health
Department:
Health
REPUBLIC OF SOUTH AFRICA

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

MEDICINE REVIEW UPDATE: 22 February 2024
ADDENDUM ADDED (*Hep B non-HIV co-infected*): 27 June 2024

Key findings

- This is an update of the May 2022 TAF review. We conducted a review of systematic reviews, and found no additional studies to synthesize. A systematic search since the last update yielded two relevant RCTs and one pooled analysis of RTCs.
- 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.
- 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) than TDF. However, most of this data originates from trials involving boosted tenofovir regimens.
- TAF-containing regimens are associated with greater weight gain than TDF-containing regimens (OR for 10% weight gain 2.58 [1.94-3.43] at 48 weeks after switching). However, this association may be largely due to TDF's weight-suppressive effects. By contrast, there was no clinically significant weight gain when switching from ABC to TAF (OR for 10% weight gain 1.12 [0.59-2.12]).
- TAF treatment is associated with slightly higher total cholesterol, LDL and HDL, but a preserved total cholesterol:HDL ratio (mean difference 0.09 mg/dL, 95% CI -0.02 to 0.21).
- Both treatments were overall 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: The Committee suggests that TAF be considered, if affordable, in patients with chronic hepatitis B co-infection and renal impairment with eGFR 30-50 ml/min/1.73m^2.

TAF could also be considered as an alternative to TDF or ABC in other ART regimens, if cost saving. (TAF- and abacavir-containing regimens were not directly compared in this review however).

Rationale:
Based on the best available evidence, TAF has similar efficacy to TDF. TAF has probable safety benefits vs TDF (renal and bone), but a slightly worse lipid profile and is associated with weight gain (though this may be mostly due to TDF's weight suppressive effects). Because TAF, when combined with emtricitabine or lamivudine, can be safely used in patients with an estimated glomerular filtration rate of >= 30 ml/min/1.73m^2, it may be considered for patients with contraindications to TDF, i.e. renal disease, especially if there are cost savings. Patients with an eGFR 30-50 ml/min/1.73m^2 and chronic hepatitis B coinfection potentially constitute the strongest use case, since a form of long-term tenofovir is required for this group of patients and TDF is contraindicated below an eGFR of 50 ml/min/1.73m^2.

Level of Evidence: Systematic Reviews and Meta-Analysis of Randomized Clinical Trials
Review indicator: New high quality evidence of a clinically relevant benefit. Significant cost savings over alternative regimens.

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.

NEMLC MEETING OF 14 MARCH 2024: The Committee supported that a TAF-containing fixed dose combination (either emtricitabine 200mg or lamivudine 300mg together with tenofovir alafenamide 25mg and dolutegravir 50mg) be added to the EML as an alternative to the current standard of care for PLHIV with hepatitis B coinfection and renal impairment (eGFR 30-50 ml/min/1.73m^2).

Monitoring and evaluation considerations

Research priorities

Long-term weight gain data comparing TAF, TDF and ABC-based regimens in LMIC.

1. Executive Summary

Date: February 2024 (Update of initial review of 06 February 2020, and v3 update May 2022)

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
Review update (February 2024): Ms Z Adam, Dr J Nel, Prof K Cohen, Dr M Reddy

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

Review update (February 2024)

Ms Z Adam: No applicable conflict of interest to declare
1) Clinton Health access Initiative (CHAI)

Dr J Nel: No applicable conflicts of interest to declare
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No applicable conflicts of interest to declare
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Dr M Reddy: No applicable conflict of interest to declare
1) SCTA

4. Introduction/ Background

Since April 2010, Tenofovir disoproxil fumarate (TDF) has been the mainstay of first line antiretroviral treatment (ART) in South Africa.(2) 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.(3–10) 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.(4) 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(11) 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%.(10) 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.(4)(12)(13)

Whilst data on the prevalence and sequelae of metabolic bone diseases among HIV-infected patients in resource-limited settings like South Africa is scanty(14), a meta-analysis reported a 60% increased fracture risk in HIV-infected individuals when compared to uninfected individuals.(15) Patients treated with TDF have been observed to have greater decline in bone mineral density (BMD) relative to some other NRTIs.(15–20)

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.(21–29) 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.

Although there were initial concerns about the impact of rifampicin coadministration on TAF, intracellular concentrations of tenofovir diphosphate in the face of rifampicin are still >4 times higher than with TDF + rifampicin.(30) TAF is as effective as TDF for the treatment of hepatitis B, with a slightly better renal and bone side-effect profile. These data derive from studies in HIV negative patients. (31,32)

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 focused on switch studies and others focused 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.

Feb 2024 Update: An electronic literature search of PubMed and EMBASE databases using the same terms was conducted to identify any additional systematic reviews of RCTs or RCTs not included in the previous systematic reviews. No additional systematic reviews were identified, but two additional RCTs (33, 35) and one pooled analysis of RCT data (34) were found.

Chinula et al 2023(33): phase 3 RCT; 643 pregnant women ≥18 years old and 14-28 weeks gestation, from LMIC including South Africa

- Comparing TAF to TDF, in each case paired with emtricitabine and dolutegravir as a fixed dose combination (TAFED vs TED), there were no significant differences in grade 3-4 maternal adverse events (absolute difference -5.6% [95% CI -14.2 to 2.9]), grade 3-4 infant adverse events (-3.2% [95% CI -12.8 to 6.3]), infant deaths (-1.0% [95% CI -3.4 to 1.3]), or infant HIV infections (0.5% [95% CI -1.2-2.1]). Participants were followed up for 50 weeks post-partum.
- Similarly, maternal virological failure rates at with TAFED at 50 weeks post-partum were not statistically significantly different to rates to TLD (difference -1.0% [95% CI -4.9 to 3.0]).

Erlandson et al 2021 (34): pooled data from 12 randomised controlled switch trials; 11,456 person-years of follow-up.

This study included pooled data from 12 Gilead Sciences-sponsored RCTs in PLHIV on ART and a viral load of <50 copies/mL for a minimum of 3 months. The primary goal of this pooled study was to compare weight gain among patients randomized to switch ART (n=4166) or to remain on their stable baseline regimen (n=3150). For participants in the switch ART arm, 1949 switched both NRTIs and the third agent, 1326 switched NRTIS only and 891 switched the third agent only. Boosted and unboosted regimens were included. The duration of follow up in 5 of the 12 studies was 48 weeks and 96 weeks in 7 of the studies, with height measured at baseline and weight being measured at each visit.

- Weight gain of an additional 1.6kg at 48 weeks was seen in those participants who switched from TDF to TAF (compared to staying on TDF). Switching from TDF to TAF (compared to staying on TDF) was associated with odds of 2.58 (95% CI 1.94-3.43) of a >= 10% weight gain by 48 weeks.
- It is not known whether the above arises due to removal of weight-suppressive effect of TDF versus a TAF-induced weight gain, but there is some evidence for the former (i.e. TAF is likely weight neutral).(34) Concordant with this, there was no associated weight gain seen when switching from abacavir (ABC) to TAF.

