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

EVIDENCE SUMMARY

Title: Recycling tenofovir in 2nd line antiretroviral therapy: evidence from NADIA and ARTIST Trials

Date: 19 May 2022 *(update of the initial review of 30 November 2021)*

Reviewer: Jeremy Nel

Affiliation and declaration of interests: Division of Infectious Diseases, Department of Medicine, Helen Joseph Hospital and Wits University. JN has received fees for lectures and advisory fees relating to HIV from HIV Clinicians Society, Cipla, Mylan, and Abbvie.

Background: According to current Department of Health and World Health Organization guidelines, if patients fail a first-line tenofovir (TDF)-based first line regimen, TDF should be switched to zidovudine (AZT) as part of 2nd-line combined antiretroviral therapy.(1, 2) This is to prevent there being only one fully active drug in the new regimen. (The other nucleoside reverse transcriptase inhibitor (NRTI) in the regimen, interchangeably either lamivudine or emtricitabine, is typically reused in 2nd line therapy as it is well-tolerated, retains significant antiviral activity even in the face of the signature M184V mutation, and viruses harbouring the M184V mutation are hyper-susceptible to AZT.)

However, using AZT has several disadvantages: it is poorly tolerated, it needs to be given twice daily, it requires more frequent monitoring, and it is more expensive. Observational data has to date suggested that the switch to AZT might not be necessary.(3, 4)

- NADIA trial

The NADIA trial was a prospective, randomized, open-label non-inferiority trial in a two-by-two factorial design that compared 2nd-line therapy with respect to: (1) darunavir versus dolutegravir, and (2) TDF versus AZT, in patients >12 years old who had failed first line therapy consisting of lamivudine or emtricitabine, tenofovir, and a non-nucleoside reverse transcriptase inhibitor (NNRTI).(5) Patients were enrolled from multiple sites in Uganda, Kenya and Zimbabwe. Randomisation was stratified according to the and viral load at screening (≥100,000 copies/mL vs <100,000 copies/mL). Baseline resistance testing was performed on all patients and was repeated for any patients who developed a confirmed viral load >1000 copies/mL during the study. The primary outcome for both comparisons was a viral load <400 copies/mL at week 48. Non-inferiority was deemed to be met if the lower limit of the two-sided unadjusted 95% confidence interval for the difference in the primary outcome between the two groups was above -12 percentage points.

464 patients were enrolled. With respect to the question of AZT vs (recycled) TDF, a viral load of <400 copies/mL was seen in 207 patients (89.6%) in the AZT group at the 48-week mark in the intention-to-treat population, compared to 215 (92.3%) in the TDF group (difference 2.7%, 95% CI -2.6-7.9%, p=0.32), which met the prespecified non-inferiority criterion. Importantly, the response rates were similar regardless of the number of fully active NRTIs at baseline, and regardless of the presence or absence of the K65R mutation (the signature mutation of TDF, associated with high-level TDF resistance). Confirmed viral rebound (>1000 copies/mL) was seen in 11 patients (4.7%) in the TDF group, versus 16 patients (6.9%) in the AZT group. 4 cases of dolutegravir resistance developed during the trial, three of which were in the AZT group. Results were similar when analysed per protocol, when thresholds of <1000 copies/mL or <50 copies/mL were used, and across multiple subgroups. Grade 3/4 adverse events and drug discontinuations occurred in 13 patients (5.6%) in the TDF group, and 16 patients (6.9%) in the AZT group. Two patients (1.3%) in the AZT group had to discontinue their regimen as a result of an adverse event, whereas none of the patients in the TDF group did.

