A, Fairlie L, Boffito M, Moorhouse M, Chersich M, Seranata C, Quevedo J, Loots G. Cutting the cost of South African antiretroviral therapy using newer, safer drugs. SAMJ 2017;107(1):28-30.</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [ ] No [x] Uncertain [ ]</td><td></td></tr>
</table>

FEASIBILITY	Is the implementation of this recommendation feasible? Yes [x] No [ ] Uncertain [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[ ]	[ ]	[ ]	[X]	[ ]

Recommendation: After the first iteration of this review, the Primary Healthcare expert review committee (ERC) recommendation was as follows:
Based on the appraisal of the evidence presented in this technical review, the Primary Healthcare ERC recommends that dolutegravir be introduced into the first-line antiretroviral regimen (in combination with 2 N(t)RTIs) for HIV-infected adult patients commencing ART.
However, in response to the neural tube defect signal, DTG is not recommended for use in early pregnancy and DTG should be avoided in women of child-bearing potential who are not on reliable contraception.
Patients requiring concomitant rifampicin-containing TB therapy would require DTG dose adjustment. Alternatively switching to efavirenz-based ART for the duration of the TB therapy could be considered.
Rationale: Evidence of superior efficacy and potenitally superior barrier to resistance of dolutegravir compared with efavirenz; though there is limited evidence for use in pregnancy. Pharmacokinetic data indicate dose adjustment is necessary with concomitant rifampicin (rifampicin is a strong inducer of UGTIA3 and CYP3A4, and reduces DTG concentrations).

Level of Evidence: I Systematic review, RCT

NEMLC MEETING OF 21 FEBRUARY 2019:

- NEMLC accepted the above-mentioned reccomendation at the meeting of 21 February 2019, noting the caution to avoid DTG in women of childbearing potential who are not on reliable contraception.
- NEMLC recommended that respective DTG drug-drug interactions would require to be appropiately documented (probably as guidance in the STGs).

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
[ ]	[x]	[ ]

VEN status:

Vital	Essential	Necessary
[ ]	[X]	[ ]

Monitoring and evaluation considerations

Research priorities: Clinical outcomes with TB treatment and in pregnancy

ANNEXURE A

Potential DTG-containing regimens

A FDC (fixed dose combination) would be preferred. Regimen options include:

1. DTG + TDF + FTC
2. DTG + TDF + 3TC
3. DTG + ABC + 3TC
1. DTG + TAF* + FTC
2. DTG + TAF* + 3TC

*not yet approved by the Medicines Control Council, South Africa

Abbreviations

DTG	Dolutegravir
TDF	Tenofovir disoproxil fumarate
FTC	Emtricitabine
3TC	Lamivudine
ABC	Abacavir
TAF	Tenofovir alafenamide fumarate

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South African National Essential Medicine List
Primary Healthcare and Adult Hospital Level Medication Review Process
Component: HIV and AIDS

ADDENDUM

Title: Initiating dolutegravir-containing antiretroviral therapy in patients receiving rifampicin-containing TB treatment

Date: 21 July 2021

Reviewer: Karen Cohen

Affiliation and declaration of interests: KC (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town) has no interests to declare with respect to dolutegravir.

Background: Dolutegravir (DTG) in people living with HIV and AIDs (PLWHA) commencing antiretroviral therapy was reviewed in January 2017, and the review updated in February 2019. This document is an addendum to the 2019 medicine review update, focussing on initiation of DTG in patients receiving rifampicin-containing TB treatment.

Dolutegravir-rifampicin interaction: Dolutegravir (DTG) metabolism is induced by concomitant rifampicin. In a phase 1 pharmacokinetic drug interaction conducted in healthy volunteers (n=12) DTG concentrations were similar when dosed at 50mg daily without rifampicin and at 50 mg 12 hourly with rifampicin 600mg daily: geometric mean ratio (GMR) for the 24-hour area under the time-concentration curve (AUC_{0-24}) 1.33 [90% confidence interval (CI): 1.14 to 1.53], GMR for the trough (C_{tau}) 1.22 (90% CI: 1.01 to 1.48)[1]. Based on this pharmacokinetic study, which was included in the 2019 review update, 12 hourly dosing of DTG is recommended with rifampicin-based TB treatment in the current Essential Medicines List (EML) standard treatment guidelines (STGs), for patients who start rifampicin-containing TB treatment when already taking DTG-containing ART. However, for patients starting antiretroviral therapy during TB treatment, efavirenz-containing ART was recommended for the duration of TB treatment, with switch to DTG on completion of TB treatment. The rationale for that recommendation was that at the time of STG compilation, there was very limited clinical outcome data on patients treated with concomitant DTG and efavirenz. In addition, efavirenz does not require dose adjustment with concomitant rifampicin.

