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

MEDICINE REVIEW
Executive Summary

Date: 06 February 2020
Medicine (INN): Tenofovir alafenamide (TAF)
Medicine (ATC): J05AF13
Indication (ICD10 code): B20
Patient population: HIV-1 infected adult patients
Prevalence of condition: An estimated 7.02 million people were living with HIV in South Africa in 2016, representing 12.7% of the national population or 19.1% of those aged 15-49 years(1)
Level of Care: Primary level of care
Prescriber Level: Nurse prescriber, doctor
Current standard of Care: Tenofovir disoproxil fumarate (TDF)
Efficacy estimates: At 48 weeks, TAF was non-inferior to TDF, viral suppression rates (HIV RNA <50 copies/mL) were 92% vs. 90% respectively.
Numbers needed to treat** for TAF vs. TDF, based on VL suppression estimates from the RCT by Sax et al, 2015: NNT = 50 (95% CI 21 - 142) (About 2% absolute risk reduction (2))
**NNT =1/Absolute RD.
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Introduction

Since April 2010, Tenofovir disoproxil fumarate (TDF) has been the mainstay of first line antiretroviral treatment (ART) in South Africa.(3) It is generally well-tolerated, however, long-term use of TDF is associated with progressive declines in glomerular function and chronic kidney disease in HIV-infected patients.(4–11) Data from a large ART cohort in South Africa showed that patients with mild or moderate renal dysfunction were at higher risk of nephrotoxicity, while those with mild or moderate renal dysfunction vs. normal renal function were at highest risk of death by 48-months of follow-up.(5) In another South African cohort study with over 15,000 patients on TDF containing regimens followed up for a median duration of 13 months, patients without

renal impairment at baseline (eGFR ≥90 mL/min) experienced small but significant declines in eGFR over time.(12) In another study from 1092 HIV-infected patients initiating tenofovir at a primary care clinic in Cape Town, South Africa, renal function was assessed for the first 12 months on ART, generally, renal function improved in the study population during the first year on ART. Renal impairment during the first 12 months of tenofovir-containing ART was 3%.(11) However, the burden of chronic kidney disease among HIV-infected patients in South Africa is high (6%) and estimates indicate that approximately 10% of patients (an estimated 702,000 patients from current HIV prevalence figures) will suffer from HIV-related renal failure or renal toxicities throughout the course of their disease.(5)(13)(14)

Whilst data on the prevalence and squeal of metabolic bone diseases among HIV-infected patients in resource-limited settings like South Africa is scanty(15), a meta-analysis reported a 60% increased fracture risk in HIV-infected individuals when compared to uninfected individuals.(16) Patients treated with TDF have been observed to have greater decline in bone mineral density (BMD) relative to some other NRTIs.(16–21)

Tenofovir alafenamide (TAF), an oral prodrug of tenofovir, is now included as a component of several recommended first-line antiretroviral therapy regimens. These recommendations are based on data from comparative trials demonstrating that TAF-containing regimens are as effective in achieving or maintaining virologic suppression as TDF-containing regimens but with more favourable effects on markers of renal and bone health.(2,22–29) Unlike TDF, which should be avoided or dose-adjusted in patients with renal dysfunction or estimated creatinine clearance (CrCl) < 80 mL/min, TAF-containing regimens appear to be safe and are FDA approved for use in patients with estimated CrCl as low as 30 mL/min.

The aim of this medicine review is to review current available evidence for the use of TAF as part of first line antiretroviral therapy in a roll-out antiretroviral therapy programme.

Question:

1. TAF is non-inferior to TDF as part of ART regimen to treat HIV-1 infection
2. TAF has a better safety profile to TDF (especially renal and bone)

PICOT criteria;

Population	HIV-1 infected adult patients
Intervention	Tenofovir alafenamide
Comparison	Tenofovir disoproxil fumarate either as comparison arm or switch study
Outcomes	Mortality, AIDS progression, Viral suppression, Immunological response, Adverse events and severity,

Search strategy:

An electronic literature search of the PubMed and EMBASE database from beginning of time till 30 January 2020 was undertaken using different combinations of:
(("HIV"[MeSH Terms] OR "HIV"[All Fields]) AND ("tenofovir disoproxil fumarate"[All Fields] OR TDF [All Fields])) AND ("tenofovir alafenamide"[All Fields] OR TAF [All Fields])
WHO HIV treatment guidelines also reviewed, as they are relevant to this setting.

Selection of Studies:
Abstracts from 180 publications were screened.
Exclusions were;

- Out of 29 review articles, 15were excluded – did not compare TAF to TDF
- Out of 69 publications, 57 excluded as they were not randomized clinical trials or systematic reviews
- To avoid repetition, review articles (including systematic reviews were scanned if they included identified RCTs)

Four meta-analyses and an expert think tank review commissioned by the WHO were finally selected for evidence synthesis.

Evidence Synthesis:

The efficacy and safety of TAF-containing regimens vs. TDF-containing regimens have been mostly evaluated in the context of the coformulation of elvitegravir, cobicistat, emtricitabine and darunavir. Comprehensive reviews were identified that included RCTs published to date of synthesis. While there is some overlap of studies in these systematic reviews below, this is little as some reviews focussed on switch studies and others focussed on direct parallel TDF vs. TAF comparisons. Where a review mainly updated a previously published review, the previous one was excluded to reduce duplication.