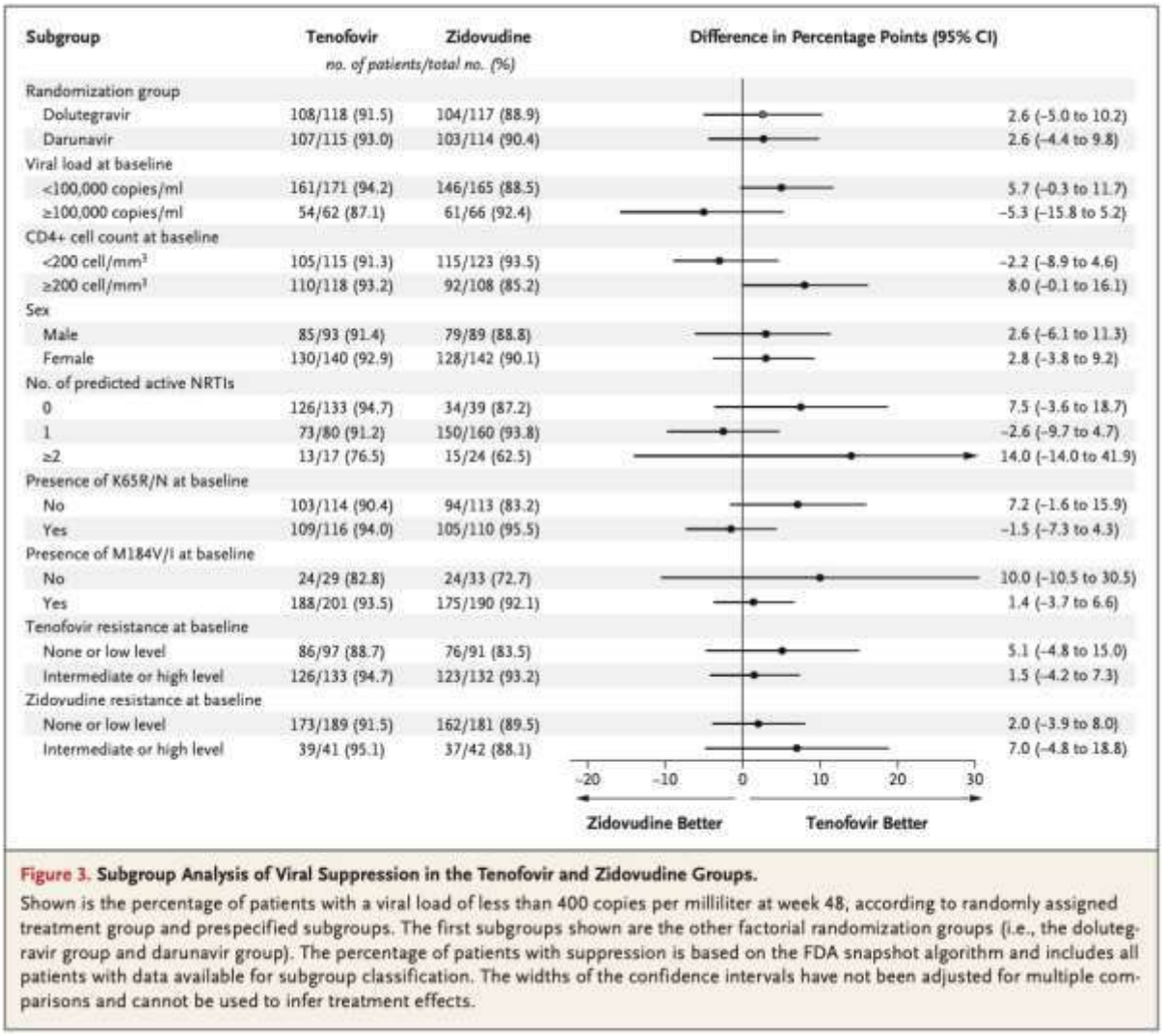

Figure 3. Subgroup Analysis of Viral Suppression in the Tenofovir and Zidovudine Groups.

Shown is the percentage of patients with a viral load of less than 400 copies per milliliter at week 48, according to randomly assigned treatment group and prespecified subgroups. The first subgroups shown are the other factorial randomization groups (i.e., the dolutegravir group and darunavir group). The percentage of patients with suppression is based on the FDA snapshot algorithm and includes all patients with data available for subgroup classification. The widths of the confidence intervals have not been adjusted for multiple comparisons and cannot be used to infer treatment effects.