Venter et al 2020 (35): 96-week data from a South African RCT (n=1053).

- Weight gain data showed greater weight gain in patients randomised to TAF (7kg) vs TDF (4kg) with identical partner drugs. This ~3kg gap persisted at 96 weeks (mean weight gain with TAF 7.1kg [SD 7.4] vs 4.3kg [SD 6.7] with TDF). (36)
- No differences in total bone density, but greater bone density seen in hip and lumbar area in patients on TAF compared to TDF.
- Minimal difference in LDL cholesterol with TAF (+0.2 mmol/L at 96 weeks [95% CI -2.7 to +2.3]) vs TDF (0.0 [-1.7 to +1.8]; confidence interval and p-value for difference not given.

Tao et al 2020 (37): Seven phase 2/3 RCTs with a total of 6269 participants who were ART naïve at study entry. TAF versus TDF. In 6/7 the regimen included cobicistat boosted elvitegravir or darunavir. (Also 1 small (n=30) phase1/2 study of TDF versus TAF for 5 weeks).

- 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 (38): Eight phase III RCTs included with a total of 7613 ART experienced patients, on a TDF containing regimen and virologically suppressed at study entry, randomised to stay on TDF or switch to a TAF containing regimen. In 3/7 studies, the background regimen included cobicistat boosted elvitegravir or darunavir.

- 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 (39): 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 (RR 1.09, 95% CI 0.95-1.25) and serious adverse events (RR 1.01, 95% CI 0.83-1.24) for TAF versus TDF were similar.

Gotham et al 2017 (22): The authors identified 10 randomized controlled trials comparing TDF with TAF (6969 patients, 8043 patient-years of follow-up. 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 was associated with an eGFR 4.07 ml/min higher (95% CI 1.47-6.67) compared to TDF at 48 weeks.
- TAF treatment higher total serum cholesterol, HDL and LDL, but a preserved total cholesterol:HDL ratio (mean difference 0.09mg/dL [95% CI -0.02 to 0.21]).

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.(40)

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 [x] Moderate [ ] Low [ ] Very low [ ] Uncertain [ ] *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	Evidence from systematic reviews and meta-analyses of RCTs and individual RCTs, including several in LMIC countries including South Africa.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [x] None [ ] Uncertain [ ]	TAF has similar efficacy to TDF (viral suppression RR, 1.02; 95% CI, 1.00-1.04). There are small renal and bone mineral density benefits to TAF versus TDF, but these are mostly seen in studies using pharmacokinetic boosting, rather than in unboosted studies. 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; $p < 0.05$).
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [ ] Moderate [x] Low [ ] 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	High quality evidence of an association between TAF and weight gain vs TDF, from both treatment initiation and switch studies. (e.g. weight gain of an additional 1.6kg at 48 weeks was seen in those participants from RCTs who switched from TDF to TAF). It is not known whether the above arises due to removal of weight-suppressive effect of TDF versus a TAF-induced weight gain, but there is some evidence for the former (i.e. TAF is likely weight neutral).
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [x] None [ ] Uncertain [ ]	Weight gain association as above. Trivial increase in LDL compared to TDF. Reassuring data now on pregnancy outcomes and general adverse events in LMIC like South Africa.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [ ] Favours control [ ] Intervention = Control *or* Uncertain [x]	There are small renal and bone mineral density benefits to TAF compared to TDF. The associated weight gain seen with TAF compared to TDF is likely not caused by TAF, but rather by the removal of TDF weight-suppressive effects. For patients with chronic hepatitis B and moderate renal dysfunction, the benefits of a TAF formulation additionally include a single fixed-dose formulation (rather than requiring an abacavir-based regimen combined with TDF taken several times a week).
THERAPEUTIC INTERCHANGE	**Therapeutic alternatives available:** Yes [X] No [ ]	Rationale for therapeutic alternatives included: Other NRTIs such as TDF, ABC. For chronic hepatitis B and renal dysfunction with an eGFR 30-50, the current regimen is 3TC/ABC/DTG PLUS TDF 48-hourly.
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	

RESOURCE USE

How large are the resource requirements?

More intensive	Less intensive	Uncertain
		X

Price of medicines/ treatment course for products registered with SAHPRA as at Feb 2024

TAF-containing Products			TDF-containing Products		
Medicine	**Pack Size**	**Cost (ZAR)***	**Medicine**	**Pack Size**	**Cost (ZAR)****
Tenofovir Alafenamide 25mg tablet		n/a	Tenofovir; 300mg	28	41.01
Dolutegravir Sodium 50mg, Lamivudine 300mg and Tenofovir Alafenamide 25mg (Envuteg) DTG/3TC/TAF	30	373.75	Tenofovir 300mg, Lamivudine 300mg, Dolutegravir 50mg	28	71.04
Dolutegravir Sodium 50mg, Emtricitabine 200mg and Tenofovir Alafenamide 25mg (Altaeda®) DTG/FTC/TAF	30	402.5			n/a
Emtricitabine 200mg and Tenofovir Alafenamide 25mg (Tafbin®) FTC/TAF	30	243.8	Tenofovir 300mg, Emtricitabine 200mg	28	65.06

IN RENAL IMPAIRMENT (eGFR of 30-50 mL/min/1.73m^2)					
TAF-containing Products			**ABC Regimen**		
Medicine	**Pack Size**	**Cost (ZAR)***	**Medicine**	**Pack Size**	**Cost (ZAR)****
Dolutegravir Sodium 50mg, Lamivudine 300mg and Tenofovir Alafenamide 25mg DTG/3TC/TAF	30	373.75	FDC: ABC/3TC/DTG	28	**223.73**
			CONCOMITANT CHRONIC HEPATITIS B		
			FDC: ABC/3TC/DTG	28	223.73
			PLUS TDF 48-hourly	28	41.01
					244.24

*SEP prices where available (SEP database 22 Dec 2023)
**MHPL prices (ave cost) where available (MHPL Feb 2024)

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		

EQUITY

Would there be an impact on health inequity?