INSPIRING study: Since formulation of the STGs, results of a randomised "non-comparative" trial assessing efficacy and safety of DTG in patients initiating DTG-containing ART while on rifampicin containing TB treatment, the "INSPIRING" study have been published[2]. This open label study randomised HIV-1–infected antiretroviral therapy–naive adults (CD4+ ≥50 cells/mm3) on rifampicin-based tuberculosis treatment for ≤8 weeks to receive DTG 50 mg twice daily both during and 2 weeks after tuberculosis therapy, then 50 mg once daily (n=69) or efavirenz 600 mg daily (n=44). Both interventions were given with 2 nucleoside reverse transcriptase inhibitors, and participants were followed up for 52 weeks. The primary endpoint was the proportion of DTG-arm participants with plasma HIV-1-RNA <50 copies/mL (responders) by the Food and Drug Administration Snapshot algorithm (intent-to-treat exposed population i.e., all participants who received at least 1 dose of study drug) at Week 48. The trial was not powered to show a difference between study arms and no formal statistical hypothesis was tested. Participants were randomised to 3:2 to DTG and efavirenz to increase precision of estimates for DTG group. A sample size of 66 to 72 participants in the DTG arm was estimated to have >85% power to detect a response rate of greater than 70%, assuming an 85% response rate at Week 48.

Results:

- Week 48 response rates: 75% virologically suppressed (52/69, 95% confidence interval [CI] 65–86%) for DTG and 82% (36/44, 95% CI 70–93%) for efavirenz. The DTG "nonresponses" were driven by non–treatment related discontinuations (10 were lost to follow-up in the DTG arm before week 48, most after completion of TB treatment).
- No deaths or study drug switches.

- Two discontinuations for toxicity, both in the efavirenz arm.
- Three protocol-defined virological failures (confirmed viral load>400 copies per mL at or beyond 24 weeks on treatment), 2 in the DTG arm, neither of which had acquired resistance, and 1 in the efavirenz arm with emergent resistance to nucleoside reverse transcriptase inhibitors and nonnucleoside reverse transcriptase inhibitors.

***Conclusions**:* The INSPIRING randomised trial was not powered to compare outcomes between DTG and efavirenz. However, it demonstrated that DTG-containing ART with DTG double dosing is well tolerated. Virological outcomes for efavirenz and DTG were similar.

Currently, the STG include double dosing of DTG during TB treatment for patients diagnosed with TB on DTG. However, for the patients initiating ART while on TB treatment, the only option in the STGs currently is efavirenz-based ART for the duration of TB treatment. Switch to DTG after TB treatment is then required.

There is to date no randomised data on standard dose DTG with rifampicin-containing TB treatment- but a trial is under way (NCT03851588. Standard Versus Double Dose Dolutegravir in Patients With HIV-associated Tuberculosis-RADIANT-TB). Efavirenz has the advantage of not requiring any dose adjustment, but regimen switches increase programmatic complexity, and TEE may become less readily available as it is no longer the preferred option for WOCP. In addition, efavirenz is not tolerated by all patients.

RECOMMENDATION

Based on this evidence summary, the PHC/Adult Hospital Level Committee recommends that dolutegravir 50mg 12 hourly be included as an option in the standard treatment guidelines for adult patients initiating antiretroviral therapy while taking rifampicin-containing TB treatment, as an alternative to using efavirenz for the duration of TB treatment.. *Rationale:* Randomised open-label INSPIRING study showed that initiation of DTG-containing ART with DTG double dosing is well tolerated; and that virological suppression for efavirenz-containing ART regimen and double-dosed DTG-containing ART regimen were similar amongst ART-naive adults initiating ART, whilst on rifampicin-based tuberculosis treatment.

Level of evidence: Low certainty evidence

NEMLC MEETING 29 JULY 2021:

The NEMLC accepted the proposed recommendation made by the PHC/Adult Hospital Level Committee above.

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