In April 2022, the 96-week follow-up data was published.(6) In the intention-to-treat population at this timepoint, 214/233 (92%) of the participants in the TDF group and 196/231 (85%) of the participants in the AZT group had a viral load <400 copies/mL (percentage difference 7.0%, 95% CI 1.2 to 12.8, p=0.002). This met criteria for both non-inferiority and superiority of TDF (a superiority analysis was pre-specified if non-inferiority was met, although the trial was powered for non-inferiority). Results were consistent, though not always statistically significant, across the predefined subgroups. Point estimates also favoured TDF when viral load thresholds of <1000 copies/mL (difference 6.1%, 95% CI 0.6-11.6, p=0.03) or <50 copies/mL (difference 5.8%, 95% CI -1.8-13.3) were used. The proportions of grade 3-4 adverse events were similar between the TDF (22; 9%) and AZT (32; 14%) groups and there were no deaths due to study medication. The 96-week data thus supports and extends the trial's 48-week data.

A grade assessment table for the 96 week results is below (table 1); note that this assesses TDF for non-inferiority, rather than superiority.

Table 1: Summary of findings of the NADIA trial, 96-week follow-up data

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TDF	AZT	Relative (95% CI)	Absolute (95% CI)		
96 weeks: viral load <400 copies/mL												
1	RCT	serious[a]	not serious	not serious	not serious	none	214/233 (91.8%)	196/231 (84.8%)	not estimable	**70 more per 1,000** (from 12 more to 128 more)[c]	⊕⊕⊕◯ Moderate	CRITICAL
96 weeks: viral load <50 copies/mL (follow-up: mean 48 weeks)												
1	RCT	serious[a]	not serious	not serious	serious[b]	none	188/233 (80.7%)	173/231 (74.9%)	not estimable	**58 more per 1,000** (from 18 fewer to 133 more)[c]	⊕⊕◯◯ Low	CRITICAL
96 weeks: viral load <1000 copies/mL												
1	RCT	serious[a]	not serious	not serious	not serious	none	216/233 (92.7%)	200/231 (86.6%)	not estimable	**61 more per 1,000** (from 116 fewer to 6 fewer)[c]	⊕⊕⊕◯ Moderate	CRITICAL
Grade 3-4 adverse events (96 weeks)												
1	RCT	serious[a]	not serious	not serious	not serious	none	22/233 (9.4%)	32/231 (13.9%)	**RR 0.68** (0.41 to 1.14)	**44 fewer per 1,000** (from 82 fewer to 19 more)	⊕⊕⊕◯ Moderate	CRITICAL

CI: confidence interval; **HR:** hazard Ratio; RCT: Randomised controlled trial; **RR:** risk ratio

Explanations

a. Lack of blinding: open-label trial

b. 95% confidence interval for absolute difference ranges from negative to positive

c. As per trial report

- **ARTIST trial**

The ARTIST trial was a single-arm prospective interventional study of patients failing first line therapy consisting of TDF, lamivudine or emtricitabine, and either efavirenz or nevirapine.(7) Patients were recruited from two primary care clinics in Khayelitsha, Cape Town and switched to a 2nd line regimen consisting of a tenofovir, lamivudine, and dolutegravir (given as a fixed dose combination), with an additional dose of dolutegravir given for the first 14 days to overcome reduced dolutegravir exposure due to interaction with efavirenz. Exclusion criteria included a CD4 count of <100 cells/µL, active AIDS-defining conditions, and active TB. Baseline resistance testing was performed for all patients, and was repeated if patients failed therapy with a repeat viral load <500 copies/mL. The primary outcome was viral load suppression to <50 copies/mL at week 24. Sixty patients were included in the published analysis.

At week 24, 51 out of 60 patients (85%, 95% CI 73.4-92.9%) achieved virologic suppression in the modified intention-to-treat analysis. In a secondary analysis using a viral load <400 copies/mL as the threshold, 57 patients (95%, 95% CI 86.1-99%) were suppressed at week 24. No patients developed virological failure (defined as two consecutive viral loads >1000 copies/mL). Only a single patient had two consecutive viral loads >500 copies/mL; however this was likely due to non-adherence (as per patient report, and corroborated by low measured drug concentrations) and resistance testing did not show the development of any NRTI or integrase-inhibitor resistance mutations.