Yes	No	Uncertain
		X

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.
3	May 2022	MR, HD	As before
4	February 2024	ZA, JN, KC	Inclusion of products registered by SAHPRA although local prices not yet available for all products. Inclusion of evidence updates: Two additional studies on weight gain (Venter et al 2020) and (Erlandson et al 2021) added Updated safety data for use in pregnancy added (Chinula et al 2023)
5	27 June 2024	ZA, JN	New Addendum added: TAF for treatment of Hep B non-HIV co-infected

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APPENDIX 1: CHARACTERISTICS OF INCLUDED STUDIES

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Chinula et al 2023 *IMPAACT 2010 VESTED trial*	RCT: Open label Phase III, multicenter study Funding source: Study funded and sponsored by the IMPAACT Network. Overall support for the IMPAACT Network was provided by the National Institute of Allergy and Infectious Diseases, with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all of which are components of the National Institutes of Health. Study drugs donated by Gilead Sciences, ViiV Healthcare, and Mylan Pharmaceuticals. COI: JvW is an employee of ViiV Healthcare and JFR is an employee of Gilead Sciences. All other authors declare no competing interests.	Pregnant women aged 18 years or older with confirmed HIV-1 infection at 14–28 weeks of gestation (n=643). Women were ART-naive, with the following exceptions permitted: 1.Up to 14 days of ART use during the current pregnancy but before enrolment (in order to not delay ART initiation during screening for the study); 2.Previous TDF or TDF with emtricitabine PrEP or 3.ART during previous pregnancies or breastfeeding if the last dose was taken at least 6 months before study entry.	Random assignment (1:1:1) to one of three oral regimens: 1. DTG/ emtricitabine, and TAF (n=217) 2.DTG emtricitabine, and TDF (n=215) or 3.efavirenz, emtricitabine, and TDF (n=211)	Prmary objectives: At 50 weeks post partum: maternal adverse events of grade 3 or higher infant adverse events of grade 3 or higher (clinical or laboratory, regardless of relatedness to study drug) Secondary objectives: Virological efficacy analyses at 50 weeks post partum: •	**Grade 3 or higher maternal adverse effects:** The estimated probability of women experiencing an adverse event of grade 3 or higher by 50 weeks post partum was: 25% in the DTG/emtricitabine/TAF group, 31% in the DTG/ emtricitabine/TDF group, and 28% in the efavirenz/ emtricitabine/TDF group Infection was the most common grade 3 event and decreased Hb was the most common laboratory grade 3 adverse event. **DTG/emtricitabine/TAF group,** 1 woman died of sepsis 2 weeks after caesarean delivery. 1 woman had type 2 diabetes **DTG/ emtricitabine/TDF group** 1 woman had gestational diabetes reported (any grade **efavirenz/ emtricitabine/TDF group** 2 women had gestational diabetes reported (any grade 1 woman had suicidal ideation **Post partum obesity:** At post partum week 50, a higher proportion of women in the dolutegravir, emtricitabine, and tenofovir alafenamide group (23%) were obese (BMI ≥30 kg/m²) than in the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group (15%; difference of 7·6%, –0·2 to 15·4) or the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (18%; difference of 4·2%, –3·9 to 12·3). **Grade 3 or higher infant adverse effects:** 28% overall, with small and non-statistically significant differences between groups. By postnatal week 50, 14 infants whose mothers were in the efavirenz-containing group (7%) died, compared with six in the combined dolutegravir groups (1%).	**SAFETY IN PREGNANCY** **Study Conclusion:** "Safety and efficacy data during pregnancy and up to 50 weeks post partum support the current recommendation of dolutegravir-based ART (particularly in combination with emtricitabine and tenofovir alafenamide) rather than efavirenz, emtricitabine, and tenofovir disoproxil fumarate, when started in pregnancy."
Erlandson et al 2021	Design: Pooled analysis of 12 RCTs Funding source: Study supported by Gilead Sciences and all 12 RCTS	PLHIV on ART with HIV-1 viral load < 50 copies/mL for a minimum of 3 months.	Experimental: Switch ART (n= 4166)	Effects of • Demographic factors, • Clinical characteristics, and	**Weight Gain:** Both groups demonstrated weight gain. Median weight gain was greater in those who switched (1.6 kg, interquartile range [IQR], –.05 to 4.0 vs 0.4 kg, [IQR], –1.8 to 2.4 at 48 weeks, P < .0001), with most weight gain occurring in the first 24 weeks after switch.	**WEIGHT CHANGE** **Study conclusion:** "Moderate weight gain after ART switch was common and usually plateaued by 48 weeks.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
	were sponsored by Gilead Sciences. COI: Authors reported on fees/grants/honoraria with multiple pharma companies including Gilead Sciences.	n= 7316	Control: Continue stable baseline regimen (SBR) (n=3150) *Boosted and unboosted regimens were included*	• ART on weight gain	**Demographic factors**: younger age and lower baseline body mass index were associated with any or ≥10% weight gain Clinical factors: Absolute values and changes in cholesterol components and systolic blood pressure were similar between switch and SBR participants who experienced ≥10% weight gain, with small reductions in HDL noted in this group. **ART**: By week 48, 4.6% gained ≥10% weight (6.4% of switch and 2.2% of SBR), the greatest risk was with switch from efavirenz (EFV) to rilpivirine (RPV) or elvitegravir/cobicistat and switch from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF). Switch from abacavir to TAF was associated with less weight gain than switch from TDF to TAF and was not associated with increased risk for ≥10% weight gain.	Baseline ART was a predictor of post-switch weight gain; participants who switched off of EFV and TDF had the greatest weight gain. The biological mechanisms that underlie the differential effects of switching ART agents on weight and associated clinical implications require further study"
Venter et al 2020 ADVANCE trial -96 week data	RCT: open-label, non-inferiority phase 3 trial based across 2 sites in S.Africa. 96 week data Funding source: Unitaid, USAID, Gilead Sciences, and ViiV Healthcare contributed to study design. COI: Authors reported on multiple pharma and non-phrama-related interests.	PLHIV aged 12 years or older weighing >/= 40kg, with no ARV exposure in the previous 6 months, CrCl > 60 mL/min (>80 mL per min in individuals aged <19yrs) and HIV-1 RNA concentration >/= 500 copies/mL. (n=1053)	Random assignment (1:1:1) to one of three oral regimens: 1. DTG/ emtricitabine, and TAF (n=351) 2.DTG emtricitabine, and TDF (n=351) or 3.efavirenz, emtricitabine, and TDF (n=351)	Primary Endpoint: Proportion of participants who had a plasma HIV-1 RNA concentration of less than 50 copies per mL at week 48 Secondary endpoint Plasma HIV-1 RNA concentration of less than 50 copies per mL at the week 96 visit	Secondary endpoint – 96 week data **% of participants reaching plasma HIV-1 RNA concentration of less than 50 copies per mL:** DTG/emtricitabine/TAF = 79% DTG/emtricitabine/TDF = 78% Efavirenz/emtricitabine/TDF = 74% Non-inferiority established and no significant treatment effects noted. Sub-group analysis **Virological failure** DTG/emtricitabine/TAF = 18% DTG/emtricitabine/TDF = 19% Efavirenz/emtricitabine/TDF =14% **Emergent diabetes** DTG/emtricitabine/TAF = 2% DTG/emtricitabine/TDF = 1% Efavirenz/emtricitabine/TDF = <1% **Weight gain (where data available among participants), mean weight gain which was higher in females**: DTG/emtricitabine/TAF = 7.1kg DTG/emtricitabine/TDF = 4.3kg Efavirenz/emtricitabine/TDF = 2.3kg **Treatment-realted discontinuation (within 48 weeks)** DTG/emtricitabine/TAF = nil DTG/emtricitabine/TDF = nil Efavirenz/emtricitabine/TDF = 3% liver dysfunction (n=4), rash (n=3), renal dysfunction (n=2), neuropsychiatric (n=1).	**EFFICACY & SAFETY** **Study conclusion:** "Medium-term and long-term metabolic and clinical consequences of the considerable increase in bodyweight observed in participants given these antiretroviral regimens and the trajectory of this weight gain over time, especially among women, require further study." **NOTES** Isoniazid prophylaxis was routinely used in participants, according to local guidelines. Women who became pregnant and participants who developed tuberculosis were allowed to continue on adapted regimens. Genotyping not done before initiating ART. There were differences in pill burden between groups.
Tao X, et al. 2020	Design: Meta-analysis - 7 RCTs including: • one-phase 1/2 trial	n=6269	Experimental: TAF containing regimen	***Efficacy outcomes:***	**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%).	**EFFICACY & SAFETY (Non-inferiority)** **Study Conclusions:**

