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

MEDICINE MOTIVATION:

1. **Executive Summary**

Date:26 January 2017
Medicine (INN): Dolutegravir
Medicine (ATC): J05AX12
Indication (ICD10 code): B24
Patient population: HIV-infected patients commencing first-line antiretroviral therapy (ART)
Prevalence of condition:
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)
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)(1) 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**

Since the recent publication of the START and TEMPRANO studies, which demonstrated that ART should be started irrespective of CD4 count (2)(3), the WHO recommended that everyone infected with HIV should

start ART(4), 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 and toxicity from ART when initiated in asymptomatic patients initiated at high CD4 counts, which may result in poor adherence and resistance, with wider public health consequences(5). 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(1)
- **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)(6). 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 (1).

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.

These 12 abstracts describe the following:

- Systematic reviews (6 publications)(7)(8)(9)(10)(11)(12)
- RCT (6 publications)(13)(14)(15)(16)(17)(18)

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)(19).
- 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 (20).

7. Summary of included and excluded studies

a. Excluded studies:

Author, date	***Type of study***	***Reason for exclusion***
You J, 2016 (8)	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 (12)	Meta-analysis of RCTs	Compares various InSTIs (EFV is a NNRTI)
Raffi F, 2015(18)	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 (7)	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 (9)	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 (10)	Systematic review of RCTs and quasi	8466 patients on EFV and	ARV-naïve HIV-infected adults	EFV-based ART versus	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

	randomised trials	9631 on comparator drug	(children included in theory but no paed studies met inclusion criteria)	non-EFV 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	with 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 (11)	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 (13); Stellbrink H, 2013(17)	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; Walmsley S, 2015	RCT phase 3	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 (16)	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.

8. Evidence synthesis

Efficacy

The SINGLE trial compared dolutegravir (DTG)/abacavir (ABC)/3TC to EFV/TDF/FTC in ART-naïve adults (14). 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 (14). 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(9).

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 (10). 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 (10). 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)(21).

DTG in pregnancy

Birth defect prevalence in South Africa was 20 per 1000 live births (2%) in the 2000 South African survey (22) and a recently established prospective pregnancy registry in Kwazulu Natal found a prevalence of 0.5% (23).

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)(24).

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. 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 (25). According to the Antiretroviral pregnancy registry (APR), with first trimester DTG exposure, there were two defects seen in 41 live births, and one defect was noted in 42live births with second and third trimester exposure (it is likely that the pregnancies reported to the APR overlap with those described above)(20).

Recent data from CROI from IMPAACT 1026 in 30 mother-infant pairs, reported four infant congenital anomalies: total anomalous pulmonary venous return; polycystic right kidney and cystic fibrosis; congenital chin tremor; filum terminale and sacral dimple. At the time of analysis data were not available showing how long the women in the study were on treatment. The investigators will also look into the family history of the infant with polycystic right kidney and cystic fibrosis. The congenital chin tremor resolved and the study sites did not consider the other two anomalies to be related to DTG (26).

Rifampicin-containing tuberculosis treatment

Dolutegravir 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) dolutegravir 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 (AUC0-24) was 1.33 [90% confidence interval (CI): 1.14 to 1.53], and the GMR for the trough (Ctau) was 1.22 (90% CI: 1.01 to 1.48) (19). Based on this pharmacokinetic study, 12 hourly dosing of dolutegravir is recommended with rifampicin-based TB treatment (19). We found no published data on treatment outcomes in HIV-infected patients treated concomitantly with rifampicin-based TB treatment and ART that includes dolutegravir 50mg 12 hourly.

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

Dolutegravir 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 (27). However this might need to be taken into account in renal function monitoring guidelines especially if dolutegravir 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. (1)

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

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [x] Not confident [ ] Uncertain [ ]	
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [x] List the members of the group. List specific exclusion from the group:	Rationale for therapeutic alternatives included: References: Rationale for exclusion from the group: References:

<table>
<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 960.39*</td></tr>
<tr><td>DTG (50mg), 30 tabs</td><td>R 806.76*</td></tr>
<tr><td>EFV (600mg), 28 tabs</td><td>R 48.31**</td></tr>
<tr><td>EFV (600mg)+FTC (200mg)+TDF (200 mg), 28 tabs</td><td>R 124.56**</td></tr>
</table>
*SEP Database 3 March 2017 - currently MCC registered products
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)
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>
<tr>
<td>FEASIBILITY</td>
<td>Is the implementation of this recommendation feasible?
Yes [x] No [ ] Uncertain [ ]</td>
<td></td>
</tr>
</table>

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: Based on the appraisal of the evidence presented in this technical review, the Primary Healthcare Expert Review Committee 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, we do not recommend DTG use in pregnancy.
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 6 APRIL 2017:
The NEMLC did not accept the PHC Expert Review Committee's recommendation.
NEMLC Recommendation: DTG not be recommended currently; and that a "watch and wait" approach be taken; as the increasing primary level NRTI resistance throughout Africa renders DTG to be an attractive alternative. In addition, price parity of DTG-containing FDC with the current regimen is recommended.
Rationale: There is limited evidence (phase III RCT) for DTG as part of a first line ART regimen; no outcome data in TB (except a pharmacokinetic study) or pregnancy. However, additional evidence will be forthcoming as trials are underway. DTG has a heightened barrier to resistance, is indicated amongst paediatrics, possibly more tolerable and efficacious than EFV and a number of applications for DTG-FDC containing regimens is still pending at the Medicines Control Council/South African Health Products Regulatory Authority. The currently available DTG-containing FDC is expensive.
Level of Evidence: I Phase III RCT
(Minutes of the NEMLC meeting of 6 April 2017)

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

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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