The ARTIST trial's limitations include its single-arm design, its small sample size, and short follow-up period (24 weeks, although 96-week results are expected).

A ROBINS-I assessment was done on the ARTIST trial. There was serious potential for bias and the study population may not be representative of patient adherence levels because more adherent patients would possibly enrol in studies. The selection of the patients was otherwise broadly comparable to those in the general South African HIV setting. The potential for bias in the outcome was moderate due to the lack of blinding, because although viral load measurements would not be susceptible to measurement bias, adherence levels that impact on viral loads may nonetheless be influenced by knowledge of treatment allocation.

- **VISEND trial**

The VISEND trial is a randomised, open-label, phase 3 non-inferiority trial performed in Zambia including 1201 patients on TEE (4). Arm A randomised patients with VL<1000 copies/mL to TLD or tenofovir alafenamide fumarate/emtricitabine/dolutegravir (TAFED) and arm B randomised patients with VL >1000 copies/mL to either TLD, TAFED or AZT/3TC and either LPV/r or ATV/r. Results have been presented at the 2022 Conference on Retroviruses and Opportunistic Infections (CROI) but have not been peer-reviewed or published to date. At week 48, TLD or TAFED regimens demonstrated superiority in viral suppression (at both <1000 copy/mL and <50 copy/mL thresholds) compared to boosted protease inhibitor regimens with AZT/3TC.

Conclusion: The NADIA, ARTIST and VISEND trials provide evidence that TDF may safely be reused in 2nd-line therapy following 1st-line failure with TDF-containing regimens. The NADIA trial provides the first such direct evidence from a randomised controlled trial; VISEND's publication is expected soon.

Together, the trials offer moderate quality evidence that recycled TDF is non-inferior to AZT with respect to viral suppression in 2nd line antiretroviral therapy, and low quality evidence that it may be superior to AZT in suppression <400 copies/mL. In addition, TDF offers substantial additional benefits over AZT: it can be given once daily (vs twice-daily), it is available as a fixed-dose combination with lamivudine and dolutegravir (i.e. TLD), it requires less intense initial monitoring, it is cheaper, and the greater harmonisation with first line TDF-based regimens would likely improve 2nd-line drug stock challenges.

Of note, 9 patients developed major treatment-related resistance mutations to dolutegravir in the NADIA trial by 96 weeks, compared to none in patients on darunavir/ritonavir. Of these 9, three were in the TDF group and 6 were in the AZT group.

Finally, it is possible that the TDF's signature K65R mutation, which has been associated with reduced HIV viral fitness, is a key driver of these results, and thus the NADIA and ARTIST data cannot necessarily be extrapolated to support the reuse of other NRTIs such as ABC or AZT.

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: Based on this evidence review, the PHC/Adult Hospital Level Committee suggest that tenofovir should be recycled in 2nd line dolutegravir-based antiretroviral therapy. *Rationale:* For patients in whom neither agent is contraindicated, recycled TDF is non-inferior to AZT in 2nd line therapy (assuming TDF use in 1st line), and adverse events rates are similar. In addition, compared to AZT, it is cheaper, can be given once daily, is available as a single fixed dose combination tablet (TLD), and requires less intense initial monitoring. **Level of Evidence: RCTs of moderate certainty evidence** **Review indicator: Evidence of harm of inferior viral suppression rates**					
NEMLC RECOMMENDATION (MEETING OF 23 JUNE 2022): **NEMLC accepted the proposed recommendation, as mentioned above.**					
Monitoring and evaluation considerations					
Research priorities					

Appendix I: 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 ☐ *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	Single large well-designed randomised controlled trial. Level of evidence for non-inferiority downgraded from "high certainty" to "moderate certainty" due to risk of bias.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☒ Small ☐ None ☐	• TDF vs AZT: Requires less intense initial monitoring: no requirement to check haemoglobin. • Reduced pill burden: 1 tablet daily vs 1 tablet 12-hourly. • Available as a single fixed-dose combination tablet (TLD).
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ 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	Large, well-designed randomised controlled trial. Downgraded from "high" to "moderate" due to risk of bias (open label study).