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
	• two-phase 2 trials • four-phase 3 trials Funding Source: Grants from National Major Scientific and Technological Special Project and the Chongqing Municipal Health and Family Planning Commission Medical Research Projects COI: Authors declared that there were none		Control: TDF containing regimen	• Virologic suppression • CD4 Cell Count • Virologic Failure • Adherence *Safety outcomes:* • Adverse events • Discontinuation due to adverse events • Grade 3 or 4 adverse events • Fractures • Bone Outcomes • Renal outcomes Lipid Profile	**CD4 Cell Count:** No significant improvement in CD4 cell count in TAF vs TDF regiments for antiretroviral-naive patients (SMD, 0.05; 95% CI, -0.08 to 0.19; $p > 0.05$) **Virologic Failure:** No significant difference in treatment-naive patients between the two groups during weeks 48 and 96 (RR, 1.25; 95% CI, 0.85–1.84; $p > 0.05$) **Adherence**: To the end of weeks 24, 48, and 96, expressed as the median cumulative adherence change in the treatment-naive patients from baseline. Measured by pill count : 91.61% in the TAF vs 88.22% in the TDF-containing regimens. Four RCTS: No significant difference for the Treatment-naive patients between the two groups (RR, 1.01; 95CI, 0.99–1.03; $p > 0.05$). **Adverse Events:** Both treatments were safe and well-tolerated, and most adverse events were similar as mild to moderate in severity. **Discontinuation due to adverse events:** Six RCTs: discontinuations because of adverse events. 1.54% TAF- vs 2.66% TDF-containing regimens. Prevalence of discontinuation due to adverse events in TAF group was significantly lower than those of the TDF-containing regimens (RR, 0.55; 95CI, 0.37–0.82; $p < 0.05$). **Grade 3 or 4 adverse events:** Six RCTs - between 48 weeks and 96 weeks of follow-up, similar adverse events for TAF and TDF (18.49% vs. 17.64%), and there was no significant difference between TAF vs TDF regimens (RR, 1.07; 95CI, 0.96–1.20; $p > 0.05$). **Fractures:** Five RCTs: including 0.35% TAF-vs 0.82% patients who received TDF-containing regimens, - with no significant difference between the two groups at weeks 48 and 96 (RR, 0.48; 95CI, 0.12–2.00; $p > 0.05$). **Bone Outcomes:** 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; $p < 0.05$). **Renal Outcomes:** 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; $p < 0.05$). **Lipid Profile:** Significant differences in the median changes between the TAF-containing regimens and the TDF-containing regimens, which included total cholesterol (30.87 vs. 11.63, $p < 0.05$), low-density lipoprotein (LDL) cholesterol (17.47 vs. 5.40, $p < 0.05$), high density lipoprotein (HDL) cholesterol (6.12 vs. 2.67, $p < 0.05$) and triglycerides (22.86 vs. 7.48, $p < 0.05$), whereas the total cholesterol/HDL cholesterol ratio remained unchanged (median increases 0.14 vs. 0.03, $p > 0.05$) for the treatment-naive patients at week 48.	"Our meta-analysis indicated that efficacy, safety, and tolerability of TAF-containing regimens were non-inferior in fixed-dose single-tablet regimens for initial treatment of HIV-1 infection. Furthermore, compared with those receiving the TDF-containing regimens, patients on the TAFcontaining regimens had significant advantages in renal function, bone parameters, and lipid profile for the naive patients."

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Tao,. Et al 2019	Design: Meta-analysis - 8 RCTs including: randomized, actively controlled, multicenter, phase 3 trials Funding Source: Grants from National Major Scientific and Technological Special Project and the Chongqing Municipal Health and Family Planning Commission Medical Research Projects COI: Authors declared that there were no conflict of interests	n=7613 patients recruited. n=4434 were participants switching from TDF-containing regimens to TAF-containing regimens n= 3179 participants received TDF-containing regimens.	Switching from TDF-containing regimens to TAF-containing regimens TDF-containing regimens.	**Efficacy Analysis:** • Virologic response • CD4+ cell counts • Virologic failure **Safety analysis:** • Adverse Events • Discontinuation due to adverse events • Grade 3 or 4 adverse events • Fractures • Bone Outcomes • Renal Outcomes • Lipid Profile	***Efficacy:*** **Viral Suppression:** Switch 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). **CD4 Cell Counts:** Virologically suppressed HIV-infected patients on the TAF-containing regimens had significant increases in CD4 cell counts vs those receiving the TDF-containing regimens, (SMD, 0.12; 95CI, 0.08 to 0.17). **Virologic Failure:** n=55 patients (from 7 RCTS) had virologic failure after 48 and 96 weeks of treatment, 31 (0.84%; N=3671) participants who received TAF-containing regimens had virologic failure with resistance. For the combined effect size of virologic failure, no significant difference was found in the ART-experienced patients between the two groups at week 48 (RR, 1.04; 95% CI, 0.44– 2.47; p > 0.05). ***Safety:*** **Adverse Events;** n=6181 patients (from 6 RCTs), reported adverse events (AEs) during 48 and 96 weeks of therapy. Safety profiles of TAF vs TDF-containing regimens were similar (72.16% vs. 70.99%) reporting any treatment-emergent adverse events. **Discontinuation due to adverse events:** Number of AEs leading to study drug discontinuation was similar n=66 (1.49%) in the TAF-containing regimens and n=50 (1.68%) in TDF-containing regimens. **Grade 3 or 4 adverse events:** After 48 and 96 weeks of therapy, 709 (18.82%) of 3767 participants in the TAF-containing regimens vs 452 (18.76%) of 2410 participants in the TDF-containing regimens had grade 3 or 4 laboratory abnormalities **Fractures:** Uncommon, non-significant (32 [0.72%] of 4434 in the TAF vs. 22 [0.72%] of 3073 in the TDF-containing regimens), (RR, 1.08; 95CI, 0.60–1.93; p > 0.05). **Secondary Outcomes** **Bone Outcomes:** At weeks 24, 48, 72 and 96, no significant improvements in bone mineral density in the hip (RR, 1.00; 95CI, 0.98–1.01; p > 0.05)) and spine (RR,1.11; 95CI, 0.98–1.01; p > 0.05) among ART-experienced patients after switching to TAF- containing regimens vs continuing TDF-containing regimens. **Renal Outcomes:** Renal AEs were reported from 6 RCTs which occurred in 34 (0.92%) of 3680 participants in the TAF-containing regimens group vs. 32 (1.38%) of 2323 participants in the TDF-containing regimens group. Fewer patients had significant renal AEs in the TAF-containing	**EFFICACY & SAFETY** Study conclusion: "Virologically suppressed HIV-infected patients on TDF-containing regimens significantly benefit from switching to TAF-containing regimens, resulting in better viral suppression, better immune reconstruction, and less bone and renal problems."

