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

MEDICINE REVIEW UPDATE

Key findings

- This is an update of the initial February 2020 TAF review. We conducted a review of systematic reviews, and found no additional studies to synthesize.
- The efficacy and safety of TAF-containing regimens vs. TDF-containing regimens have been mostly evaluated in the context of coformulations of elvitegravir, cobicistat, emtricitabine and darunavir. There is insufficient data where it has been evaluated in standard formulation used in LMICs.
- In a recent systematic review, by Tao et al (2020) including 9 RCTs with 6269 participants virologic suppression rates were similar for TAF and TDF: (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%). Similarly, no significant difference was noted in the per-protocol (PP) analysis (RR, 1.00; 95CI, 0.99-1.01) in a systematic review by Tao et al (2019) including 8 RCTs with 7613 participants.
- Gotham et al showed in a synthesis of 10 RCTs that TAF treatment was associated with higher HDL levels requiring patients to be started on statins. Similarly, Tao et al (2019) showed that a slightly higher percentage of patients on the TAF containing regimens vs TDF containing regimens (5.2% vs 3.8%) started lipid-lowering drugs, but 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).
- TAF overall, showed slightly lower toxicity with regard to renal and bone health markers (e.g. 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). However, the clinical significance of these differences in markers was not clear.
- Both treatments were safe and well-tolerated, and most adverse events were similar as mild to moderate in severity.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	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.
- **No new evidence sourced to be added on review update (May 2022)**

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 formulations 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. There 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 and 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: Systematic Reviews and Meta-Analysis of Randomized Clinical Trials
Review indicator: New high quality evidence of a clinically relevant benefit

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

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.

NEMLC MEETING OF 23 JUNE 2022:

NEMLC Discussion

- *Renal impairment:* It was noted that patients with renal impairment are generally referred to the tertiary level of care and TAF may be potentially advantageous for this cohort so there may be some consideration to limit access to tertiary centres
- *SAHPRA registration:* TAF is currently not registered locally.

NEMLC Recommendation

The NEMLC upheld the previous decision from 2019 which was not to recommend TAF for the inclusion on the national EML. **However, TAF could be accessed by Provinces for individual patients on a named-patient basis**. NEMLC also acknowledged that TAF-containing fixed-dose combination formulations are currently not SAHPRA registered.

Monitoring and evaluation considerations

Research priorities

Safety and efficacy in pregnancy and HIV-TB co-treatment.
Long term safety data using coformulation used in LMICs

1. Executive Summary

Date: May 2022 (Update of initial review of 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
Motivator/reviewer name(s): Dr S Takuva, Mr NJ Nabyoma, Prof G Maartens, Dr M Reddy, Dr H Dawood
PTC affiliation: HD: Provincial KwaZulu-Natal PTC

2. Name of author(s)/motivator(s):
Initial review (February 2020): Dr S Takuva, Mr NJ Nabyoma, Prof G Maartens
Review update (May 2022): Dr M Reddy, Dr H Dawood

3. Author affiliation and conflict of interest details
Initial review (February 2020):
Dr S Takuva: No applicable conflict of interest to declare
1) School of Health Systems and Public Health, Faculty of Health Sciences, University of Pretoria, South Africa
2) Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
3) Adult Hospital Level Committee, 2017-2020

Mr NJ Nabyoma: No applicable conflict of interest to declare
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2) Adult Hospital Level Committee, 2017-2020

Prof G Maartens: No applicable conflict of interest to declare
1) Department of Pharmacology, University of Cape Town, South Africa
2) National Essential Medicines List Committee, 2017-2020

Review update (May 2022)
Dr M Reddy: No applicable conflict of interest to declare
1) BHPSA

Dr H Dawood: No applicable conflict of interest to declare
1) Gray's Hospital, University of KwaZulu-Natal
2) Combined Primary Healthcare/Adult Hospital Level Committee, 2021-2023
3) National Essential Medicines List Committee, 2020-2023

4. Introduction/ Background

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.

5. Purpose/Objective i.e. PICO

Question:

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

-P: HIV-1 infected adult patients
-I: Tenofovir alafenamide
-C: Tenofovir disoproxil fumarate either as comparison arm or switch study
-O: Mortality, AIDS progression, Viral suppression, Immunological response, Adverse events and severity

6. Methods:

a. **Data sources:** PubMed and EMBASE
b. **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]). In May 2022, an additional literature search was conducted. No additional relevant MA's and SRs were identified. All applicable RCTs in SR/MAss had already been included in the review.

WHO HIV treatment guidelines were also reviewed, as they are relevant to this setting.

c. Excluded studies:

Abstracts from 180 publications were screened.

Exclusions were;

- Out of 29 review articles, 15 were 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 to determine if they included identified RCTs)

d. Evidence synthesis:

Four meta-analyses and an expert think tank review commissioned by the WHO were selected for 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 the systematic reviews selected, is the duplication is minor 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 review published earlier was excluded to reduce duplication.

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 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 with a total of 7613 patients 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 findings

- HIV-infected patients on TAF based regimens reduced HIV-RNA<50RNAc/ml by 13% compared to TDF containing 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;

- No significant differences in treatment efficacy, resistance, or adverse events between TAF and TDF arms.
- 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 enough evidence to support the efficacy and safety of DTG, TAF and EFV400 to justify their use in millions of people in low and middle income countries (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 summarised at 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	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [ ] Very low [ ] Uncertain [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	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.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [ ] None [ ] Uncertain [X]	The synthesis 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. There is a need for trials comparing or evaluating efficacy and especially safety of TAF head for head in standard coformulations used in LMICs.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [X] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	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. Compared to TDF, TAF overall, showed slightly lower toxicity with regard to renal and bone health markers (e.g. 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; $p < 0.05$). However, the clinical significance of these differences in markers was not clear.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge [ ] Moderate [ ] Small [ ] None [ ] Uncertain [X]	See above.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [ ] Favours control [ ] Intervention = Control *or* Uncertain [X]	See above.
THERAPEUTIC INTERCHANGE	**Therapeutic alternatives available:** Yes [X] No [ ] **List the members of the group:** Other NRTIs like TDF, ABC	Rationale for therapeutic alternatives included: Other NRTIs References: n/a
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive: [ ] Less intensive: [ ] Uncertain: [X]</td><td>Price of medicines/ treatment course
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>Not currently SAHPRA registered.</td><td></td></tr></table>
Other resources:</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: [ ] No: [ ] Uncertain: [X]</td><td></td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes: [ ] No: [ ] Uncertain: [X]</td><td></td></tr>
</table>

Version	Date	Reviewer(s)	Recommendation and Rationale
1	6 February 2020	ST, MJN, GM	TAF not be recommended, as TAF-containing fixed-dose combination formulations are currently not SAHPRA registered and thus available. TAF is no better in efficacy than TDF, and there is uncertainty regarding the comparative clinical safety profile of TAF vs TDF.
2	May 2022	MR, HD	As before

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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®),
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