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small ☐ None ☒	TDF and AZT appear approximately equally well tolerated. Proportions of grade 3-4 adverse events were similar between TDF (9%) and AZT (14%) groups. No deaths due to study medication. The emergence of treatment-related resistance mutations to DTG, compared to none in patients on DRV/r is noted; was more numerous in AZT-containing arms, but not statistically significant)
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a Yes ☐ No ☐	n/a
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	• TDF is already readily available as part of 1st line therapies. • Will require retraining of staff.
RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☒ Uncertain ☐	**Price of medicines/ month (28 days):** **Medicine** / **Price (ZAR)*** AZT 300mg, tab/cap (56) — 76.49 AZT/3TC 300/150mg, tab/cap (56) — 95.40** TDF 300mg, tab/cap (28) — 40.12 TDF/FTC 300/200mg, tab/cap (28) — 68.71** Dolutegravir 50mg tablets — 51.74** TLD (TDF/3TC/DTG 300/300/50mg) tab/cap (28) — 95.34** DRV/r 400/50 mg, 60 tablets — 647.62** * Contract circulars RT71-2019ARV, HP13-2019ARV/01 ** Weighted average price *** NDoH notice (ref 2020/11/03/EDP/01 – quotation price from Mylan) Approximately 250,000 patients on 2nd-line therapy in South Africa currently. Possible switches: • 3TC/AZT → FTC/TDF • 3TC/AZT + DTG → TLD • 3TC/AZT + TDF (if chronic hep B)→ FTC/TDF • 3TC/AZT + TDF + DTG (if chronic hep B) → TLD
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor ☐ Major ☐ Uncertain ☒ **Is the option acceptable to key stakeholders?** Yes ☒ No ☐ Uncertain ☐	Survey data not available but TDF likely to be favoured by patients due to decreased pill burden and single-day dosing. Healthcare practitioners would likely find the switch to TDF acceptable as it entails less frequent initial monitoring.
EQUITY	**Would there be an impact on health inequity?** Yes ☐ No ☒ Uncertain ☐	Survey data not available, but the Committee was of the opinion that there would be no significant impact on equity in health for marginalized groups.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	16 August 2021	JN	TDF not be recycled in 2nd line DTG-based antiretroviral therapy. Await 96-week NADIA data, then reassess.
Second	19 May 2022	JN	Suggested that TDF be recycled in 2nd line DTG-based antiretroviral therapy (in patients with no renal impairment, as 96-week NADIA trial data shows that recycled TDF is non-inferior to AZT (assuming TDF use in 1st line), and adverse events rates are similar. Management with DTG-regimen is more affordable and pragmatic.

References:

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2. World Health Organization. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach2021 17th August 2021. Available from: https://www.who.int/publications/i/item/9789240031593.
3. Paton NI, Kityo C, Hoppe A, Reid A, Kambugu A, Lugemwa A, et al. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. N Engl J Med. 2014;371(3):234-47.
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5. Paton NI, Musaazi J, Kityo C, Walimbwa S, Hoppe A, Balyegisawa A, et al. Dolutegravir or Darunavir in Combination with Zidovudine or Tenofovir to Treat HIV. N Engl J Med. 2021;385(4):330-41.
6. Paton NI, Musaazi J, Kityo C, Walimbwa S, Hoppe A, Balyegisawa A, et al. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. Lancet HIV. 2022.
7. Keene CM, Griesel R, Zhao Y, Gcwabe Z, Sayed K, Hill A, et al. Virologic efficacy of tenofovir, lamivudine and dolutegravir as second-line antiretroviral therapy in adults failing a tenofovir-based first-line regimen. AIDS. 2021;35(9):1423-32.