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
					regimens group than in the TDF-containing regimens group through 48 and 96 weeks (RR, 0.50; 95CI, 0.27–0.94; p < 0.05) **Lipid Profile:** 5.2% of all TAF-containing regimen patients vs 3.8% TDF-containing patients started lipid-lowering drugs. 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	Design: Meta-analysis -18 RCTs included Funding Source: Not declared COI: The authors have not declared any conflict of interests.	HIV-infected adult patients.	Intervention = TAF contained regimens Control = TDF contained regimens	**Primary Outcomes:** • Viral load • Serum clearance creatinine • Proteinuria • HBV DNA • HBsAg **Secondary Outcomes:** • Bone mineral density • CD4 count • Hepatic transminases • Adverse events	**Virological failure (48 to 144 weeks):** 5RCTs: TAF less likely to treatment failure vs TDF group (OR 0.92, 95% CI 0.65 to 1.29). **Creatinine Clearance rate(ml/min) (48 to 144 weeks):** 10 RCT: s Random-effects meta-analysis of glomerular filtration rate yielded a pooled MD estimate of -3.94(95% CI -6.07 to-1.81, P P<0.000001) with I2=100%. Not statistically significant (P=0.63). **Proteinuria (48 to 144 weeks):** Proteinuria was higher in TDF group OR 1.11 (95% CI 0.8 1 to 1.54, P=0.03). **HBV DNA: After 96 weeks:** 4 RCTs: Significant in one study - OR 1.29 (95%CI 1.05 to 1.59, P=0.02). 3 studies reported a non-significant increase of HBV DNA odds. **Mean percentage change Spine BMD (%) (48 to 144 weeks):** 11 RCTs All statistically significant with random effect model. Transforming from fixed to random effect, the overall results decreased to 1.6%. The mean difference of percentage change spine BMD was decreased in TFD compared to TAF -1.77 (-1.97 to -1.58) with P=0.001 **CD4 count (cells/µl) (48 to 144 weeks):** TDF group had a low MD of CD4 count than TAF group (MD -18.99, 95% CI -19.61,- 18.37, <00001). **ALT above ULN (96 weeks):** ALT above ULN reached the lowest odds in TAF group compared to TDF group (OR 0.75, 0.57 to 0.98), 2 studies included in this meta-analysis were not statistically. **Any adverse events (96 weeks):** TAF vs TDF on any adverse event was not statistically significant with OR 1.09 (95% CI 0.95 to 1.25, 7 studies, P=0.21), **Serious adverse events (48 to 144 week):** Balanced in TAF and TDF groups.	**RENAL TOXICITY.** **EFFICACY IN HIV/HEP B CO-INFECTION** **Study Conclusion:** "Evidence suggests that use of TAF is more protective and effective than either TDF. Improving renal and hepatic related comorbidities in HIV-infected population, TAF may be beneficial in public health policy, specifically in high HIV epidemic regions."
Gotham et al 2017	Design: Meta-analysis -10 RCTs included. Funding Source: Not declared COI: Nothing to declare *(Reviewers have declared consultancy*	HIV-1 (n=5671 in 8/10 RCTs) and chronic hepatitis B (CHB) (n= 6969)	TAF (n=4000) versus TDF (n=2969) Dose of TAF 10mg in HIV	Efficacy and Safety	**Efficacy** **Virological effects:** No significant difference noted for both treatment-naïve and treatment-experienced groups. **Resistance**: No significant difference in rates of emergent primary genotypic resistance. **Safety** No significant differences in the estimated effect of TAF compared to TDF, across measures of any adverse event (experienced by 83% of	RCTs included predominantly white, male participants around 40 years of age, with a baseline CD4+ count greater than 350. Boosted TDF may have resulted in supratherapeutic levels of TDF as doses not adjusted.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
	and speaker fees from various pharma companies unrelated to the project)		studies and 25mg in CHB. Dose of TDF not adjusted when boosted.		participants in TAF arms versus 83% in TDF arms, risk difference 0.02, 95% CI 0.00–0.03, P = 0.11), Grade 3 or 4 adverse events: 7% in TAF arms versus 8% in TDF arms, risk difference -0.01, 95% CI -0.02 to 0.01, P= 0.52), Grade 3 or 4 laboratory abnormalities: 23% in TAF arms versus 20% in TDF arms, 0.02, 95%CI -0.02 to 0.06, P= 0.32 Serious adverse events: 7% in TAF arms versus 7% in TDF arms, risk difference 0.00, 95%CI -0.01 to 0.02, Death from any cause: 0.3% in TAF arms versus 0.2% in TDF arms, risk difference 0.00, 95% CI 0.00–0.00, P = 0.33 **Differences noted in BMD and Renal effects** **Higher BMD with TAF** BMD Hip – Week 48 Estimated effect of TAF compared to TDF 1.75% (95% CI 1.48–2.01) BMD Hip – Week 96 Estimated effect of TAF compared to TDF 2.57% (95% CI 2.18–2.96) BMD Spine – Week 48 Estimated effect of TAF compared to TDF 1.73% (95% CI 1.54–1.91) BMD Spine – Week 48 Estimated effect of TAF compared to TDF 1.88% (95% CI 1.36–2.41) No significant difference in effect estimate for the incidence of bone fracture events [risk difference 0.00 (95% CI -0.01 to 0.00)]. **Renal Effects – Week 48:** eGFR Treatment with TAF resulted in an estimated 4.07 ml/min (95% CI 1.47–6.67) higher eGFR compared to TDF Change from baseline in serum creatinine – week 96 Slight decrease with TAF -0.02 (95% CI -0.04 to -0.01) *Fewer cases of discontinuation because of renal adverse events using unboosted TDF versus boosted TDF.* **Lipid effects** The estimated difference in effect of TAF on lipids, relative to TDF, was a 13.97 mg/dl (95% CI 3.05–24.89) higher total serum cholesterol, a 2.25 mg/dl (95% CI 1.10–3.39) higher serum HDL, a 8.68 mg/dl (95% CI 2.07–15.29) higher serum LDL, and a 14.22 mg/dl (95% CI 6.28–22.16) higher serum TGs. *Treatment with TAF was associated with a 1% greater risk (95% CI 0.00–0.02, P = 0.03) of being started on lipid-lowering therapy.*	