Systematic Reviews and Review Articles:

Tao et al 2020: Seven RCTs with a total of 6269 participants.

- Virologic suppression rates were similar: (RR, 1.02; 95% CI, 1.00-1.04; p > 0.05) at week 24 (94.0% vs. 94.2%,), week 48 (90.7% vs. 89.5%), and week 96 (86.2% vs. 84.8%).
- Both treatments were safe and well-tolerated, and most adverse events were similar as mild to moderate in severity.
- Compared with the TDF-containing regimens, the TAF-containing regimens in patients had significantly smaller reductions in both hip (RR, 0.33; 95CI, 0.29-0.39; p < 0.05) and spine (RR, 0.58; 95CI, 0.51-0.65; p < 0.05).
- Additionally, the TAF-containing regimens in patients had significantly fewer increases for renal events than those of the TDF-containing regimens through 48 weeks (0.31; 95% CI, 0.18-0.55; p < 0.05).

Tao et al 2019: Eight eligible phase III RCTs included and altogether 7613 patients were recruited.

- patients switched to TAF-containing regimens had significantly better viral suppression than those continuing TDF-containing regimens at weeks 48 and 96 (RR, 1.02; 95CI, 1.00-1.03), but no significant difference in the per-protocol (PP) analysis (RR, 1.00; 95CI, 0.99-1.01).
- Compared with those receiving the TDF-containing regimens, virologically suppressed HIV-infected patients on the TAF-containing regimens had significant increases in CD4 cell counts (SMD, 0.12; 95CI, 0.08 to 0.17), renal and bone parameters at the hip (RR, 2.86; 95CI, 2.24-3.64) and the spine (RR, 2.43; 95 CI, 2.03-2.90) between weeks 48 and 96.
- Among these RCTs, 5.2% of all participants in the TAF-containing regimens and 3.8% of all participants in the TDF-containing regimens started lipid-lowering drugs, and no statistical differences were found between the two groups after 48 weeks and 96 weeks of treatment (RR, 1.27; 95%CI, 0.94–1.71)

Tamuzi et al 2018: 18 randomized controlled trials were used in the Meta-analysis and these are the finding

- HIV-infected patients on TAF based regimens reduced HIV-RNA<50RNAc/ml by 13% compared to TDF contained group (P=0.02)
- TAF to TFD based regimens, the glomerular filtration rate yielded a pooled MD estimate of -3.94(-6.07 to-1.81, P<0.000001
- The MD of percentage change hip bone mineral density was decreased in TDF compared to TAF -1.93 with P<0.00001. MD of percentage change spine bone mineral density was decreased in TDF compared to TAF -1.77 (-1.97 to -1.58) with P=0.001.
- Adverse events and serious adverse events were not significant in both TAF and TDF groups.

Gotham et al 2017: The authors identified 10 randomized controlled trials comparing TDF with TAF (6969 patients, 8043 patient-years of follow-up). (23)The key points from this Meta-analysis were;

- There were no significant differences in treatment efficacy, resistance, or adverse events between TAF and TDF arms.
- There were significant differences, favouring TAF, in BMD and renal function measures, but no significant differences in treatment discontinuations because of bone or renal toxicity.
- TAF treatment was associated with higher HDL levels. A few patients were started on statins.
- There is a lack of data for safety of TAF in pregnancy, TB co-infection, and patients with low CD4 count (<50 cells/mm3).

Vitoria M et al 2017: There were 60 experts invited, including members of the WHO HIV Guidelines committee, specialists in paediatrics and HIV drug resistance, UNITAID, the Clinton Health Access Initiative, USAID, Centres for Disease Control and PEPFAR. The two main questions discussed at this WHO Think-Tank meeting were;

- Is there already enough evidence to support the efficacy and safety of DTG, TAF and EFV400 to justify their use in millions of people in LMICs?
- What clinical trials and pharmacovigilance studies are needed to assess drug safety when these new treatments are used more widely.(31)

These were the key points from the think tank;

- It was agreed that additional safety and efficacy data on DTG, TAF and EFV400 in some subpopulations are needed, particularly for pregnant women and people with HIV–TB coinfection.
- At the meeting, there was limited support for the introduction of TAF as part of first-line antiretroviral treatment in low-income and middle-income settings.
- There was an overall agreement for 6-monthly reviews of safety and efficacy data, in parallel with a phased introduction of the new antiretrovirals.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: [ ] Not confident: [ ] Uncertain: [x]	Rationale (also see under Recommendations): -The efficacy and safety of TAF-containing regimens vs. TDF-containing regimens have been mostly evaluated in the context of the coformulation of elvitegravir, cobicistat, emtricitabine and darunavir. There is insufficient data where it has been evaluated in standard formulation used in LMICs. -The synthesis below shows that TAF is no more effective than TDF. TAF overall, shows slightly lower toxicity in these studies especially regarding renal and bone health markers – the clinical significance of these differences in markers is not clear. However, these findings should be interpreted cautiously as in most studies TAF was co-formulated with cobicistat, where the TAF dose is reduced from 25mg to 10mg. The is a need for trials comparing or evaluating efficacy and especially safety of TAF head for head in standard coformulations used in low middle-income countries. -Emerging observational data suggests switching from TDF to TAF may cause a statistically significant worsening of the lipid profile that may have clinical relevance. This is likely seen in patients with cardiovascular risk factors such as older age and high BMI. The lower concentrations of TDF in plasma from TAF as compared with TDF, and the lipid-lowering effect of TDF may explain the increases in total cholesterol in the TAF group compared with the TDF group. It may be important to weigh the possible benefit of lipid changes associated with TDF against the possible benefit of TAF for bone and kidney.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [ ] Harms outweigh benefits: [ ] Benefits = harms or Uncertain: [x]	See above.

THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes: x No: List the members of the group. Other NRTIs like TDF, ABC List specific exclusion from the group: n/a	Rationale for therapeutic alternatives included: Other NRTIs References: n/a
VALUES & PREFERENCES / ACCEPTABILITY	**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: No: Uncertain: X	
RESOURCE USE	**How large are the resource requirements?** More intensive: Less intensive: Uncertain: x	Cost of medicines/ month: **Medicine** | **Cost (ZAR)** Not currently SAHPRA registered. | **Additional resources:** n/a
EQUITY	**Would there be an impact on health inequity?** Yes: No: Uncertain: x	
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: TAF not be considered for inclusion in the Adult Hospital Level EML, currently.

Note:

- Based on the best available evidence, TAF is no better in efficacy than TDF and may have small safety benefits whose clinical relevance is still uncertain. TAF can be considered in first line regimens in the future should the TAF/FTC co-formulation or FDCs be licensed in RSA (FTC/TAF/DTG) – for patients with contraindications to TDF i.e. advanced renal disease.
- There is very limited clinical experience of TAF in pregnancy and we therefore do not recommend TAF use in pregnancy.
- The potential for the interaction of TAF with rifampicin exists and concurrent therapy still needs further evaluation.

Rationale:

- The efficacy and safety of TAF-containing regimens vs. TDF-containing regimens have been mostly evaluated in the context of the coformulation of elvitegravir, cobicistat, emtricitabine and darunavir. There is insufficient data where it has been evaluated in standard formulation used in LMICs.
- The synthesis shows that TAF is no more effective than TDF. TAF overall, shows slightly lower toxicity in these studies especially with regard to renal and bone health markers – the clinical significance of these differences in markers is not clear. However, these findings should be interpreted cautiously as in most studies TAF was co-formulated with cobicistat, where the TAF dose is reduced from 25mg to 10mg. The is a need for trials comparing or evaluating efficacy and especially safety of TAF head for head in standard coformulations used in low middle-income countries.
- Emerging observational data suggests switching from TDF to TAF may cause a statistically significant worsening of the lipid profile that may have clinical relevance. This is likely seen in patients with cardiovascular risk factors such as older age and high BMI. The lower concentrations of TDF in plasma from TAF as compared with TDF, and the lipid-lowering effect of TDF may explain the increases in total cholesterol in the TAF group compared with the TDF group. It may be important to weigh the possible benefit of lipid changes associated with TDF against the possible benefit of TAF for bone and kidney.

Level of Evidence: I Systematic Reviews and Meta-Analysis of Randomized Clinical Trials

NEMLC MEETING OF 19 MARCH 2019:

NEMLC accepted this evidence review and the proposal as recommended by the Adult Hospital Level Expert Review Committee, above.

NEMLC also acknowledged that TAF-containing fixed-dose combination formulations are currently not SAHPRA registered and thus not currently available on the South African market. The current antiretroviral recommendations, as recommended in the Standard Treatment Guidelines (Adult Hospital Level, 2019 edition) and National HIV Guidelines, 2019 edition are sufficient.

Proposed TAF-containing antiretroviral regimens - refer to Annexure A.

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
x		

VEN status: n/a

Vital	Essential	Necessary

Monitoring and evaluation considerations: n/a

Research priorities

Safety and efficacy in pregnancy and HIV-TB co-treatment.

Long term safety data using coformulation used in LMICs

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ANNEXURE A
Potential TAF-containing regimens

*The following 4 tenofovir alafenamide-containing FDC tablets are FDA-approved for HIV treatment:
1) elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (brand name: Genvoya®),
2) emtricitabine/rilpivirine/tenofovir alafenamide (brand name: Odefsey®), and
3) Descovy®. As a stand-alone agent, tenofovir alafenamide (brand name: Vemlidy®) is FDA-approved for chronic hepatitis B virus (HBV) infection treatment.
4) Dolutegravir/emtricitabine/tenofovir alafenamide (brand name: Kocitaf)

Abbreviations

DTG	Dolutegravir
TDF	Tenofovir disoproxil fumarate
FTC	Emtricitabine
3TC	Lamivudine
ABC	Abacavir
TAF	Tenofovir alafenamide fumarate
EVG/c	Elvitegravir/cobicistat