South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Alimentary (Hepatic Disorders)
Addendum to the NDoH review: Tenofovir alafenamide for PLHIV (Adults)

Date: 27 June 2024
Reviewers: [1.] Dr Nel, [2.] Ms Z Adam
Affiliation and declarations:
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[2.] Consultant to NDoH EML program (Clinton Health Access Initiative).
Both reviewers have no applicable conflicts of interest to declare.

Use of Tenofovir alafenamide (TAF) for the treatment of chronic hepatitis B (non-HIV co-infection) in patients with renal impairment.

Introduction
Hepatitis B virus (HBV) infection is deemed to be endemic in South Africa, and is predominantly seen in adult PLHIV. The predominant strain of HBV circulating in SA is subgenotype A1, is regarded as having unique molecular characteristics with a high hepato-carcinogenic potential (Maepa MB et al, 2022).

The main goal of chronic hepatitis B (CHB) therapy is to improve survival and quality of life by preventing disease progression to cirrhosis and liver failure and to avert disease-related complications such as hepatocellular carcinoma. Two classes of antiviral drugs are generally recommended for the treatment of chronic hepatitis B, namely interferon alpha and nucleoside analogues. The nucleoside analogues are preferentially considered as they are available as oral treatments which are usually cheaper than interferon alpha, are generally regarded to be well tolerated, and are options for a wider range of patients than interferon (Spearman CWN et al, 2013).

Several nucleoside analogues are used for the management of hepatitis B, including lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (LdT), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) (Scherer de Fraga R et al, 2020), although not all are registered by SAHPRA for local use. ETV, TDF and TAF are generally preferred as they have demonstrated a higher barrier to resistance (Scherer de Fraga R et al, 2020).

Locally, the South African Adult Hospital EML includes the use of TDF tenofovir disoproxil fumarate (TDF) for the treatment of chronic hepatitis B in the non-HIV cohort with eGFR > 50mL/min. There is currently **no** recommended treatment in the Adult Hospital level EML for patients whose eGFR <50 mL/min, because TDF is contraindicated in with renal dysfunction. Until recently, TAF was not SAHPRA registered.

Background
In March 2024, a decision was taken by the NEMLC to include a TAF-containing fixed dose combination (either emtricitabine 200mg or lamivudine 300mg together with tenofovir alafenamide 25mg and dolutegravir 50mg) to the EML for PLHIV with hepatitis B coinfection and renal impairment (eGFR 30-50 ml/min/1.73m2).[1] As part of the deliberations on equity of care, the NEMLC supported the inclusion

[1] NDoH Evidence review. Tenofovir alafenamide (TAF) for HIV_Adult review_14 March 2024_v4.0

of TAF 25mg once daily for the management of hepatitis B for the non-HIV cohort with renal impairment[2], specifically for patients with a eGFR 15-50mL/min or requiring haemodialysis. A summary of the evidence in support this decision is included below, which will be added as an Addendum to the original evidence review in PLHIV. Note that tenofovir disoproxil fumarate (TDF) is retained on the EML for the treatment of chronic hepatitis B in the non-HIV cohort with eGFR > 50mL/min.

PICO

The following eligibility criteria was approved for the review.

Population	HIV negative patients with chronic hepatitis B
Intervention	Tenofovir alafenamide (TAF)
Comparator	Tenofovir Disoproxil Fumarate (TDF)
Outcome	Efficacy outcomes: • Virological response Safety outcomes: • Adverse events
Studies	Systematic reviews and/or meta-analysis
Excluded studies	• Studies in PLHIV with Hepatitis B co-infection (subject of original review) • Studies involving mother to child transmission of Hepatitis B (subject of summary included in Addendum 2)

Literature search

A Pubmed search was conducted on 13 June 2024 for systematic reviews (refer to appendix 1 below) which yielded 39 citations. During the title screen and abstract screen, 31 titles were excluded as studies involved co-infected PLHIV or mother to child transmission during pregnancy and a further 3 titles were excluded as, one was a letter to the editor in response to a SR, one an economic evaluation and the third, a network meta-analysis (NMA) of *only cohort studies* (i.e. no RCTs included). A search of the Cochrane database did not yield any citations relevant to our PICO. One title (Chen L et al) was identified from a manual search as a pre-print e-publication which has not been included as not yet subject to peer review.

The existing literature compares TAF to TDF in a scenario where both are available as first line therapies. However, it should be noted that historically there has not been any treatment option in the EML for those with an eGFR <50.

Summary of Evidence

EFFICACY

1. Tenofovir Alafenamide Fumarate (TAF), Tenofovir Disoproxil Fumarate (TDF) and Entecavir (ETV): Which is the Most Effective Drug for Chronic Hepatitis B? A Systematic Review and Meta-analysis (Ma X, Liu S et al., 2021)

This SR included 28 studies that compared 3 antiviral agents in the management of chronic hepatitis B (TDF v ETV [n=17], TAF vs TDF [n=5] and TDF+ETV v TDF [n=6]). This comprised of 13 RCTs, 14 cohort studies and 1 cross sectional study in which patients co-infected with HIV or other hepato-tropic viruses were excluded. For the TAF v TDF comparison, which is the focus of our evidence summary, 5 studies *which were all RCTs* were included and which included a total of 5192 participants. Virological response was reported at 48 weeks in 4 of the studies and at 96 weeks in 2 of the studies. Virological response of TAF was equivalent to that of TDF (OR=0.97, 95% CI: 0.83–1.14, p>0.05) at 48 weeks (see figure 1 below). According to the review authors, results at 96 weeks suggested that there was no obvious differences in the virological response after treatment with TAF and TDF. Limitations of the meta-analysis was that factors associated with virological response such as age, sex, hepatitis B e antigen status, cirrhosis stage, and HBV DNA level before therapy, duration of previous therapy, and baseline HBV DNA level were not accounted and which the review authors acknowledged.

[2] Adult Hospital EML. AH Chp 1 Alimentary Section 1.2.4.2 Hepatitis B, Chronic (Non-HIV con-infection)_2020-4 review

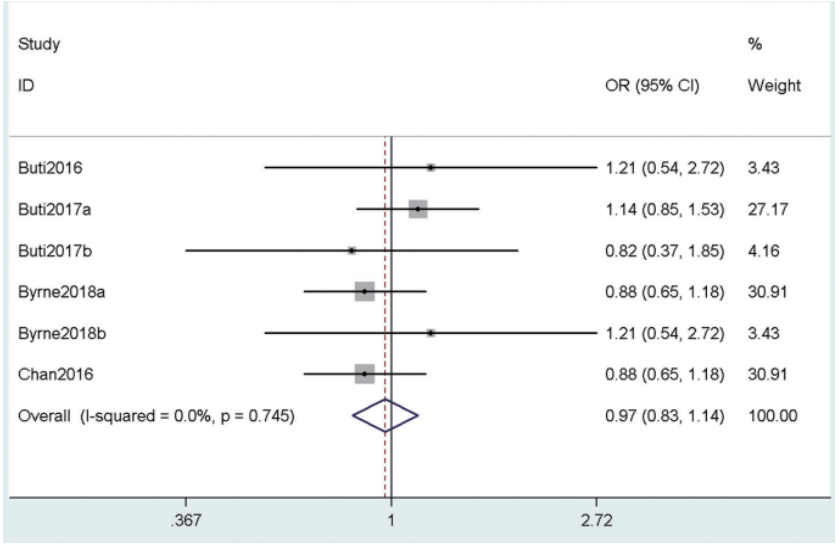

Fig 1: Pooled OR of virological response in TAF-treated vs. TDF-treated CHB patients after 48 weeks of treatment

2. Antiviral treatment for treatment-naïve chronic hepatitis B: systematic review and network meta-analysis of randomized controlled trials (Wong WL et al., 2019))

This review involved a network meta-analysis of RCTs investigating the comparative effectiveness of different treatments for hepatitis B (PEG-IFN, ADV, LAM, ETV, TBV, TDF, TAF as monotherapy or combination therapy) in a treatment-naïve adult population who were either HBeAg-positive or negative, without co-infections, decompensated cirrhosis, hepatocellular carcinoma, and liver transplantation. Efficacy endpoints for the HBeAg-positive population included: virologic response (VR), normalization of alanine aminotransferase level (ALT norm), HBeAg loss, HBeAg seroconversion, and hepatitis B surface antigen (HBsAg) loss; and two efficacy endpoints for the HBeAg-negative population included: VR and ALT norm. RCTs that compared at least two antiviral treatments or one treatment with placebo/no treatment were included in the SR. The review included 12 885 participants across 42 publications of which, 23 studies were in HBeAg-positive patients, 13 in HBeAg-negative patients and 6 included both patient groups. In the case of HBeAg-positive patients, for the comparison of TAF v TDF, the authors reported an OR = 0.88, 95CrI 0.38–1.99. TDF had a probability of 43% being the best treatment for achieving virologic response, followed by the combination strategy ETVTDF (29%) and TAF (26%). In HBeAg-negative patients, TAF and TDF had the highest probabilities of achieving viral suppression (48% and 28% respectively). The authors concluded that *"across all outcomes and in both HBeAg-positive and HBeAg-negative populations, TAF emerged as the treatment with the most consistent performance."*

ADVERSE EFFECTS

3. Renal and bone side effects of long-term use of entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide fumarate in patients with Hepatitis B: a network meta-analysis (Liu Z et al., 2023)

This study was a network meta-analysis of RCTs assessing the safety of longterm use of ETV, TAF and TDF with respect to bone and kidney effects. Quantitative measures of renal function were assessed by a decrease in eGFR and increase in creatinine, and decreased bone mineral density (BMD) and blood phosphorous for assessing bone injury. The analysis included 4278 participants across 16 RCTs, however the sample represents a limited ethnic pool as all studies were conducted in Asia. The authors reported that ETV and TAF were associated were less of an effect on eGFR reduction compared to TDF (SMD = -3.60; 95%CI: -1.94 ~ -5.26 and SMD = -4.27; 95%CI: -2.62 ~ -5.93, respectively) and there was not a statistically significant increase in creatinine with TAF or TDF (SMD=0.06; 95%CI: -0.03~0.15). TAF exhibited the lowest eGFR reduction probability (SUCRA 8.8%) and TDF the highest eGFR reduction probability (SUCRA 100.0%). The authors concluded that overall, TDF was associated with a greater

degree of renal damage compared to TAF or ETV (refer to Figure 2 for more detail). With regard to BMD, TAF was associated with a lower reduction in BMD compared to TDF (SMD = -0.02; 95%CI: -0.01 ~ -0.02). Furthermore, the authors reported no statistically significant differences in the levels of blood phosphorus among the three drugs. TAF exhibited the lowest probability of decreasing BMD (SUCRA 19.6%), and TDF the highest probability TDF (SUCRA 79.7%).

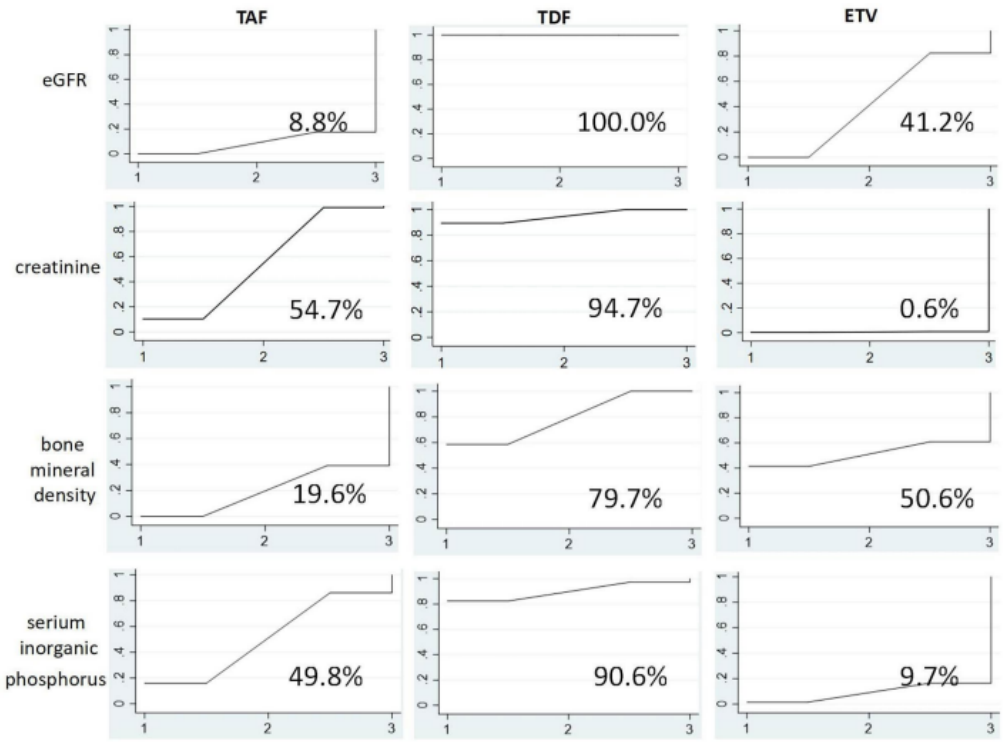

Figure 2: SUCRA diagram of side effects. The figure shows the probability of the effects of three drugs on eGFR, creatinine, bone mineral density, and blood phosphorus before and after medication. According to the level of area under the curve (SUCRA), the larger the area, the greater the index change value.

The authors also undertook a subgroup analysis of the duration of exposure to treatment. As this was a comparison of TDF versus ETV, we have not reported on these findings as ETV is not included in our PICO.

4. Adverse events of nucleos(t)ide analogues for chronic hepatitis B: a systematic review (Scherer de Fraga R et al, 2020)

This aim of this SR, which included both RCTs and observational studies, was to address 3 key research questions, namely:

- What are the most common AEs with the use of NAs in the CHB treatment?
- Is there any difference in the incidence of AEs between the different NAs?
- Do patients receiving TAF have fewer AEs compared to TDF?

The analysis was based on 120 publications, with 6419 participants receiving lamivudine (LAM), 5947 receiving ETV, 3566 receiving TDF, 3096 receiving telbivudine (LdT), 1178 receiving Adefovir dipivoxil (ADV) and 876 receiving TAF. We have limited our reporting on the comparison of TAF vs TDF in line with our PICO.

Data from 2 studies comparing TDF and TAF and *which were both RCTs,* informed the following conclusion by the study authors (refer to Figure 3 and 4 below for details):

- TDF caused greater bone loss in both hip and spine compared to TAF
- There was no clinically significant difference between the two drugs regarding the elevation of serum creatinine, but there was a greater reduction in the glomerular filtration rate in patients who received TDF

The authors however do acknowledge that "t*he number of patients treated with TAF still is too small to consolidate that TAF is really safer than TDF*".

Study	Follow-up		TAF	TDF	p
Buti, 2016 [29]	48 weeks	hip	− 0.29%	− 2.16%	< 0.0001
		spine	− 0.88%	− 2.51%	0.0004
Chan, 2016 [30]	48 weeks	hip	− 0.1%	− 1.72%	< 0.0001
		spine	− 0.42%	− 2.29%	< 0.0001

Figure 3: Mean percentage decrease in hip and spine bone mineral density with TDF and TAF in studies comparing the two drugs

Study	Follow-up		TAF	TDF	*p*
Buti, 2016 [29]	48 weeks	↑Cr (mg/dl)	0.01	0.02	0.32
		↓eGFR (ml/min)	1.8	4.8	0.004
Chan, 2016 [30]	48 weeks	↑Cr (mg/dl)	0.01	0.03	0.02
		↓eGFR (ml/min)	0.6	5.4	< 0.0001

Figure 4: Mean increase in serum creatinine (Cr) from baseline and the median decrease in estimated glomerular filtration rate (eGFR) with TDF and TAF in studies comparing the two drugs

5. Risk of dyslipidemia in chronic hepatitis B patients taking tenofovir alafenamide: a systematic review and meta-analysis. (Hwang EG et al, 2023)

This aim of this SR was to assess changes in the lipid profile of chronic hepatitis B sufferers following treatment with TAF and other drugs used to treat hepatitis B. The review included 12 studies, 5 (2 RCTs and 3 retrospective cohort studies) of which compared TAF vs TDF, 3 cohort studies comparing TAF vs ETC or TDF, 3 cohort studies where TAF was compared to placebo and 1 study with TAF v ETV. Clinical outcomes were reported as a change in lipid profile under 2 scenarios: i) pre and post TAF treatment in the same patient and ii) difference between TAF and non-TAF antiviral groups. In line with our PICO, we have limited reporting to the comparison between TAF v TDF only, which the study authors included as a sub-group analysis: the mean difference in the TAF group versus the TDF group was reported as follows: LDL-cholesterol level 14.52 mg/dL (95% CI 10.95–18.10), total cholesterol 23.72 mg/dL (95% CI 19.12–28.33) and triglycerides 14.25 mg/dL (95% CI 12.64–15.86).

Outcome	No. of studies	Mean difference	95% CI	I^2	*p* for heterogeneity
HDL-cholesterol	4	7.93	7.44 to 8.42	99	< 0.01
LDL-cholesterol	4	14.52	10.95 to 18.10	100	< 0.01
Total cholesterol	5	23.72	19.12 to 28.33	100	< 0.01
Triglyceride	2	14.25	12.64 to 15.86	91	< 0.01

TAF Tenofovir Alafenamide Fumarate; *TDF* Tenofovir Disoproxil Fumarate; *HDL-cholesterol* High-Density Lipoprotein cholesterol; *LDL-cholesterol* Low-Density Lipoprotein cholesterol

Figure 5: Change in lipid profle during TAF treatment (vs. TDF only)

Recommendation*

The Committee supports the inclusion of TAF on the EML for the management of chronic hepatitis B without HIV co-infection as treatment for eligible patients who have renal impairment i.e.

If eGFR 15-50mL/min (or on haemodialysis):

- Tenofovir alafenamide, oral, 25 mg daily.

***Note:** *At the time of publication, TAF 25mg tablets were listed on the SAHPRA website as locally registered products. However as there is no confirmed SEP, this NEMLC recommendation is subject to review following price confirmation.*

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APPENDIX

Pubmed search History

History and Search Details

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Search	Actions	Details	Query	Results	Time
#5	•••	›	Search: **#1 AND #2** Filters: **Meta-Analysis, Systematic Review**	39	05:36:46
#4	•••	›	Search: **#1 AND #2** Filters: **Systematic Review**	27	05:30:05
#3	•••	›	Search: **#1 AND #2**	1,311	05:29:59
#2	•••	›	Search: **Tenofovir Disoproxil Fumarate**	10,196	05:29:33
#1	•••	›	Search: **Tenofovir Alafenamide**	1,311	04:44:36
#0	•••	›	Search: **Clipboard**	5	06:53:30